RESIDUAL RISK IN VASCULAR DISEASE AND HEART FAILURE

PASCAL M. BURGER

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Risk factors and individualized prevention

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Residuaal risico in patiënten met vaatziekten en hartfalen
Risicofactoren en geïndividualiseerde preventie

(met een samenvatting in het Nederlands)

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Chapter 1.

General introduction

Cardiovascular disease (CVD), including atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF), is the most common non-communicable disease worldwide.[1] In 2020, the global prevalence of CVD was estimated at 607 million cases.[2] An estimated 64 million people are living with HF worldwide, which comes down to 1-2% of the general adult population.[3] CVD is also the leading cause of death, with 19 million deaths attributable to CVD each year, accounting for 32% of all deaths.[1,2] Patients with HF have an especially poor prognosis, with 5-year mortality rates as high as 43-75%.[3] Besides imposing a burden on patients, CVD also imposes a huge economic burden, with a yearly expenditure of $407 billion in the United States alone, and $100 billion for HF globally.[2,4] Due to population ageing, unhealthy lifestyle habits, and the growing burden of obesity, the prevalence of CVD is on the rise. From 2010 to 2020, prevalence increased by 29%, and CVD mortality by 19%.[2] These numbers are expected to increase even further in upcoming years. Therefore, efforts to reduce the global burden of CVD are of paramount importance.

Residual risk in cardiovascular disease

Over the years, several factors contributing to the development of CVD have been identified. Risk factors most commonly recognized in clinical practice include smoking, hypertension, hypercholesterolemia, and diabetes mellitus (DM). Traditionally, preventive treatments for CVD have mainly focussed on modifying these conventional risk factors. Evidence collected across numerous clinical trials conducted over several decades has shown that agents lowering low-density lipoprotein cholesterol (LDL-C), and systolic blood pressure (SBP) significantly reduce the risk of (recurrent) CVD by ~20% per 1 mmol/L, and 10 mmHg reduction respectively.[5,6] The same has been proven for smoking cessation, antithrombotic agents, and glucose-lowering therapies.[7–9] Consequently, these therapies have become the cornerstones of CVD prevention. For years, international guidelines have recommended the following preventive measures for all patients with established ASCVD: stop smoking, lower LDL-C to <1.8 mmol/L, lower SBP to <140 mmHg, and use antithrombotic therapy.[10,11] Therefore, most patients with ASCVD in current clinical practice receive lipid-lowering, blood pressure-lowering, and antithrombotic treatments.[12] However, despite the routine use of these conventional therapies, patients with ASCVD still remain at high risk of recurrent CVD events. As already indicated above, the numbers of CVD cases and deaths are increasing rather than decreasing. Also, it has been shown that even when conventional risk factors are treated to guideline-recommended targets, more than half of all patients with ASCVD would still have a 10-year risk of recurrent CVD >10%, which is classified as very high risk.[13,14] The risk of CVD events that remains after efforts have been made to institute conventional preventive treatment options to a maximum extent, is referred to as 'residual risk'.

Residual risk in heart failure

The phenomenon of residual risk is also applicable to patients with HF. Over the last few decades most patients with HF have been treated with a loop diuretic, beta-blocker, and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).[15] These drugs have been demonstrated to reduce hospitalizations for HF and mortality in clinical trials.[16–18] Nevertheless, epidemiological data show that patients with HF remain at high risk of hospitalization and mortality. In fact, mortality trajectories have stagnated over the last few decades, despite considerable advances in HF therapy during that time.[19,20] Recent data show that HF patients, on average, are still hospitalized about once each year, and that the 5-year mortality rate is still as high as 57%.[20,21]

Unresolved questions relating to residual risk

The fact that patients with ASCVD and HF have a high residual risk of CVD events and mortality is concerning, and gives rise to the following questions:

1. Which factors contribute to the residual risk of CVD?
2. How can the residual risk of CVD be predicted for individual patients?
3. Which treatments can be used to reduce residual risk, and which patients benefit the most from these treatments?

Factors contributing to residual risk

Before one can move to predicting and treating residual CVD risk, one first has to identify factors that contribute to this risk. In addition to the previously mentioned conventional risk factors, over the years, several novel risk factors for the development of ASCVD and HF have been discovered. Many of these novel risk factors are linked to obesity. With the growing burden of obesity, i.e. currently one-third of the global population is classified as overweight or obese which has been estimated to increase to more than half of the population by the year 2030, these factors are becoming increasingly important.[22]

Adverse effects of obesity

Obesity gives rise to several health issues. Most importantly, increased abdominal fat leads to adipose tissue dysfunction which can increase blood pressure and triglyceride levels, lower high-density lipoprotein cholesterol (HDL-c) concentrations, and cause insulin resistance. These metabolic disturbances are often clustered in the metabolic syndrome.[23] In addition, adipose tissue dysfunction also causes systemic inflammation, which is therefore sometimes seen as an additional component of the metabolic syndrome.[24] This

can be measured by increases in the concentrations of C-reactive protein (CRP), an easily obtainable plasma marker of systemic inflammation.[25]

Relevance to patients with established CVD

The metabolic syndrome, its individual components, and systemic inflammation have all been shown to be associated with an increased risk of CVD.[26–29] However, previous studies have almost exclusively been performed in apparently healthy people, without a history of CVD. So, the association between these novel risk factors and future CVD events in patients with established CVD is largely unknown. Establishing these associations specifically in patients with established CVD, may be important for several reasons. First, the pathophysiology of CVD events may be different in patients who have already had an event in the past, and therefore the influence of metabolic and inflammatory risk factors may be different. Second, patients with established CVD regularly use drugs such as statins, antiplatelet drugs, and antihypertensive agents, with effects on metabolic and inflammatory risk factors as well as CVD risk, potentially affecting the association between these factors and CVD.[30] Finally, patients with established CVD have a far greater risk of future CVD events than individuals without a history of CVD. Therefore, identifying novel risk factors for CVD events in these patients is especially important, as interventions targeting these factors will likely be more (cost-)effective in this population. This has become increasingly relevant in the light of the results of recent clinical trials, which have shown that anti-inflammatory drugs as well as an agent that lowers triglyceride levels, further reduce future ASCVD events on top of conventional therapy in patients with coronary artery disease (CAD) and any type of ASCVD respectively.[31–33] Establishing the association of metabolic and inflammatory risk factors with various cardiovascular outcomes (i.e. different types of ASCVD events, and HF) in patients with various types of CVD, could help to identify new potential target populations for these novel therapies.

In this way, identifying factors that contribute to residual CVD risk may have important implications for both risk stratification (i.e. identification of patients with high residual risk), and treatment (i.e. reducing residual risk in these patients).

Individualized prediction of residual CVD risk

Just knowing which factors contribute to residual CVD risk is not enough to find out the risk of an individual patient, as this is usually determined by a combination of risk factors, i.e. both conventional and novel risk factors. As risk factor levels vary considerably between patients, there is also a wide distribution of residual risk, with some patients being at very high risk of future CVD events, whereas others have a relatively low residual risk

under conventional therapy.[13] Knowing the residual risk for individual patients in clinical practice is important for several reasons. First, it allows physicians to communicate an individualized prognosis to their patients. Patients often want to know what they can expect in the future, in terms of their risk of recurrent events, and their anticipated (event-free) life expectancy. Second, showing patients estimates of their residual CVD risk may increase disease awareness, and thereby promote a healthy lifestyle and adherence to preventive treatments. Finally, individualized risk predictions are an important basis for treatment decisions. In patients with a high residual risk, intensive treatment may often be warranted in order to reduce their risk to an acceptable level. Whereas in patients with a low residual risk under conventional therapy, the benefits of adding more treatments may not outweigh the costs, and risk of adverse events. International guidelines therefore recommend that treatment decisions in the context of CVD prevention are based on an individual's risk factor levels, and predicted future risk of CVD events.[10]

Multivariate risk prediction

As an individual's residual CVD risk is determined by a combination of multiple risk factors, predicting this risk requires a multivariate approach. One such approach is the use of multivariable prediction models. These models combine information on a selection of patient characteristics to predict an individual's risk of future events over a certain time span. For patients with ASCVD, models that have been developed in line with the most recent quality standards already exist.[34] The SMART2 risk score can be used to predict the 10-year risk of recurrent CVD events in patients with established ASCVD.[35] The SMART-REACH model can be used to predict lifetime CVD risk, and CVD-free life expectancy in this same population.[36] The use of these models to support clinical and shared decision-making in patients with ASCVD is recommended by the 2021 European Society of Cardiology (ESC) CVD Prevention Guidelines.[10]

Limitations of current prediction models for patients with heart failure

For patients with HF, over the years, numerous prediction models estimating the risk of hospitalization for HF, and/or mortality have been developed.[37–39] However, these models have several limitations. First, they often include a large number of predictors, and/or measurements that are not routinely available, hampering their implementation in clinical practice. Second, most models have not, or only to a limited extent, been validated in external data, so their performance in new patients from outside the development cohort remains unsure. Third, models predicting HF hospitalization and/or cardiovascular mortality have mostly not been adjusted for competing risks, while patients with HF generally have a high risk of non-cardiovascular death.[40] Finally, the model predictions are

limited to 2- to 5-year risks. To date, a model predicting lifetime risk, in terms of an overall or HF hospitalization-free life expectancy, in patients with HF has not been developed. Lifetime risk estimates for HF patients would be informative, as HF is a chronic disease, and lifetime risks therefore are a more complete representation of a patient's prognosis than its short-term counterparts. Relying on short-term risk estimates to guide treatment decisions may lead to undertreatment in younger patients with less advanced HF. As these patients have a relatively low short-term risk of HF hospitalization and cardiovascular death, intensive treatment may not seem beneficial. While in fact these patients may have a high lifetime risk, and so their benefits from treatment may be considerable in the long term. At the same time, it may lead to overtreatment in older patients with advanced HF, as treatment benefits may be expected to be large in these patients due to their high short-term risk, while in fact they have a relatively short life expectancy and can therefore only benefit from treatment for a limited period of time. This concept is also applicable to patients with ASCVD, and gave rise to the development of the earlier mentioned SMART-REACH lifetime prediction model.[36] The development of a similar model for patients with HF, that also overcomes the other limitations described above, could be of significant value in the management of patients with HF.

So, the prediction of individual residual CVD risk is an important first step in identifying patients who could benefit from intensified treatment, which can be followed by the prediction of individualized treatment effects.

Individualized prediction of treatment effects to reduce residual CVD risk

In recent years, several new treatment options have become available, which can be used to reduce residual risk in CVD patients. In patients with ASCVD, clinical trials have proven that novel therapies including proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, low-dose rivaroxaban, icosapent ethyl, and anti-inflammatory drugs such as low-dose colchicine, reduce the risk of recurrent ASCVD events on top of conventional therapy.[32,33,41,42] Similarly, trials have demonstrated that mineralocorticoid receptor antagonists (MRAs) and angiotensin receptor-neprilysin inhibition (ARNI) in patients with HF with reduced ejection fraction (HFrEF), and sodium/glucose cotransporter 2 (SGLT2) inhibitors in both patients with HFrEF and HF with preserved ejection fraction (HFpEF), further reduce the risk of HF hospitalization and cardiovascular mortality when added on top of a beta-blocker, and an ACE inhibitor/ARB (or as a replacement for an ACE inhibitor/ARB in the case of ARNI).[43–45] Current international guidelines include class I and II recommendations for the novel preventive therapies in patients with ASCVD, as

well as class I recommendations for the new HF therapies in patients with HFrEF.[10,46–48] However, despite guideline recommendations, the implementation of these therapies in clinical practice is lacking.[15,49,50]

Potential reasons for suboptimal uptake of novel therapies in clinical practice

A potential reason for this is clinical inertia. Regarding patients with ASCVD, physicians may think that as long these patients reach their LDL-C and blood pressure targets under conventional therapy, they will by definition have an acceptable residual risk. Regarding patients with HF, physicians may think that as long as a patient's symptoms are stable and/or mild, there is no need to consider additional treatment options. However, CVD by nature is a progressive disease, and the 'stable' CVD patient therefore does not exist. Prediction models estimating the residual CVD risk for individual patients may improve awareness of this risk among physicians, as well as patients. Another reason could be that it may be hard for physicians to convince their patients that the benefits of an additional treatment outweigh the potential harms (i.e. side effects), and that it is therefore worthwhile to add more medications to several they might already be taking. Finally, translating trial results to individual patients in clinical practice is challenging. In trials, treatment effects are usually reported in terms of an average hazard ratio. But it is often hard to judge whether this hazard ratio is applicable to an individual. Relative treatment effects (i.e. the hazard ratio of a treatment) can be influenced by individual patient characteristics, as well as a patient's baseline CVD risk.[51,52] Also, even in case of a homogeneous relative treatment effect, there will still be large differences between individuals in the absolute effects of treatment, due to differences in residual CVD risk and remaining life expectancy.[51,53] For example, a treatment causing a 20% relative risk reduction will afford an absolute risk reduction (ARR) of 6% in a patient with a residual risk of 30%, as compared to an ARR of only 2% in a patient with a residual risk of 10%. In other words, on an absolute scale, the treatment is three times as effective in the former as compared to the latter patient. The 2021 ESC CVD Prevention Guidelines therefore recommend that decisions on the initiation of intensified treatments are based on an individual's predicted residual CVD risk, and that these treatments should predominantly be considered in patients with a high or very high residual risk.[10]

Translating trial results to individual treatment effects

A way to translate group-level trial results to individual patients is through individualized prediction of treatment effects. Heterogeneity of relative treatment effects can be assessed by using trial data to derive multivariate models including treatment-by-covariate or treatment-by-risk interaction terms.[51,52] Absolute treatment effects can be estimated for individual

patients by combining models predicting an individual's CVD risk, with hazard ratios from trials or meta-analyses.[36,53] Previous studies have already used these methods to predict individualized treatment effects of conventional therapies, and selected novel therapies (e.g. PCSK9 inhibitors, and low-dose rivaroxaban) in patients with ASCVD.[36,52,54,55] However, this has not yet been done for icosapent ethyl or anti-inflammatory drugs such as low-dose colchicine, two therapies that modify metabolic and inflammatory risk factors that may play an important role in residual CVD risk. In patients with HFrEF, a previous study has estimated the lifetime benefits of a comprehensive treatment regimen including a beta-blocker, ARNI, MRA, and SGLT2 inhibitor, on a group level.[56] But the prediction of individual treatment benefits in patients with HF is yet to be performed.

Clinical implications of individualized treatment effects

Predicting individualized treatment effects of novel therapies in patients with ASCVD, and HF could have several clinical implications. First, it could help identify patients with a clinically relevant benefit from intensified treatment. Second, it might emphasize the benefits of additional therapies, also in younger patients with less advanced disease in whom the effects of treatment may often be underestimated in current practice. Third, it could allow physicians and patients to weigh the anticipated benefits of a treatment against its costs, and potential harms. Fourth, it might help physicians to communicate treatment benefits to their patients, supporting shared decision-making, and potentially promoting treatment adherence. All could support treatment decisions with respect to the initiation of novel therapies, improving their use in patients that could benefit from them, which could contribute to reductions in the residual risk of patients with ASCVD and HF.

Relevance of lifetime treatment benefits

Individualized estimates of lifetime treatment benefits in particular could be relevant as in both patients with ASCVD and HF, therapies are usually continued lifelong. Lifetime benefits therefore provide a more complete overview of the total benefit that can be expected from a certain treatment in a certain patient. As with estimates of CVD risk, relying on short-term estimates of treatment benefits may lead to undertreatment in younger patients with less advanced disease.[53] These patients have relatively small expected treatment benefits in the short term, but a long projected treatment duration during which the treatment may slow down the progression of the disease, which may result in substantial lifetime benefits. Older patients with more advanced disease may be overtreated, as they have large expected short-term benefits due to their high short-term risk of events, while in fact they may have rather small lifetime benefits due to their short life expectancy limiting the total treatment duration.[53] The 2021 ESC CVD Prevention Guidelines therefore recommend

that decisions on the initiation of intensified prevention strategies are not only based on an individual's 10-year residual CVD risk, but also on estimates of an individual's lifetime risk and treatment benefit.[10]

Thesis objectives

The general objectives of this thesis are:

1. To investigate potential risk factors that contribute to the residual risk of ASCVD and HF in patients with established CVD.
2. To predict residual CVD risk and the effects of intensified treatment for individual patients with ASCVD and HF.

Thesis outline

Part I of this thesis focuses on potential inflammatory and metabolic risk factors contributing to the residual risk of ASCVD and HF. In **Chapter 2**, the association of CRP, as a marker of systemic inflammation, with ASCVD events and mortality is assessed in patients with established CVD from the UCC-SMART cohort. **Chapter 3** examines the association between CRP and incident HF in this population. In **Chapter 4**, the relation between the metabolic syndrome and incident HF is investigated in non-diabetic patients with established CVD from the UCC-SMART cohort.

Part II of this thesis focuses on the prediction of residual CVD risk and treatment effects in individual patients with ASCVD and HF. In **Chapter 5**, a prediction model for individualized lifetime prediction of survival and treatment benefit in HFrEF is derived and validated using data from over 66,000 patients with HFrEF. In **Chapter 6**, the lifetime benefits of anti-inflammatory treatment with low-dose colchicine are estimated for over 36,000 individuals with coronary artery disease, and compared to those of intensified lipid- and blood pressure-lowering therapy. In **Chapter 7**, modification of the treatment effects of icosapent ethyl, a triglyceride-lowering agent, by individual residual CVD risk is assessed in patients with ASCVD and elevated triglyceride levels from the REDUCE-IT trial. In **Chapter 8**, the course of the effects of LDL-C reduction on CVD risk over time, i.e. treatment duration and age, is investigated through a meta-analysis of 60 randomized controlled trials.

The main findings of this thesis are discussed in **Chapter 9**.

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Part I.

Inflammatory and metabolic risk

Chapter 2.

C-reactive protein and risk of cardiovascular events and mortality in patients with various cardiovascular disease locations

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Abstract

Background

Anti-inflammatory drugs reduce the risk of cardiovascular events in patients with coronary artery disease (CAD), but less is known about the relation between inflammation and outcomes in patients with cerebrovascular disease (CeVD), peripheral artery disease (PAD), and abdominal aortic aneurysm (AAA).

Methods

This study assessed the association between C-reactive protein (CRP) and clinical outcomes in patients with CAD (n = 4,517), CeVD (n = 2,154), PAD (n = 1,154), and AAA (n = 424) from the prospective UCC-SMART cohort. The primary outcome was recurrent CVD, defined as myocardial infarction, ischemic stroke, or cardiovascular death. Secondary outcomes were major adverse limb events (MALE) and all-cause mortality. Associations between baseline CRP and outcomes were assessed using Cox proportional hazards models adjusted for age, sex, smoking, diabetes mellitus, body-mass index, systolic blood pressure, non-high-density lipoprotein cholesterol, and glomerular filtration rate. Results were stratified by CVD location.

Results

During a median follow-up of 9.5 years, 1,877 recurrent CVD events, 887 MALE, and 2,341 deaths were observed. CRP was independently associated with recurrent CVD (hazard ratio [HR] per 1 mg/L 1.08; 95% confidence interval [CI] 1.05-1.10), and all secondary outcomes. Compared to the first quintile of CRP, HRs for recurrent CVD were 1.60 (95% CI 1.35-1.89) for the last quintile ≤10 mg/L, and 1.90 (95% CI 1.58-2.29) for the subgroup with CRP >10 mg/L. CRP was associated with recurrent CVD in patients with CAD (HR per 1 mg/L 1.08; 95% CI 1.04-1.11), CeVD (HR 1.05; 95% CI 1.01-1.10), PAD (HR 1.08; 95% CI 1.03-1.13), and AAA (HR 1.08; 95% CI 1.01-1.15). The association between CRP and all-cause mortality was stronger for patients with CAD (HR 1.13; 95% CI 1.09-1.16) compared to other CVD locations (HRs 1.06-1.08; p = 0.002). Associations remained consistent beyond 15 years after the CRP measurement.

Conclusion

In conclusion, higher CRP is independently associated with an increased risk of recurrent CVD and mortality, irrespective of prior CVD location.

Introduction

Patients with established cardiovascular disease (CVD) are at high risk of recurrent cardiovascular events, despite the routine use of lipid-lowering, blood pressure-lowering, and antithrombotic therapy.[1] Besides traditional risk factors, chronic low-grade inflammation has emerged as a driving force of atherosclerotic disease.[2] High-sensitivity C-reactive protein (CRP) is a well-established plasma marker of chronic low-grade inflammation.[3,4] In people without a history of CVD, CRP has been shown to be associated with cardiovascular events and mortality.[5]

However, the association between CRP and clinical outcomes is less well established in patients with various types of CVD. Several studies have been performed in patients with coronary artery disease (CAD), cerebrovascular disease (CeVD), and peripheral artery disease (PAD), but these studies were limited by either a relatively small sample size, short follow-up duration, or strict eligibility criteria, and all only focused on one type of CVD.[6–13] To date, a study simultaneously assessing the association between CRP and clinical outcomes in patients with various CVD locations has not been performed. In recent clinical trials in patients with CAD, anti-inflammatory drugs have been proven to reduce the risk of recurrent CVD.[14–16] Establishing the association between chronic low-grade inflammation, as measured by CRP, and outcomes in patients with various CVD locations could reveal a broader potential for anti-inflammatory therapy in atherosclerotic CVD, which may guide future trials.

This study aimed to determine the association between CRP and recurrent CVD and mortality in patients with various CVD locations.

Methods

Study population

Patients were from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) study, an ongoing prospective cohort study of patients with established CVD at the University Medical Centre Utrecht, the Netherlands.[17] The study was approved by the local Medical Ethics Committee (reference number 22-088), and all participants gave their written informed consent. All patients with CAD, CeVD, PAD, and/or abdominal aortic aneurysm (AAA; definitions in Table S1), enrolled between September 1996 and January 2020 were included (n = 9,005). Patients were enrolled in the cohort at least 2 months after the qualifying event. Patients with multiple CVD locations were assigned to the subgroup of their main CVD location at time of inclusion (i.e. their primary diagnosis which led to their inclusion in the cohort). As CRP concentrations >10 mg/L are

often assumed to be associated with an acute inflammatory response, these patients (n = 756) were analyzed as a separate group.[18]

Data collection

Information on medical history and lifestyle, and physical examination and laboratory measurements were obtained at baseline according to a standardized screening protocol.[17] From 1996 to 2012, CRP was measured by immunonephelometry, and from 2013, it was determined in heparin plasma on an AU5811 routine chemistry analyzer. These techniques provide comparable results.[19] Missing data (<2.0% for all variables), were imputed by single imputation using predictive mean matching.

Outcomes

The primary outcome was recurrent CVD, i.e. a composite of non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular death. Secondary outcomes were the primary outcome components, major adverse limb events (MALE), and all-cause mortality (definitions in Table S2). Outcomes were adjudicated by 3 independent physicians from the endpoint committee.

Statistical analysis

Baseline characteristics were displayed stratified by CRP quintiles, and CVD location. Associations between clinical variables and CRP were assessed using linear regression models. Kaplan-Meier curves were plotted for CRP quintiles and the subgroup with CRP >10 mg/L.

Cox proportional hazards models were derived to determine the association between CRP and primary and secondary outcomes, adjusted for potential confounders. First, models were adjusted for age and sex. Then, models were additionally adjusted for CVD location, smoking, diabetes mellitus (DM), body-mass index (BMI), systolic blood pressure (SBP), non-high density lipoprotein cholesterol (non-HDL-c), and estimated glomerular filtration rate (eGFR). In exploratory analyses, models were additionally adjusted for alcohol consumption, HDL-c, triglycerides, statin and antiplatelet use, and year of inclusion. Visual inspection of restricted cubic splines revealed no violations of the linearity assumption. The proportional hazards assumption, assessed visually on plotted Schoenfeld residuals, was not violated. The association between CRP and outcomes was assessed continuously, and categorically with CRP divided in quintiles and CRP >10 mg/L as a separate group.

Reverse causality was assessed by repeating the analyses after excluding patients with events within 1, 2, and 5 years after inclusion. Consistency of the effects over time was determined in 5-year intervals. Effect modification by age, sex, smoking, DM, BMI, non-HDL-c, and statin and antiplatelet use was evaluated by testing interaction terms and performing stratified analyses. Potential differences in the association between CRP and outcomes between patients with different CVD locations were assessed by testing an interaction term of CVD location with CRP, and performing analyses stratified by CVD location. To quantify the proportion of events attributable to low-grade inflammation as measured by elevated levels of CRP, the population attributable fraction (PAF) was estimated for various CRP thresholds.

As some patients, beside their main CVD location at baseline, also had a history of another vascular disease type, first, a sensitivity analysis was performed in which patients with multiple CVD locations were included in all applicable subgroups. In a second sensitivity analysis a separate subgroup for patients with multiple CVD locations (i.e. polyvascular disease) was created. Finally, subgroups of CVD location were further divided into subtypes based on the severity of the CVD event.

In subgroup analyses, the significance level was corrected for multiple testing using a Bonferroni correction.[20]

All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

Results

Baseline characteristics

Baseline characteristics of all patients (n = 9,005) are shown stratified by CRP quintiles in Table 1, and stratified by CVD location (CAD, n = 4,517; CeVD, n = 2,154; PAD, n = 1,154; AAA, n = 424) in Table S3. Median CRP was 1.8 mg/L (interquartile range [IQR] 0.9-3.6; distribution in Figure S1). CRP concentrations (median; IQR) were higher in patients with PAD (2.6; 1.3-4.7 mg/L) and AAA (2.8; 1.8-5.0 mg/L), compared to CAD (1.6; 0.8-3.1 mg/L) and CeVD (1.8; 0.8-3.6 mg/L) (Figure S1C-E).

Table 1. Baseline characteristics stratified by quintiles of C-reactive protein

Characteristic	1st Quintile (n = 1,604)	2nd Quintile (n = 1,621)	3rd Quintile (n = 1,725)	4th Quintile (n = 1,649)	5th Quintile (n = 1,650)	CRP >10 mg/L (n = 756)
CRP (mg/L), median (range)	*0.50 (0.10-0.79)*	*1.00 (0.80-1.39)*	*1.80 (1.40-2.39)*	*3.10 (2.40-4.14)*	*5.91 (4.15-10.0)*	*17.0 (10.1-247.4)*
Age	58.8±10.3	60.0±10.3	61.1±10.1	61.4±9.9	61.0±10.3	61.9±10.9
Sex (male)	1,232 (77%)	1,233 (76%)	1,277 (74%)	1,214 (74%)	1,149 (70%)	521 (69%)
Smoking status						
Former	796 (50%)	817 (50%)	855 (50%)	781 (47%)	697 (42%)	338 (45%)
Current	328 (20%)	366 (23%)	475 (28%)	572 (35%)	672 (41%)	291 (39%)
Alcohol (units/week)						
Never drinker	240 (15%)	248 (15%)	319 (19%)	286 (17%)	333 (20%)	169 (22%)
<1	150 (9%)	182 (11%)	196 (11%)	160 (10%)	168 (10%)	74 (10%)
1-10	779 (49%)	771 (48%)	709 (41%)	708 (43%)	676 (41%)	290 (38%)
10-20	300 (19%)	275 (17%)	315 (18%)	329 (20%)	281 (17%)	143 (19%)
>20	135 (8%)	145 (9%)	186 (11%)	166 (10%)	192 (12%)	80 (11%)
CVD location						
Coronary artery disease	958 (60%)	992 (61%)	980 (57%)	860 (52%)	727 (44%)	309 (41%)
Cerebrovascular disease	461 (29%)	416 (26%)	431 (25%)	418 (25%)	428 (26%)	183 (24%)
Peripheral artery disease	146 (9%)	161 (10%)	219 (13%)	282 (17%)	346 (21%)	183 (24%)
Abdominal aortic aneurysm	39 (2%)	52 (3%)	95 (6%)	89 (5%)	149 (9%)	81 (11%)
Diabetes mellitus	221 (14%)	252 (16%)	296 (17%)	272 (17%)	341 (21%)	157 (21%)
Body mass index (kg/m2)	25.6±3.4	26.4±3.4	27.1±4.2	27.3±4.1	27.7±4.5	27.6±4.9
Systolic blood pressure (mmHg)	136±20	137±20	139±20	140±21	142±22	141±21
Laboratory values						
LDL-cholesterol (mg/dL)	100±37	102±37	108±39	111±41	118±42	116±45
HDL-cholesterol (mg/dL)	51±15	49±14	48±14	47±14	45±13	45±13
Non-HDL-cholesterol (mg/dL)	124±43	128±43	137±45	142±48	151±49	147±51
Triglycerides (mg/dL)	123±87	137±84	150±98	159±130	166±154	160±119
eGFR (mL/min/1.73 m2)	80±16	79±16	78±17	76±18	76±19	73±21
Medication use						
Statin	1,223 (76%)	1,228 (76%)	1,217 (71%)	1,105 (67%)	992 (60%)	415 (55%)
Antiplatelet therapy	1,311 (82%)	1,332 (82%)	1,366 (79%)	1,261 (77%)	1,178 (71%)	522 (69%)
Antihypertensive agent	1,170 (73%)	1,245 (77%)	1,327 (77%)	1,233 (75%)	1,234 (75%)	555 (73%)

All data in n (%) or mean±SD, unless otherwise specified.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein, PAD = peripheral artery disease, SD = standard deviation.

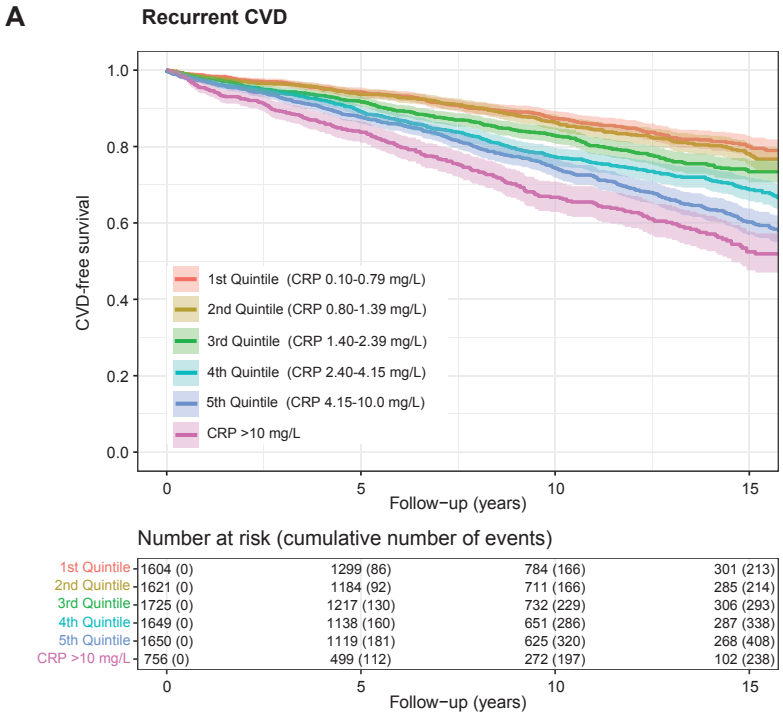
Determinants of CRP concentration

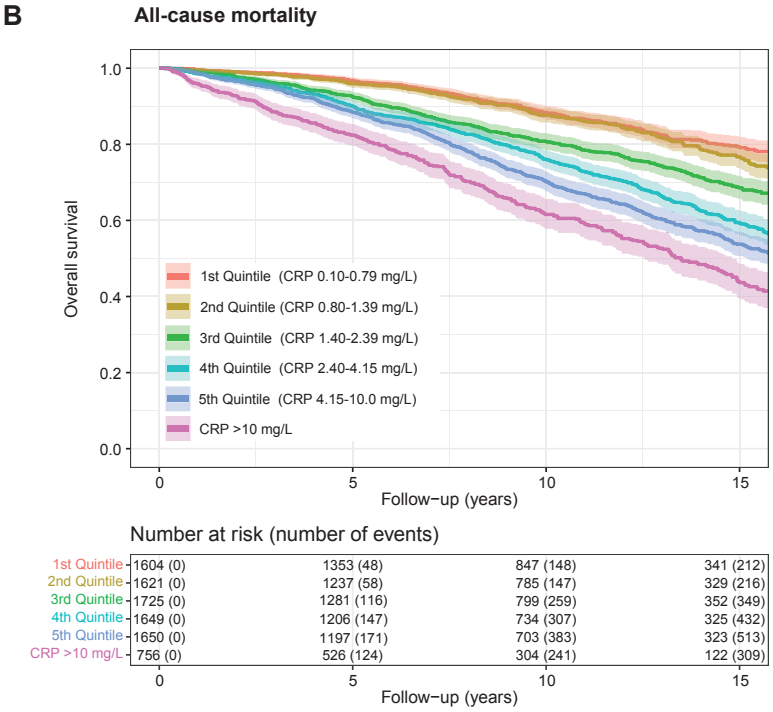
Factors independently associated with higher concentrations of CRP included higher BMI, current smoking, lower HDL-c, higher non-HDL-c, female sex, and older age, as well as having PAD or AAA instead of CAD (Figure S2).

Outcomes

During a median follow-up of 9.5 years (IQR 5.1-13.9) 1,631 recurrent CVD events, 1,998 all-cause deaths, and 774 MALE were observed in patients with CRP ≤10 mg/L (and 246 recurrent CVD events, 343 all-cause deaths, and 113 MALE in patients with CRP >10 mg/L). The unadjusted incidence of recurrent CVD and all-cause mortality increased with each quintile of CRP, and was highest in the subgroup with CRP >10 mg/L (Figure 1; other outcomes in Figure S3). With respect to CVD location, incidence rates were highest for patients with AAA, followed by patients with PAD, CeVD, and CAD (Figure S4).

Figure 1. Kaplan-Meier curves stratified by CRP quintiles





Unadjusted CVD-free (A) and overall survival (B) in quintiles of CRP, and the subgroup with CRP >10 mg/L.

Association between CRP and outcomes in the total population

CRP was independently associated with recurrent CVD (hazard ratio [HR] per 1 mg/L CRP 1.08; 95% confidence interval [95% CI] 1.05-1.10), and all secondary outcomes (Table 2). Additional adjustment for alcohol consumption, HDL-c, triglycerides, statin and antiplatelet use, and year of inclusion hardly altered the results. A dose-response relationship was observed between CRP in quintiles and all outcomes (Figure 2). HRs for the last (CRP 4.15-10.0 mg/L) compared to the first quintile (CRP <0.80 mg/L) were 1.60 (95% CI 1.35-1.89) for recurrent CVD, 1.52 (95% CI 1.16-1.98) for non-fatal myocardial infarction, 1.48 (95% CI 1.07-2.06) for non-fatal ischemic stroke, 1.69 (95% CI 1.34-2.13) for cardiovascular death, 1.84 (95% CI 1.57-2.16) for all-cause mortality, and 1.48 (95% CI 1.16-1.88) for MALE. A CRP >10 mg/L was associated with the highest risk of recurrent CVD (HR vs. first quintile 1.90; 95% CI 1.58-2.29), and all-cause mortality (HR 2.39; 95% CI 2.02-2.83).

Table 2. Association between C-reactive protein and clinical outcomes

Outcome	N events	Event rate (events/100 PY)	Unadjusted, HR (95% CI) per 1 mg/L	Adjusted for age and sex, HR (95% CI) per 1 mg/L	Main adjustment[a], HR (95% CI) per 1 mg/L	Additional adjustment[b], HR (95% CI) per 1 mg/L
Recurrent CVD	1,631	2.2	1.12 (1.10-1.14)	1.12 (1.10-1.14)	1.08 (1.05-1.10)	1.07 (1.05-1.09)
Non-fatal myocardial infarction	608	0.8	1.08 (1.04-1.11)	1.08 (1.05-1.12)	1.06 (1.02-1.10)	1.05 (1.01-1.09)
Non-fatal ischemic stroke	408	0.5	1.08 (1.04-1.13)	1.08 (1.04-1.13)	1.04 (1.00-1.09)	1.04 (1.00-1.09)
Cardiovascular death	900	1.1	1.17 (1.14-1.20)	1.17 (1.14-1.20)	1.11 (1.08-1.14)	1.10 (1.07-1.13)
All-cause mortality	1,998	2.5	1.14 (1.12-1.16)	1.14 (1.12-1.16)	1.10 (1.08-1.12)	1.10 (1.08-1.12)
Major adverse limb event	774	1.0	1.17 (1.14-1.20)	1.17 (1.14-1.20)	1.08 (1.05-1.12)	1.09 (1.06-1.12)

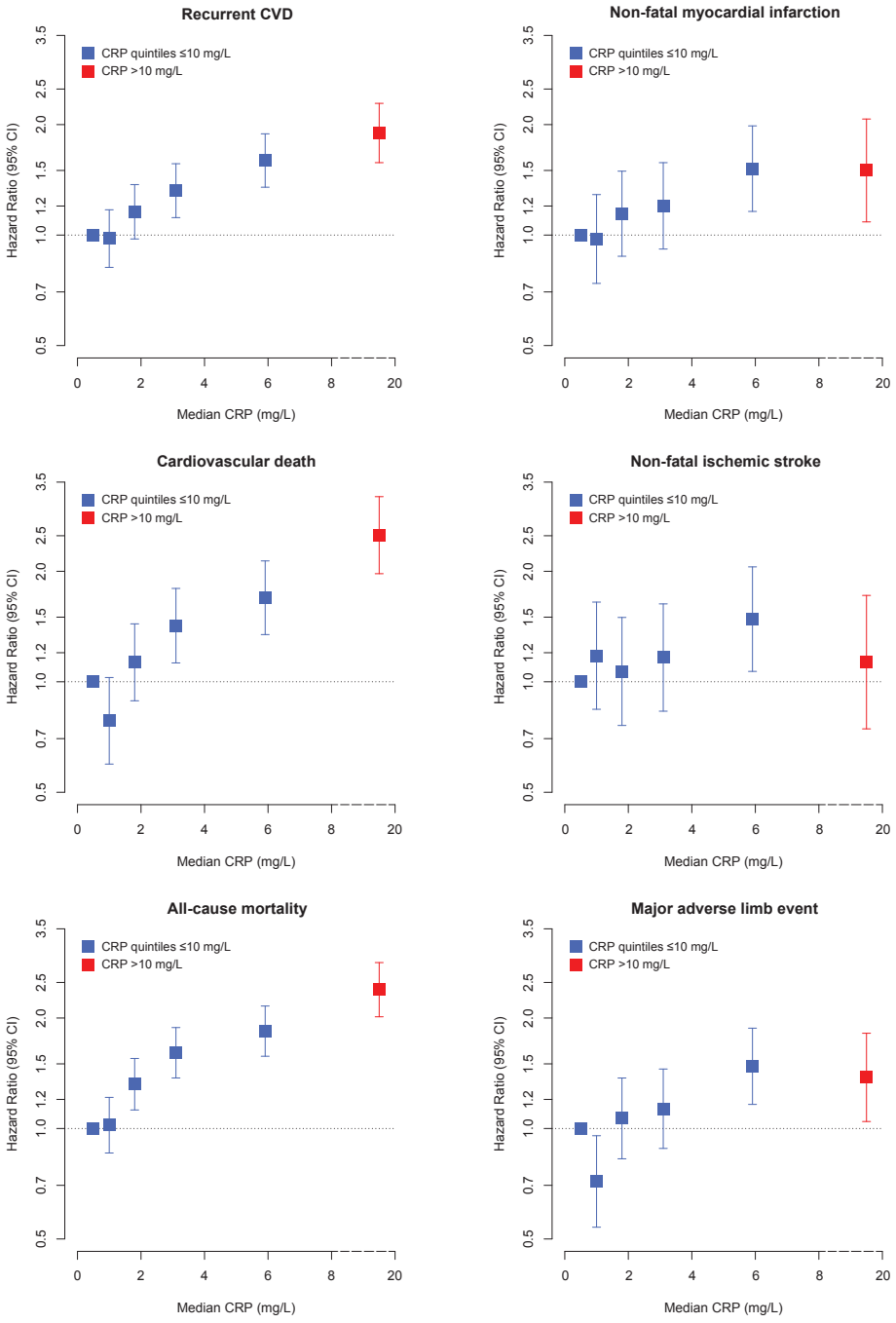
Hazard ratios per 1 mg/L increase in CRP in patients with CRP ≤10 mg/L (n = 8,249).

[a] Adjusted for age, sex, prior CVD location, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

[b] Main adjustment + alcohol consumption (units/week), HDL-c, triglycerides, statin use, antiplatelet use, and year of inclusion in the cohort.

Abbreviations: BMI = body-mass index, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HR = hazard ratio, PY = person years, SBP = systolic blood pressure.

Figure 2. Association between CRP quintiles and cardiovascular outcomes



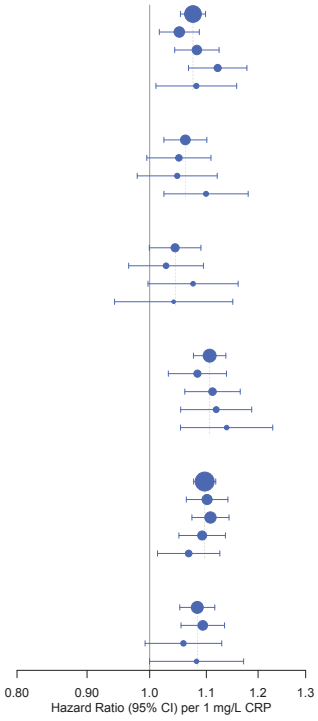
Hazard ratios for the association between CRP and outcomes in quintiles of CRP, and the subgroup with CRP >10 mg/L, as compared to the first CRP quintile (i.e. the reference). Hazard ratios are adjusted for age, sex, prior CVD location, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

Reverse causality, consistency over time, and effect modification

Excluding patients with events within the first 1, 2, and 5 years after inclusion hardly altered the results (Table S4). Baseline CRP remained significantly associated with cardiovascular events and mortality beyond 15 years after the initial measurement (Figure 3). The association between CRP and recurrent CVD was not significantly modified by any of the pre-specified clinical variables (Figure S5).

Figure 3. Association between CRP and cardiovascular outcomes over time

Outcome	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)
Recurrent CVD			
Total follow−up duration	**1631/8249**	**2.2**	**1.08 (1.05−1.10)**
Years 0−5	649/8249	1.8	1.05 (1.02−1.09)
Years 5−10	518/5957	2.2	1.08 (1.04−1.12)
Years 10−15	299/3503	2.5	1.12 (1.07−1.18)
Years 15+	165/1447	3.9	1.08 (1.01−1.16)
Non−fatal myocardial infarction			
Total follow−up duration	**608/8249**	**0.8**	**1.06 (1.02−1.10)**
Years 0−5	263/8249	0.7	1.05 (1.00−1.11)
Years 5−10	185/6040	0.8	1.05 (0.98−1.12)
Years 10+	160/3596	0.9	1.10 (1.02−1.18)
Non−fatal ischemic stroke			
Total follow−up duration	**408/8249**	**0.5**	**1.04 (1.00−1.09)**
Years 0−5	193/8249	0.5	1.03 (0.97−1.09)
Years 5−10	128/6150	0.5	1.08 (1.00−1.16)
Years 10+	87/3729	0.5	1.04 (0.94−1.15)
Cardiovascular death			
Total follow−up duration	**900/8249**	**1.1**	**1.11 (1.08−1.14)**
Years 0−5	281/8249	0.8	1.08 (1.03−1.14)
Years 5−10	305/6274	1.2	1.11 (1.06−1.16)
Years 10−15	199/3868	1.5	1.12 (1.05−1.19)
Years 15+	115/1670	2.3	1.14 (1.05−1.23)
All−cause mortality			
Total follow−up duration	**1998/8249**	**2.5**	**1.10 (1.08−1.12)**
Years 0−5	540/8249	1.5	1.10 (1.06−1.14)
Years 5−10	704/6274	2.8	1.11 (1.07−1.14)
Years 10−15	478/3868	3.5	1.09 (1.05−1.14)
Years 15+	276/1670	5.4	1.07 (1.01−1.13)
Major adverse limb event			
Total follow−up duration	**774/8249**	**1.0**	**1.08 (1.05−1.12)**
Years 0−5	485/8249	1.4	1.09 (1.05−1.13)
Years 5−10	178/5875	0.8	1.06 (0.99−1.13)
Years 10+	111/3522	0.7	1.08 (1.00−1.17)

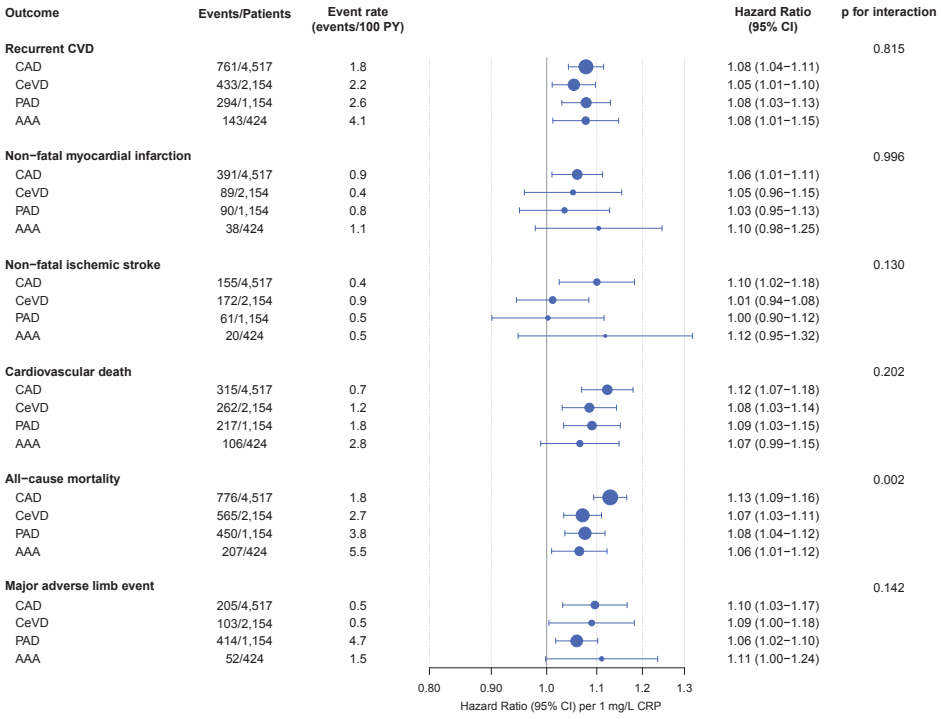


Hazard ratios (per 1 mg/L CRP) for the association between CRP and outcomes over time, i.e. within the first 5 years, between 5 and 10 years, between 10 and 15 years, and beyond 15 years after the baseline CRP measurement. For non-fatal MI, non-fatal ischemic stroke, and MALE, years 10+ (instead of years 15+) was chosen as the last time interval as numbers of events after 15 years were too low for reliable analysis. Hazard ratios are adjusted for age, sex, CVD location, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

Association between CRP and outcomes stratified by CVD location

CRP was independently associated with recurrent CVD, cardiovascular death and MALE irrespective of prior CVD location (Figure 4). The association between CRP and all-cause mortality was significant in all subgroups, but strongest for patients with CAD (p for interaction = 0.002). When assessed in CVD location-specific quartiles, the higher levels of CRP in the third and fourth quartiles in patients with PAD and AAA were accompanied by a stronger increase in the risk of recurrent CVD (Figure 5A). Despite smaller increases in CRP, the increase in the risk of all-cause mortality across quartiles was strongest for patients with CAD (Figure 5B).

Figure 4. Association between CRP and cardiovascular outcomes stratified by CVD location

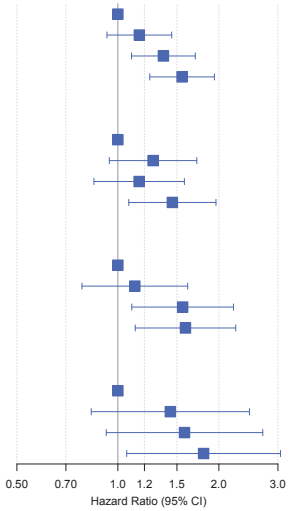


Hazard ratios (per 1 mg/L CRP) for the association between CRP and outcomes in subgroups of prior CVD location. Hazard ratios are adjusted for age, sex, history of other CVD locations, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR. P-values for the interaction between CRP and CVD location are provided for each outcome. Following a Bonferroni correction for multiple testing, only p-values <0.008 should be regarded significant.

Figure 5. Association between CVD location-specific CRP quartiles and outcomes

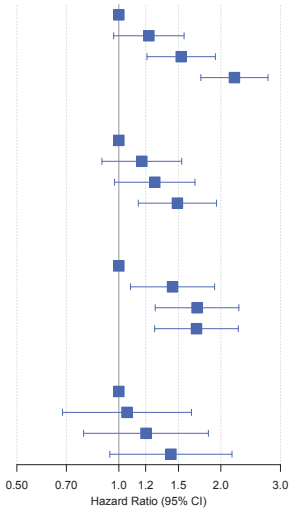
A **Recurrent CVD**

Prior CVD location	CRP (mg/L), median (range)	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)
CAD (n = 4,517)				
CRP quartile 1	0.59 (0.10–0.82)	144/1,130	1.3	Reference
CRP quartile 2	1.20 (0.83–1.60)	179/1,172	1.6	1.16 (0.93–1.45)
CRP quartile 3	2.26 (1.61–3.10)	210/1,109	2.1	1.37 (1.10–1.70)
CRP quartile 4	4.74 (3.12–10.0)	228/1,106	2.5	1.55 (1.24–1.94)
CeVD (n = 2,154)				
CRP quartile 1	0.50 (0.10–0.80)	73/543	1.4	Reference
CRP quartile 2	1.30 (0.81–1.80)	108/574	2.1	1.27 (0.94–1.72)
CRP quartile 3	2.52 (1.82–3.57)	107/499	2.3	1.16 (0.85–1.58)
CRP quartile 4	5.44 (3.59–10.0)	145/538	3.1	1.45 (1.08–1.96)
PAD (n = 1,154)				
CRP quartile 1	0.80 (0.16–1.30)	56/305	1.8	Reference
CRP quartile 2	1.90 (1.34–2.60)	66/282	2.4	1.12 (0.78–1.62)
CRP quartile 3	3.56 (2.62–4.73)	80/279	3.0	1.56 (1.10–2.21)
CRP quartile 4	6.60 (4.74–10.0)	92/288	3.2	1.59 (1.13–2.25)
AAA (n = 424)				
CRP quartile 1	0.94 (0.18–1.50)	24/116	2.4	Reference
CRP quartile 2	2.07 (1.58–2.80)	32/97	3.9	1.43 (0.83–2.47)
CRP quartile 3	3.98 (2.81–5.00)	42/107	4.8	1.58 (0.92–2.70)
CRP quartile 4	7.25 (5.08–10.0)	45/104	5.3	1.80 (1.06–3.05)



B **All-cause mortality**

Prior CVD location	CRP (mg/L), median (range)	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)
CAD (n = 4,517)				
CRP quartile 1	0.59 (0.10–0.82)	117/1,130	1.0	Reference
CRP quartile 2	1.20 (0.83–1.60)	167/1,172	1.4	1.23 (0.97–1.56)
CRP quartile 3	2.26 (1.61–3.10)	212/1,109	2.0	1.53 (1.21–1.93)
CRP quartile 4	4.74 (3.12–10.0)	280/1,106	2.8	2.19 (1.75–2.76)
CeVD (n = 2,154)				
CRP quartile 1	0.50 (0.10–0.80)	88/543	1.6	Reference
CRP quartile 2	1.30 (0.81–1.80)	135/574	2.5	1.17 (0.89–1.53)
CRP quartile 3	2.52 (1.82–3.57)	152/499	3.1	1.28 (0.97–1.68)
CRP quartile 4	5.44 (3.59–10.0)	190/538	3.7	1.49 (1.14–1.94)
PAD (n = 1,154)				
CRP quartile 1	0.80 (0.16–1.30)	85/305	2.6	Reference
CRP quartile 2	1.90 (1.34–2.60)	114/282	4.0	1.44 (1.08–1.92)
CRP quartile 3	3.56 (2.62–4.73)	122/279	4.3	1.70 (1.28–2.26)
CRP quartile 4	6.60 (4.74–10.0)	129/288	4.2	1.70 (1.28–2.25)
AAA (n = 424)				
CRP quartile 1	0.94 (0.18–1.50)	42/116	4.0	Reference
CRP quartile 2	2.07 (1.58–2.80)	43/97	4.8	1.06 (0.68–1.64)
CRP quartile 3	3.98 (2.81–5.00)	58/107	6.2	1.20 (0.79–1.84)
CRP quartile 4	7.25 (5.08–10.0)	64/104	6.9	1.42 (0.94–2.16)



Association between CRP and recurrent CVD (A) and all-cause mortality (B) in CVD location-specific quartiles of CRP. Hazard ratios are adjusted for age, sex, history of other CVD locations, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

Population attributable fraction

For recurrent CVD, the PAF of CRP at a threshold of >2.0 mg/L was 15.2% (95% CI 10.7%-19.6%), indicating that approximately 15% of recurrent CVD events in this population might be attributable to low-grade inflammation (Figure S6A). The PAF of CRP >2.0 mg/L exceeded those of higher thresholds, and was similar to the PAF of CRP >1.5 mg/L (16.2%; 95% CI 10.4%-22.0%). PAF ranged from 7.0% (95% CI 0.0%-16.9%) for non-fatal ischemic stroke to 22.5% (95% CI 16.0%-28.9%) for cardiovascular death (Figure S6B). For recurrent CVD, PAF was largest in patients with PAD, followed by patients with AAA, CAD, and CeVD (Figure S6C).

Sensitivity analyses

Including patients with multiple CVD locations in all applicable subgroups only minimally changed the results (Figure S7A). Analyzing patients with multiple CVD locations (i.e. polyvascular disease; n = 1,178) in a separate subgroup, showed a non-significant trend towards an association between CRP and cardiovascular outcomes in these patients (Figure S7B). CRP appeared to be more strongly associated with cardiovascular outcomes in subgroups of patients with only 1 CVD location, while the association with all-cause mortality was similar. Within patients with polyvascular disease, the results were not significantly different between various combinations of CVD locations (Figure S8). There were no signs of effect modification by the severity of the qualifying CVD event (Figure S9).

Discussion

In this study of 9,005 patients with various CVD locations, higher CRP was shown to be associated with an increased risk of recurrent cardiovascular events and all-cause mortality, independent of traditional CVD risk factors and the use of preventive medication. Associations remained consistent even beyond 15 years after the initial CRP measurement. CRP concentrations were higher in patients with PAD and AAA as compared to CAD and CeVD, but the magnitude of the association between CRP and cardiovascular outcomes was similar across subgroups of CVD location. Patients with CRP concentrations exceeding the defined limits of low-grade inflammation (>10 mg/L), had an even higher adjusted risk of recurrent CVD and all-cause mortality than patients in the highest CRP quintile ≤10 mg/L.

The results of this study extend prior work in people without a history of CVD and patients with one specific CVD location.[5–13] A meta-analysis in people without CVD has reported risk ratios per three-fold higher CRP of 1.37 for coronary heart disease, 1.27 for ischemic stroke, and 1.55 for vascular mortality.[5] In patients with CAD, studies have reported HRs for CRP >3 mg/L compared to <1 mg/L of 1.37-1.62 for recurrent CVD, and 1.57-3.45 for all-cause mor-

tality.[6,7,11] Meta-analyses have reported HRs per 1-SD increase in $\log_e$CRP of 1.14 for recurrent stroke and 1.21 for recurrent CVD in patients with CeVD, and an HR per 1-unit increase in $\log_e$CRP of 1.38 for recurrent CVD in patients with PAD.[12,13] The estimates of previous studies are roughly comparable to the HRs for the fourth and fifth quintiles (compared to the first quintile) of CRP found in this study. However, previous studies in patients with established CVD were limited by either a relatively small sample size, short follow-up duration, strict eligibility criteria, and/or a categorical analysis of CRP based on pre-specified cut-off points, and all studies only included patients with one specific CVD location.[6–13] To our knowledge, no previous studies simultaneously assessed the association between CRP and recurrent CVD in a mixed population of patients with various CVD locations.

Randomized clinical trials have recently demonstrated the efficacy of anti-inflammatory drugs in reducing the risk of cardiovascular events in patients with CAD. In the CANTOS trial, canakinumab reduced the risk of recurrent CVD by 15% in patients with a previous MI.[14] In the COLCOT and LoDoCo2 trials, low-dose colchicine reduced the risk of recurrent CVD (including coronary revascularization) by 23% in patients with a recent MI, and 31% in patients with chronic CAD respectively.[15,16] As our study shows that inflammation is strongly related to recurrent CVD and mortality irrespective of CVD location, it implicates that anti-inflammatory drugs might be effective, and trials of these drugs might be warranted in patients with various types of CVD. Ongoing and planned trials studying low-dose colchicine in patients with CAD, CeVD, and PAD, i.e. the CLEAR-SYNERGY (acute coronary syndrome), CONVINCE (non-cardioembolic stroke or TIA), and LEADER-PAD (symptomatic PAD) trials, as well as the ZEUS trial studying ziltivekimab (a monoclonal antibody targeting the IL-6 ligand) in patients with CVD and chronic kidney disease, will help cement the potential of anti-inflammatory drugs in atherosclerotic CVD.[21–24]

CRP is a well-established and stable marker of chronic low-grade inflammation, but is not thought to be part of the causal pathway between inflammation and CVD itself.[3] Therefore, a reduction in CRP would not necessarily be matched by an equivalent reduction in CVD risk. However, a secondary analysis of the CANTOS trial showed that in participants who achieved on-treatment CRP concentrations <2 mg/L, both cardiovascular and all-cause mortality were reduced by 31%, while no significant reductions were observed among participants who did not achieve this concentration.[25] In both the JUPITER and the CANTOS trial, achieving CRP <2 mg/L was related to greater reductions in the risk of recurrent CVD.[25,26] These results suggest that reductions in CRP driven by upstream effects either in lipid metabolism (with statins) or in the canonical NLRP3 to IL-1 to IL-6 signaling system (with canakinumab or colchicine) are associated with reductions in CVD risk. The current data emphasize the potential benefit of anti-inflammatory therapy in patients with PAD and AAA, as this study showed that CRP concentrations are usually

higher in these patients and more often exceed 2 mg/L. Even though definitive conclusions on causality cannot be made, this study at least shows that CRP is strongly associated with CVD risk, and is therefore rightfully included in cardiovascular risk scores.[27] In practice, clinicians should pay attention to CRP levels and residual inflammatory risk, and consider intensification of preventive therapy in patients with high CRP concentrations (e.g. >2 mg/L), while taking other risk factors and predicted CVD risk into account.[1,28]

CRP concentrations >10 mg/L are often assumed to be associated with an acute inflammatory response caused by infection, or inflammation of another non-cardiovascular source, and are therefore often disregarded.[18] However, as shown in this study, patients with CRP >10 mg/L are at especially high risk of CVD and mortality, even up to 15 years after the initial measurement. A CRP concentration >10 mg/L was independently associated with recurrent CVD and all-cause mortality, with relative risks exceeding those of the highest quintile ≤10 mg/L. Previous studies had similar findings.[6,7] These results indicate that, regardless of the underlying source of the elevated CRP level, concentrations >10 mg/L are a clinically relevant indicator of risk that should be fully appreciated. Trials of anti-inflammatory drugs (or other preventive therapies) in patients with very high concentrations of CRP might be warranted. Based on current knowledge, intensification of preventive therapy in these patients might already be justified, especially if another cause of the elevated CRP concentration cannot be established.

Strengths of this study are the use of a practice-based cohort with a prospective design, long follow-up, low proportions of missing data, and the inclusion of patients with various CVD locations. Some limitations should be considered. This was an observational study, so subject to potential residual confounding. CRP was based on a single measurement. However, previous research has shown that repeated CRP measurements are stable both in our and other cohorts, and we showed that the association with clinical outcomes remained consistent over time, even beyond 15 years after the initial measurement.[4,5,29] Data on infections and auto-immune disease, and upstream inflammatory markers, such as IL-1 and IL-6, were not available. Numbers of non-fatal myocardial infarctions and non-fatal ischemic strokes were insufficient for reliable subgroup analyses.

In conclusion, in patients with established CVD, higher CRP as a measure of chronic low-grade inflammation is independently associated with an increased risk of recurrent CVD and mortality, irrespective of prior CVD location. Taking into account the positive results of anti-inflammatory therapy in patients with CAD, this study's findings support ongoing and future trial efforts to evaluate the efficacy of anti-inflammatory drugs in patients with CeVD, PAD, and/or AAA.

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Supplementary material

Table S1. Definitions of qualifying cardiovascular disease events

CVD location	Definition
Coronary artery disease	A history of a myocardial infarction, cardiac arrest, or coronary revascularization (i.e. PCI or CABG).
Cerebrovascular disease	A history of a transient ischemic attack (TIA), or ischemic or hemorrhagic stroke.
Peripheral artery disease	A symptomatic obstruction of distal arteries of the leg with an ankle-brachial index (ABI) ≤0.90, or a history of a percutaneous transluminal angioplasty or bypass surgery of the leg, or amputation.
Abdominal aortic aneurysm	A history of abdominal aortic surgery, or an abdominal aortic anteroposterior diameter of ≥3 cm.

Abbreviations: CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention.

Table S2. Outcome definitions

Outcome	Definition
Non-fatal myocardial infarction	Non-fatal myocardial infarction, characterized by at least two of the following criteria: 1) Chest pain for at least 20 minutes not disappearing after administration of nitrates. 2) ST-elevation >1 mm in two following leads or a left bundle branch block on the ECG. 3) CK elevation of at least two times the normal value of CK and an MB-fraction >5% of the total CK.
Non-fatal ischemic stroke	Relevant clinical features which have caused an increase in handicap of at least one grade on the modified Rankin scale, accompanied by a fresh infarct on a repeat CT scan.
Cardiovascular death	Sudden death (i.e. unexpected cardiac death occurring within 1 hour after onset of symptoms or within 24 hours given convincing circumstantial evidence), death from ischemic stroke, death from heart failure, death from myocardial infarction, death from rupture of abdominal aortic aneurysm, or cardiovascular death from another cause (deemed to be cardiovascular by three independent physicians from the endpoint committee).
Major adverse limb event (MALE)	Lower limb revascularization (vascular intervention or thrombolysis), or major amputation (at the level of the ankle or more proximal). Interventions already planned at time of inclusion in the cohort, and minor amputations were not regarded MALE endpoints.
All-cause mortality	Death from any cause, reported by relatives of the patient, the general practitioner or the treating specialist.

Abbreviations: CK = creatine kinase, CT = computed tomography, ECG = electrocardiogram, MALE = major adverse limb event, MB = myocardial band.

Table S3. Baseline characteristics stratified by cardiovascular disease location

Characteristic	CAD (n = 4,517)	CeVD (n = 2,154)	PAD (n = 1,154)	AAA (n = 424)
Age (years)	60.9±9.4	59.2±11.3	59.3±10.6	65.0±10.0
Sex (male)	3,677 (81%)	1,324 (62%)	740 (64%)	364 (86%)
Smoking status				
Former	2,364 (52%)	935 (43%)	423 (37%)	224 (53%)
Current	980 (22%)	664 (31%)	621 (54%)	148 (35%)
Alcohol (units/week)				
Never drinker	738 (16%)	412 (19%)	214 (19%)	62 (15%)
<1	465 (10%)	246 (11%)	100 (9%)	45 (11%)
1-10	2,142 (47%)	889 (41%)	442 (38%)	170 (40%)
10-20	780 (17%)	379 (18%)	242 (21%)	99 (23%)
>20	392 (9%)	228 (11%)	156 (14%)	48 (11%)
History of other CVD locations				
CAD	-	259 (12%)	226 (20%)	135 (32%)
CeVD	165 (4%)	-	97 (8%)	32 (8%)
PAD	114 (3%)	79 (4%)	-	37 (9%)
AAA	102 (2%)	44 (2%)	54 (5%)	-
Diabetes mellitus	814 (18%)	293 (14%)	221 (19%)	54 (13%)
Body mass index (kg/m^2)	27.3±3.9	26.4±4.1	26.0±4.2	26.2±3.6
Systolic blood pressure (mmHg)	136±19	141±21	145±22	144±20
Laboratory values				
CRP (mg/L), median (IQR)	1.6 (0.8-3.1)	1.8 (0.8-3.6)	2.6 (1.3-4.7)	2.8 (1.8-5.0)
LDL-cholesterol (mg/dL)	99±35	113±41	125±43	125±41
HDL-cholesterol (mg/dL)	46±12	51±16	49±15	47±15
Non-HDL-cholesterol (mg/dL)	128±42	139±46	157±47	157±49
Triglycerides (mg/dL)	147±119	134±99	170±124	161±106
eGFR (mL/min/1.73 m^2)	78±16	78±18	78±20	71±20
Medication use				
Statin	3,782 (84%)	1,234 (57%)	557 (48%)	192 (45%)
Antiplatelet therapy	4,039 (89%)	1,553 (72%)	653 (57%)	203 (48%)
Antihypertensive agent	4,132 (92%)	1,223 (57%)	581 (50%)	273 (64%)

All data in n (%) or mean±SD. Patients with CRP >10 mg/L are not included in the table because they are not included in the stratified analyses.
Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, IQR = interquartile range, LDL = low-density lipoprotein, PAD = peripheral artery disease, SD = standard deviation.

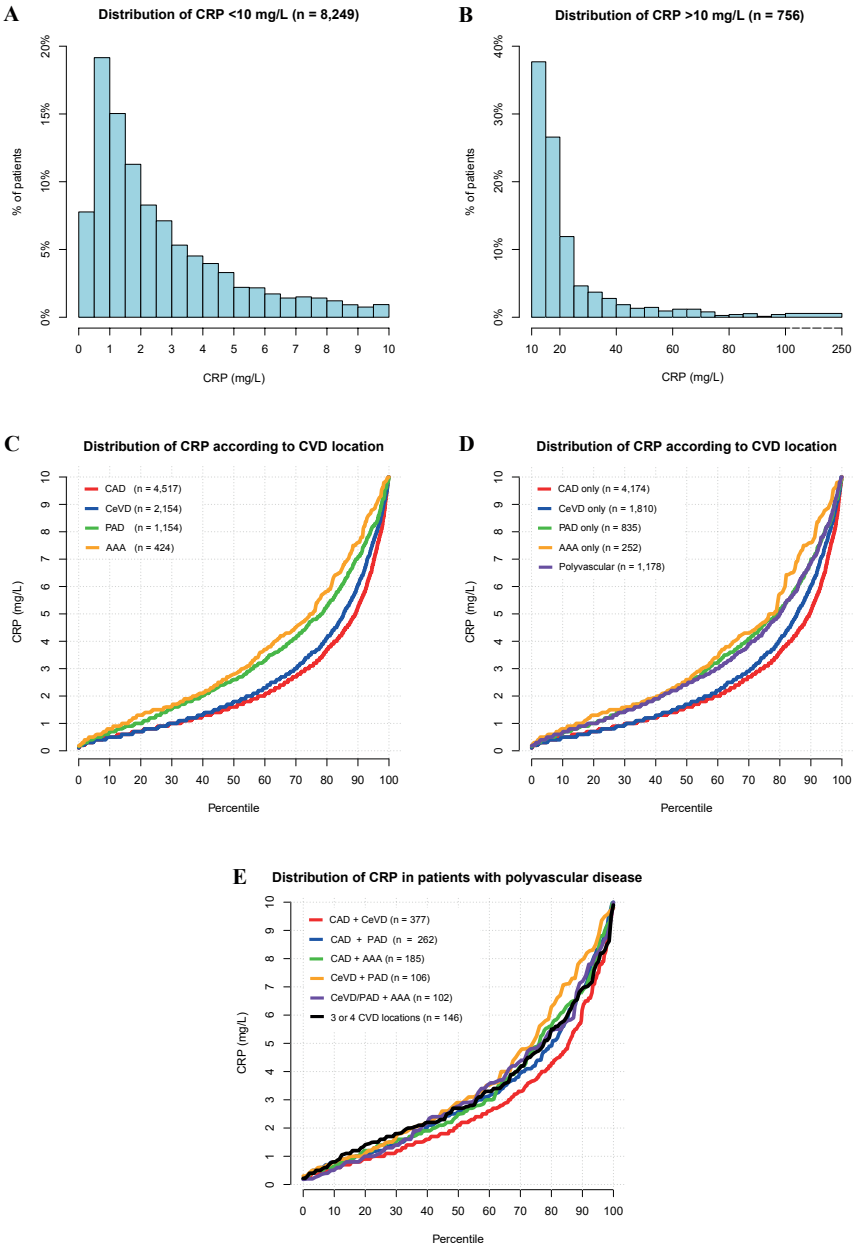
Table S4. Reverse causality assessment

	Total population (n = 8,249)	Exclude events <1 year (n = 7,866)	Exclude events <2 years (n = 7,605)	Exclude events <5 years (n = 6,961)
Recurrent CVD (events)	1,631	1,394	1,246	886
HR (95%CI) per 1 mg/L	1.08 (1.05-1.10)	1.08 (1.05-1.10)	1.08 (1.06-1.11)	1.09 (1.06-1.12)
Non-fatal MI (events)	608	504	435	320
HR (95%CI) per 1 mg/L	1.06 (1.02-1.10)	1.07 (1.03-1.11)	1.06 (1.02-1.11)	1.07 (1.02-1.13)
Non-fatal ischemic stroke (events)	408	335	292	188
HR (95%CI) per 1 mg/L	1.04 (1.00-1.09)	1.04 (0.99-1.10)	1.06 (1.01-1.12)	1.07 (1.00-1.14)
Cardiovascular death (events)	900	783	702	490
HR (95%CI) per 1 mg/L	1.11 (1.08-1.14)	1.11 (1.08-1.14)	1.11 (1.08-1.15)	1.12 (1.08-1.16)
All-cause mortality (events)	1,998	1,789	1,636	1,203
HR (95%CI) per 1 mg/L	1.10 (1.08-1.12)	1.10 (1.08-1.12)	1.10 (1.08-1.12)	1.10 (1.07-1.12)
Major adverse limb event (events)	774	583	471	269
HR (95%CI) per 1 mg/L	1.08 (1.05-1.12)	1.08 (1.05-1.12)	1.08 (1.04-1.12)	1.07 (1.01-1.12)

Hazard ratios per 1 mg/L CRP in the total population, and after excluding patients with a CVD event or death within the first 1, 2, and 5 years after inclusion. Models were adjusted for age, sex, prior CVD location, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

Abbreviations: BMI = body-mass index, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HR = hazard ratio, SBP = systolic blood pressure.

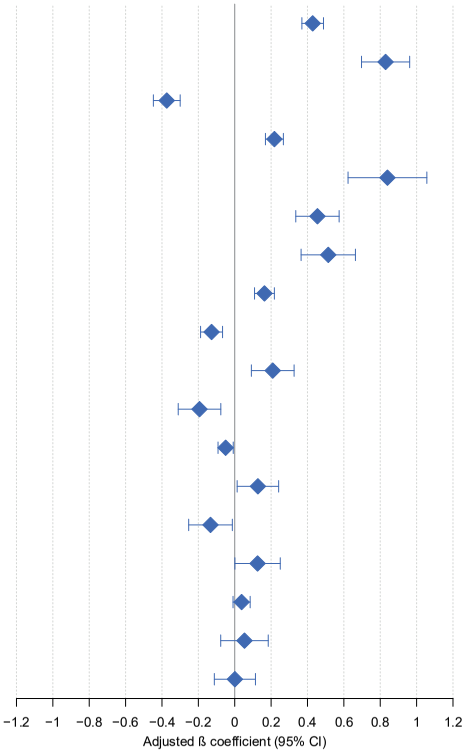
Figure S1. Distribution of CRP in the study population



Distribution of CRP ≤10 mg/L (A) and CRP >10 mg/L (B) in the total study population, and distribution of CRP ≤10 mg/L in CVD location-specific percentiles (based on main CVD location in C, and with polyvascular disease as a separate subgroup in D), and distribution of CRP ≤10 mg/L in patients with polyvascular disease and various combinations of CVD locations (E). In E, patients with CeVD + AAA and PAD + AAA were combined, and patients with three or four CVD locations were combined to have at least 100 patients per subgroup.
Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CRP = C-reactive protein, CVD = cardiovascular disease, PAD = peripheral artery disease.

Figure S2. Determinants of plasma CRP concentration

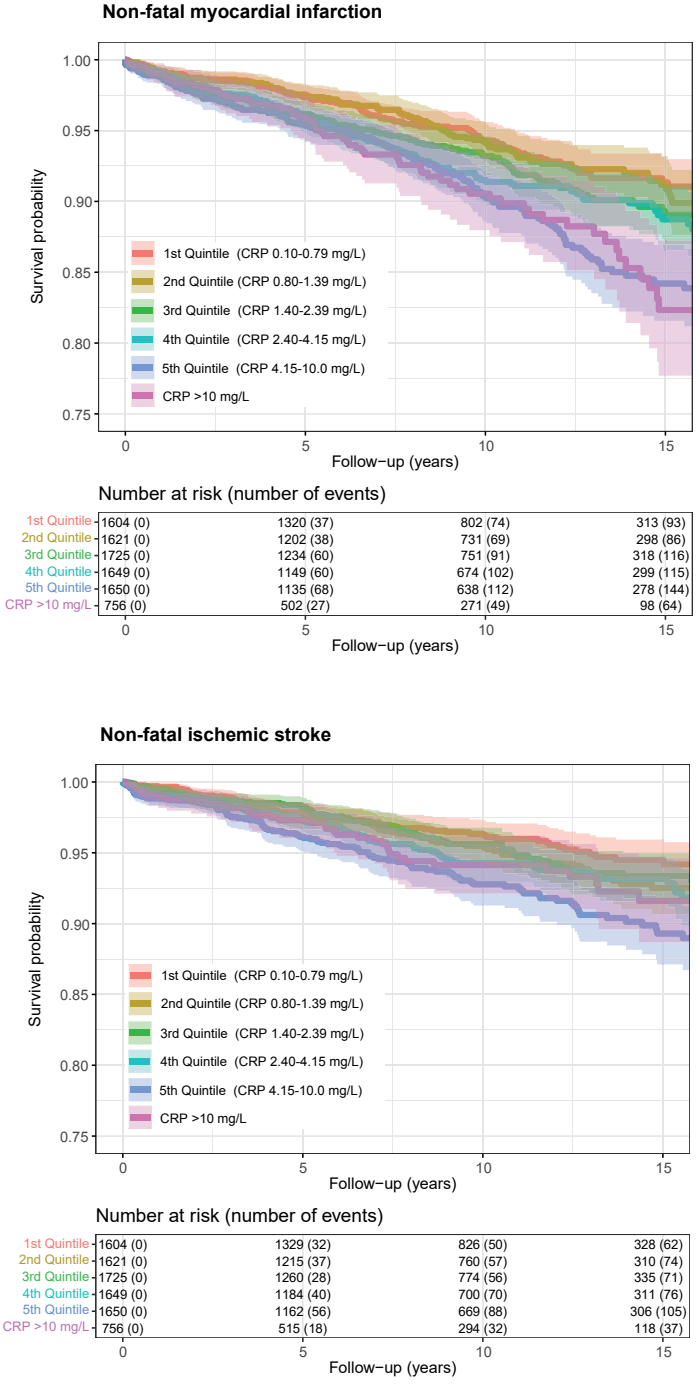
Factor	Crude ß coefficient, mg/L CRP (95% CI)	Adjusted ß coefficient, mg/L CRP (95% CI)	p−value	F−statistic
Body−mass index (per 5 kg/m²)	0.427 (0.368, 0.486)	0.429 (0.369, 0.488)	<0.001	200.1
Current smoking	0.938 (0.806, 1.069)	0.829 (0.697, 0.962)	<0.001	150.8
HDL−cholesterol (per 0.5 mmol/L)	−0.401 (−0.466, −0.335)	−0.374 (−0.447, −0.300)	<0.001	98.8
Non−HDL−cholesterol (per 1 mmol/L)	0.358 (0.319, 0.398)	0.218 (0.169, 0.267)	<0.001	75.3
CVD location = AAA	1.229 (1.012, 1.445)	0.840 (0.623, 1.056)	<0.001	57.7
Female sex	0.301 (0.192, 0.409)	0.455 (0.336, 0.574)	<0.001	56.0
CVD location = PAD	0.928 (0.787, 1.068)	0.514 (0.365, 0.664)	<0.001	45.5
Age (per 10 years)	0.110 (0.063, 0.156)	0.163 (0.109, 0.218)	<0.001	34.5
Estimated GFR (per 20 mL/min/1.73m²)	−0.212 (−0.266, −0.158)	−0.127 (−0.188, −0.067)	<0.001	17.1
Former smoking	0.281 (0.161, 0.400)	0.209 (0.092, 0.326)	<0.001	12.2
Statin use	−0.611 (−0.714, −0.508)	−0.194 (−0.311, −0.077)	0.001	10.5
Triglycerides (per 1 mmol/L)	0.180 (0.144, 0.217)	−0.050 (−0.092, −0.008)	0.019	5.5
CVD location = CeVD	0.222 (0.111, 0.334)	0.127 (0.013, 0.241)	0.029	4.8
Antiplatelet use	−0.524 (−0.639, −0.409)	−0.133 (−0.253, −0.013)	0.030	4.7
Diabetes mellitus	0.329 (0.202, 0.457)	0.126 (0.001, 0.250)	0.049	3.9
Systolic blood pressure (per 20 mmHg)	0.170 (0.124, 0.217)	0.038 (−0.009, 0.085)	0.116	2.5
Alcohol >10 glasses/week	−0.084 (−0.212, 0.043)	0.054 (−0.077, 0.184)	0.421	0.6
Alcohol 1−10 glasses/week	−0.225 (−0.341, −0.110)	0.001 (−0.112, 0.114)	0.987	0.0



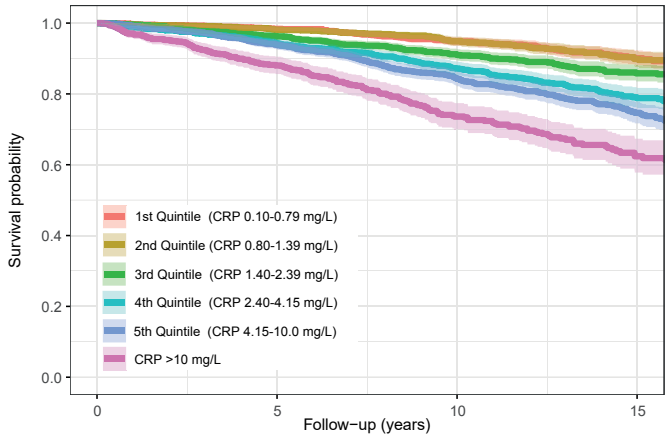
Associations between clinical variables and CRP in patients with CRP ≤10 mg/L (n = 8,249). β coefficients represent differences in CRP concentration in mg/L, and were derived from linear regression models only including one factor of interest (crude β coefficient), and a linear regression model including all factors displayed in the figure (adjusted β coefficient). From top to bottom, factors are ranked from most to least strongly associated with CRP (highest to lowest F-statistic). For CVD location the reference group was CAD, for alcohol consumption the reference group was <1 glass/week.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, GFR = glomerular filtration rate, HDL = high-density lipoprotein, PAD = peripheral artery disease.

Figure S3. Additional Kaplan-Meier curves stratified by quintiles of CRP



Cardiovascular death

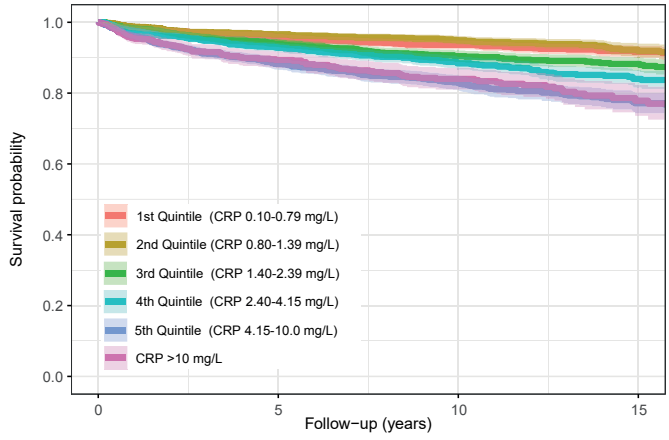


Number at risk (number of events)

1st Quintile	1604 (0)	1353 (24)	847 (65)	341 (93)
2nd Quintile	1621 (0)	1237 (27)	785 (59)	329 (87)
3rd Quintile	1725 (0)	1281 (58)	799 (115)	352 (149)
4th Quintile	1649 (0)	1206 (83)	734 (158)	325 (209)
5th Quintile	1650 (0)	1197 (89)	703 (189)	323 (247)
CRP >10 mg/L	756 (0)	526 (82)	304 (154)	122 (188)
	0	5	10	15

Follow−up (years)

Major adverse limb event



Number at risk (number of events)

1st Quintile	1604 (0)	1296 (64)	808 (90)	323 (102)
2nd Quintile	1621 (0)	1191 (51)	746 (68)	298 (82)
3rd Quintile	1725 (0)	1209 (90)	727 (131)	315 (144)
4th Quintile	1649 (0)	1121 (106)	654 (149)	276 (172)
5th Quintile	1650 (0)	1058 (174)	587 (225)	252 (254)
CRP >10 mg/L	756 (0)	474 (72)	262 (95)	96 (108)
	0	5	10	15

Follow−up (years)

Figure S4. Kaplan-Meier curves stratified by CVD location

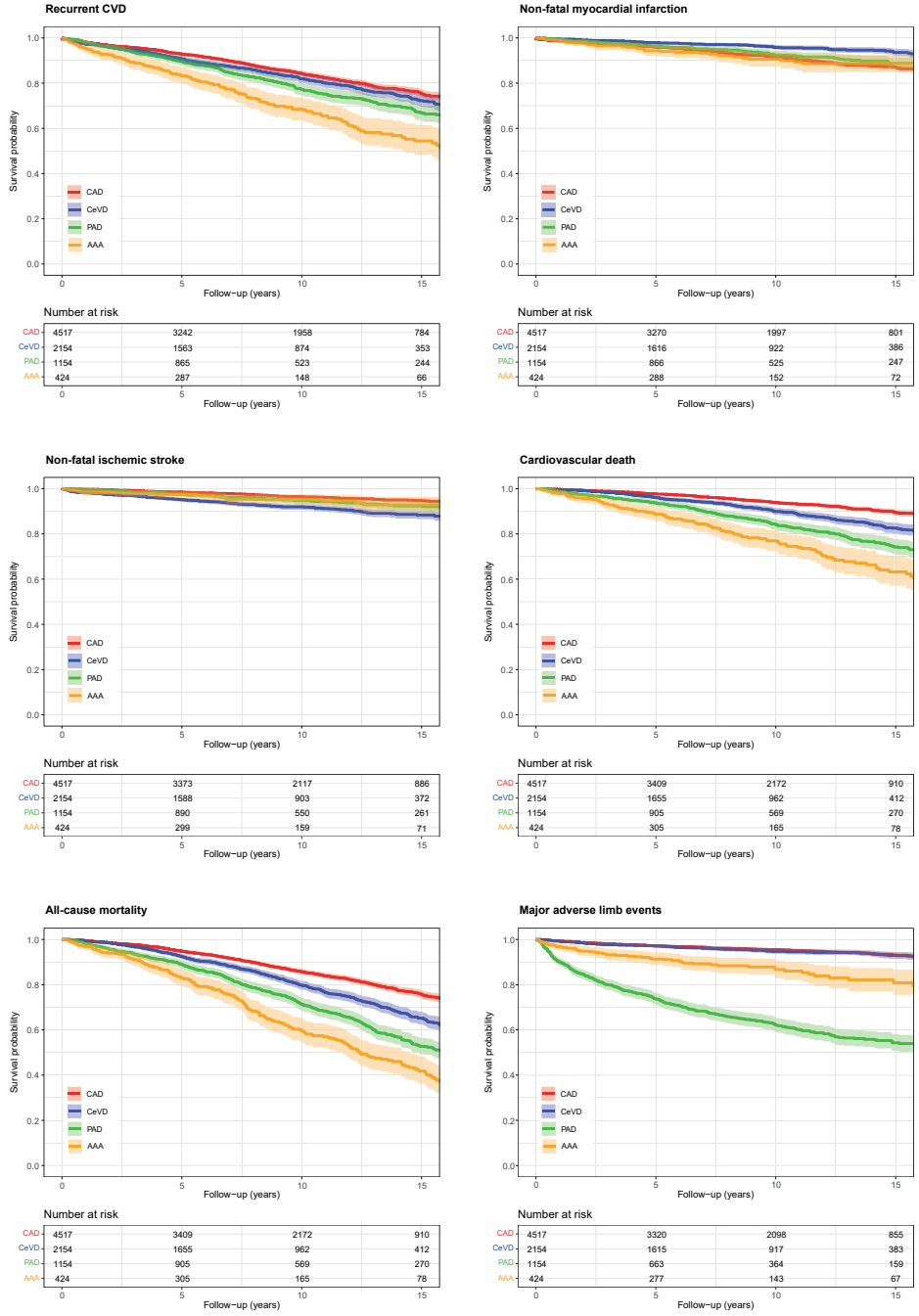
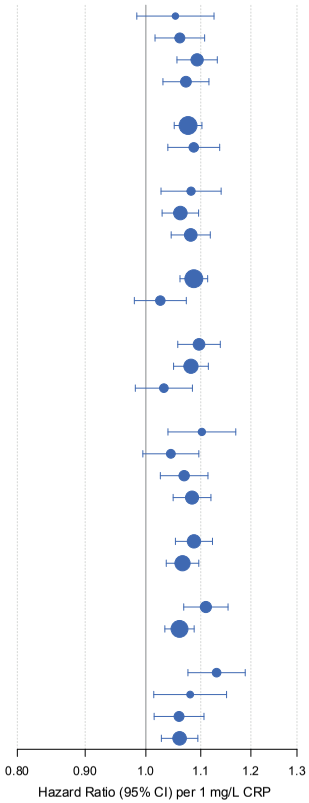


Figure S5. Potential effect modifiers in the association between CRP and recurrent CVD

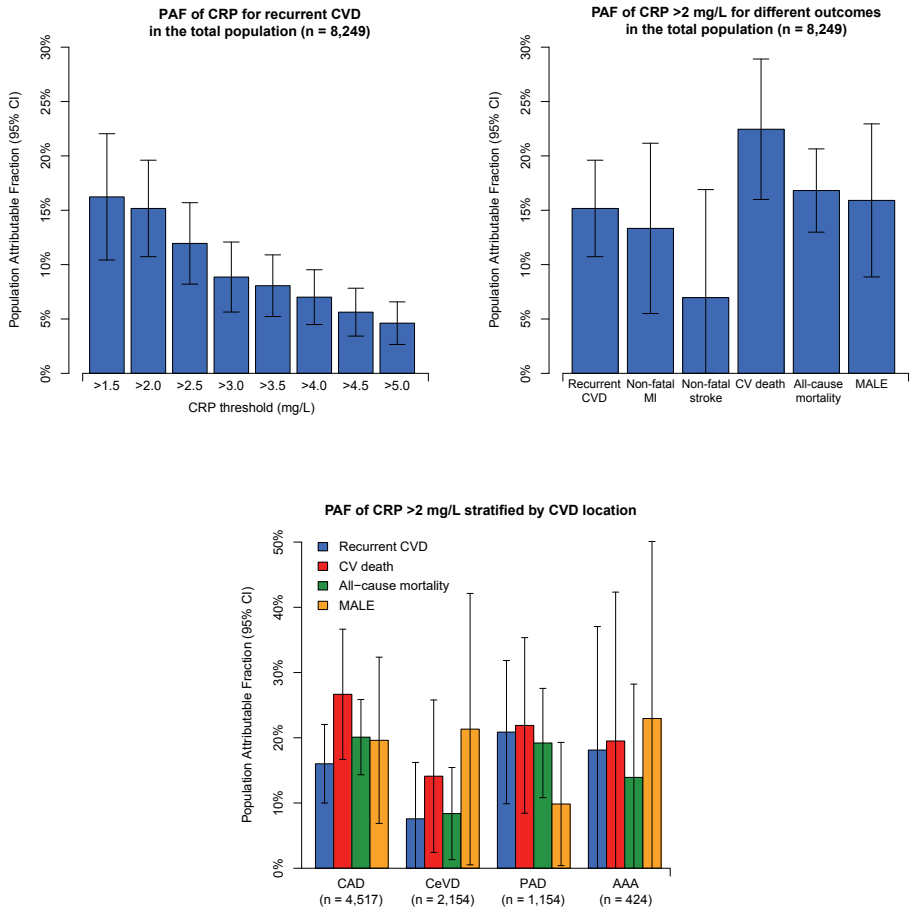
Subgroup	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)	p for interaction
Age				0.056
<50 years	173/1312	1.3	1.05 (0.98−1.13)	
50−59 years	416/2469	1.7	1.06 (1.02−1.11)	
60−69 years	571/2854	2.3	1.09 (1.06−1.13)	
≥70 years	471/1614	3.9	1.07 (1.03−1.12)	
Sex				0.924
Male	1288/6105	2.3	1.08 (1.05−1.10)	
Female	343/2144	1.7	1.09 (1.04−1.14)	
Smoking				0.735
Never	276/1890	1.7	1.08 (1.03−1.14)	
Former	790/3946	2.2	1.06 (1.03−1.10)	
Current	565/2413	2.4	1.08 (1.04−1.12)	
Diabetes mellitus				0.084
No	1264/6867	2.0	1.09 (1.06−1.11)	
Yes	367/1382	3.2	1.03 (0.98−1.07)	
Body−mass index				0.069
<25 kg/m2	540/2763	2.1	1.10 (1.06−1.14)	
25−30 kg/m2	807/3948	2.2	1.08 (1.05−1.11)	
≥30 kg/m2	284/1538	2.1	1.03 (0.98−1.08)	
Non−HDL−cholesterol				0.484
<2.6 mmol/L	237/1888	1.6	1.10 (1.04−1.17)	
2.6−3.3 mmol/L	377/2349	1.8	1.04 (0.99−1.10)	
3.4−4.1 mmol/L	407/1885	2.2	1.07 (1.03−1.11)	
≥4.2 mmol/L	610/2127	2.8	1.08 (1.05−1.12)	
Statin use				0.475
No	615/2484	2.4	1.09 (1.05−1.12)	
Yes	1016/5765	2.0	1.07 (1.04−1.10)	
Antiplatelet use				0.142
No	410/1801	2.3	1.11 (1.07−1.15)	
Yes	1221/6448	2.1	1.06 (1.03−1.09)	
Statin and antiplatelet use				0.146
Neither	237/1092	2.2	1.13 (1.08−1.19)	
Statin only	173/709	2.4	1.08 (1.01−1.15)	
Antiplatelet only	378/1392	2.6	1.06 (1.01−1.11)	
Both	843/5056	1.9	1.06 (1.03−1.09)	



Hazard ratios (per 1 mg/L CRP) for the association between CRP and recurrent CVD in subgroups of potential effect modifiers. Hazard ratios are adjusted for age, sex, CVD location, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR where appropriate. P-values for the interaction between CRP and the potential effect modifiers are provided. Following a Bonferroni correction for multiple testing, only p-values <0.006 should be regarded significant.

Abbreviations: BMI = body-mass index, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, non-HDL-c = high-density lipoprotein cholesterol, PY = person years, SBP = systolic blood pressure.

Figure S6. Population attributable fraction of CRP



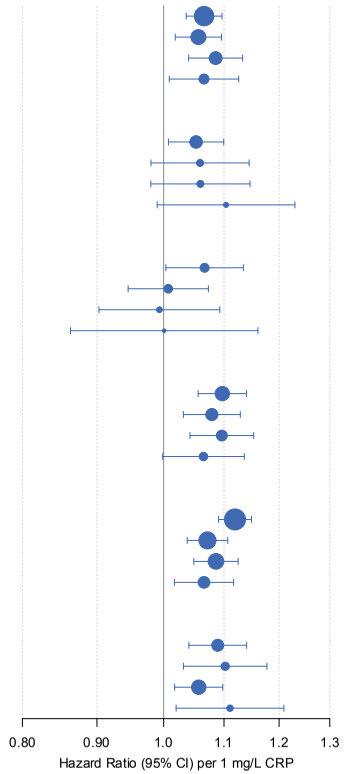
Population attributable fraction (PAF) of low-grade inflammation as measured by CRP concentration. PAF is the proportion of events attributable to the presence of a certain risk factor in the population, i.e. the proportion of events that might be prevented if a risk factor would be removed from the population completely (e.g. if none of the patients would have a CRP >2 mg/L). The PAF of CRP for recurrent CVD in the total population (n = 8,249) is shown for various CRP thresholds (A). Using a threshold of >2 mg/L, the PAF of CRP is shown for all primary and secondary outcomes in the total population (B), and stratified by CVD location (C). PAF estimates for non-fatal myocardial infarction and non-fatal stroke are not shown stratified by CVD location due to the low number of events in subgroups. PAF estimates were adjusted for age, sex, CVD location (only in A & B), smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR. Error bars represent 95% confidence intervals.

Abbreviations: AAA = abdominal aortic aneurysm, BMI = body-mass index, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, PAD = peripheral artery disease, PAF = population attributable fraction, SBP = systolic blood pressure.

Figure S7. Sensitivity analyses with modified subgroups of CVD location

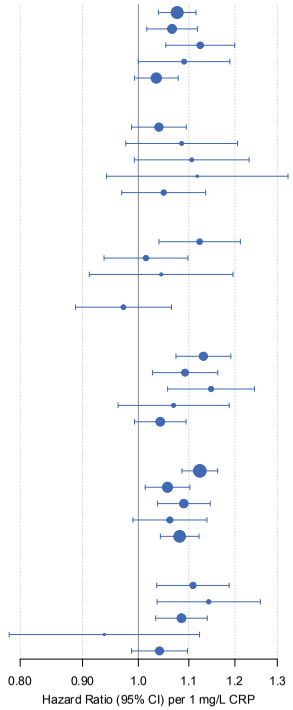
A. Non-exclusive subgroups of CVD location (i.e. patients with multiple CVD locations included in all applicable subgroups)

Outcome	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)	p for interaction
Recurrent CVD				0.362
CAD	1,038/5,137	2.3	1.07 (1.04−1.10)	
CeVD	525/2,444	2.4	1.06 (1.02−1.10)	
PAD	354/1,372	2.7	1.09 (1.04−1.13)	
AAA	204/624	4.0	1.07 (1.01−1.13)	
Non−fatal myocardial infarction				0.729
CAD	461/5,137	1.0	1.05 (1.01−1.10)	
CeVD	118/2,444	0.5	1.06 (0.98−1.14)	
PAD	107/1,372	0.8	1.06 (0.98−1.15)	
AAA	50/624	1.0	1.10 (0.99−1.23)	
Non−fatal ischemic stroke				0.060
CAD	217/5,137	0.4	1.07 (1.00−1.13)	
CeVD	199/2,444	0.9	1.01 (0.95−1.07)	
PAD	79/1,372	0.6	0.99 (0.90−1.09)	
AAA	31/624	0.6	1.00 (0.86−1.16)	
Cardiovascular death				0.220
CAD	519/5,137	1.0	1.10 (1.06−1.14)	
CeVD	330/2,444	1.4	1.08 (1.03−1.13)	
PAD	258/1,372	1.8	1.10 (1.04−1.15)	
AAA	153/624	2.8	1.06 (1.00−1.14)	
All−cause mortality				0.010
CAD	1,109/5,137	2.2	1.12 (1.09−1.15)	
CeVD	675/2,444	2.9	1.07 (1.04−1.11)	
PAD	539/1,372	3.9	1.09 (1.05−1.12)	
AAA	283/624	5.2	1.07 (1.02−1.12)	
Major adverse limb event				0.043
CAD	339/5,137	0.7	1.09 (1.04−1.14)	
CeVD	147/2,444	0.7	1.10 (1.03−1.18)	
PAD	470/1,372	4.5	1.06 (1.02−1.10)	
AAA	89/624	1.8	1.11 (1.02−1.21)	



B. Exclusive subgroups of CVD location with a separate subgroup for patients with multiple CVD locations (i.e. polyvascular disease)

Outcome	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)	p for interaction
Recurrent CVD				0.427
CAD	686/4,174	1.8	1.08 (1.04−1.12)	
CeVD	300/1,810	1.8	1.07 (1.02−1.12)	
PAD	150/835	1.7	1.12 (1.05−1.20)	
AAA	68/252	3.0	1.09 (1.00−1.19)	
Polyvascular	427/1,178	4.6	1.03 (0.99−1.08)	
Non−fatal myocardial infarction				0.626
CAD	366/4,174	0.9	1.04 (0.99−1.09)	
CeVD	59/1,810	0.3	1.09 (0.98−1.21)	
PAD	55/835	0.6	1.11 (0.99−1.23)	
AAA	17/252	0.7	1.12 (0.94−1.33)	
Polyvascular	111/1,178	1.2	1.05 (0.97−1.14)	
Non−fatal ischemic stroke				0.081
CAD	130/4,174	0.3	1.12 (1.04−1.21)	
CeVD	131/1,810	0.8	1.01 (0.94−1.10)	
PAD	38/835	0.4	1.04 (0.91−1.20)	
AAA	9/252	0.4	1.25 (0.98−1.61)*	
Polyvascular	100/1,178	1.0	0.97 (0.89−1.06)	
Cardiovascular death				0.096
CAD	272/4,174	0.7	1.13 (1.07−1.19)	
CeVD	170/1,810	0.9	1.09 (1.03−1.16)	
PAD	96/835	1.1	1.15 (1.06−1.25)	
AAA	51/252	2.2	1.07 (0.96−1.19)	
Polyvascular	311/1,178	3.1	1.04 (0.99−1.09)	
All−cause mortality				0.040
CAD	684/4,174	1.7	1.12 (1.09−1.16)	
CeVD	403/1,810	2.2	1.06 (1.01−1.10)	
PAD	273/835	3.0	1.09 (1.04−1.15)	
AAA	110/252	4.6	1.06 (0.99−1.14)	
Polyvascular	528/1,178	5.2	1.08 (1.04−1.12)	
Major adverse limb event				0.092
CAD	157/4,174	0.4	1.11 (1.04−1.19)	
CeVD	61/1,810	0.3	1.14 (1.04−1.26)	
PAD	293/835	4.4	1.08 (1.03−1.14)	
AAA	22/252	1.0	0.94 (0.78−1.12)	
Polyvascular	241/1,178	2.8	1.04 (0.99−1.10)	

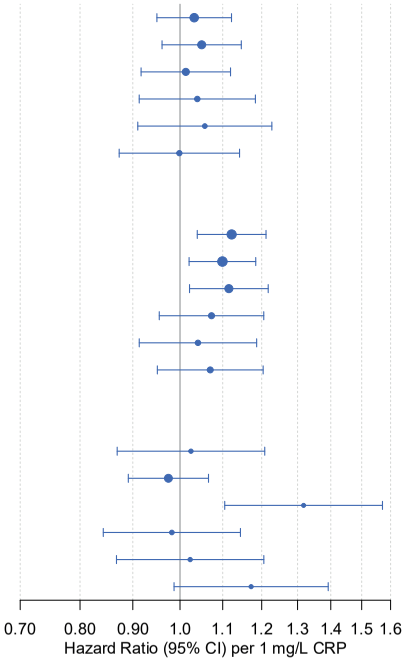


Hazard ratios (per 1 mg/L CRP) for the association between CRP and outcomes in modified subgroups of prior CVD location. In a first sensitivity analysis, patients were divided in non-exclusive subgroups, i.e. patients with multiple CVD locations were included in all applicable subgroups (A). In a second sensitivity analysis, patients were divided in exclusive subgroups with a separate subgroup for patients with multiple CVD locations, i.e. polyvascular disease (B). Hazard ratios are adjusted for age, sex, CVD locations (only in A, and in the subgroup with polyvascular disease in B), smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR. P-values for the interaction between CRP and CVD location are provided for each outcome. Following a Bonferroni correction for multiple testing, only p-values <0.008 should be regarded significant.

* Due to the low number of events (9), the HR for non-fatal ischemic stroke in patients with AAA is not graphically displayed in figure B.
Abbreviations: AAA = abdominal aortic aneurysm, BMI = body-mass index, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, PAD = peripheral artery disease, PY = person years, SBP = systolic blood pressure.

Figure S8. Sensitivity analysis in patients with various combinations of CVD locations

Outcome	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)	p for interaction
Recurrent CVD				0.953
CAD + CeVD	129/377	4.5	1.03 (0.95−1.12)	
CAD + PAD	92/262	3.9	1.05 (0.96−1.15)	
CAD + AAA	71/185	5.1	1.01 (0.92−1.12)	
CeVD + PAD	40/106	4.6	1.04 (0.91−1.18)	
CeVD/PAD + AAA	33/102	4.1	1.06 (0.91−1.23)	
3−4 CVD locations	62/146	6.3	1.00 (0.87−1.14)	
All−cause mortality				0.733
CAD + CeVD	143/377	4.5	1.12 (1.04−1.21)	
CAD + PAD	123/262	4.8	1.10 (1.02−1.18)	
CAD + AAA	87/185	5.7	1.12 (1.02−1.22)	
CeVD + PAD	54/106	5.5	1.07 (0.95−1.21)	
CeVD/PAD + AAA	44/102	5.2	1.04 (0.91−1.19)	
3−4 CVD locations	77/146	7.1	1.07 (0.95−1.20)	
Major adverse limb event				0.071
CAD + CeVD	32/377	1.1	1.02 (0.87−1.21)	
CAD + PAD	100/262	5.4	0.97 (0.89−1.07)	
CAD + AAA	22/185	1.6	1.32 (1.10−1.57)	
CeVD + PAD	31/106	4.0	0.98 (0.84−1.14)	
CeVD/PAD + AAA	26/102	3.7	1.02 (0.87−1.21)	
3−4 CVD locations	30/146	3.3	1.17 (0.99−1.39)	



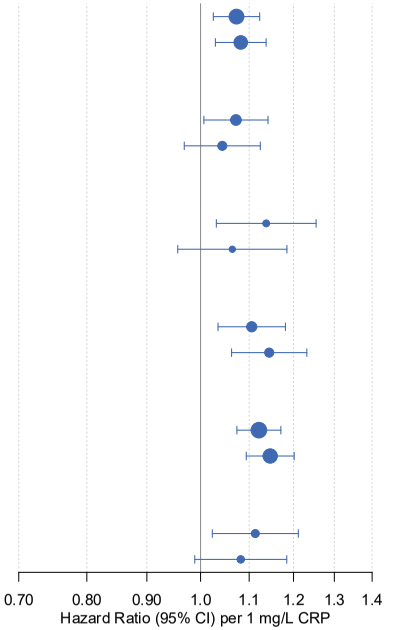
Hazard ratios (per 1 mg/L CRP) for the association between CRP and outcomes in patients with polyvascular disease (n = 1,178) divided into subgroups based on combinations of prior CVD locations. Patients with CeVD + AAA and PAD + AAA were combined, and patients with three or four CVD locations were combined to have at least 100 patients per subgroup. Results are not shown for the individual primary outcome components due to an insufficient number of events in the subgroups. Hazard ratios are adjusted for age, sex, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR. P-values for the interaction between CRP and combination of CVD locations are provided for each outcome. Following a Bonferroni correction for multiple testing, only p-values <0.016 should be regarded significant.

Abbreviations: AAA = abdominal aortic aneurysm, BMI = body-mass index, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, PAD = peripheral artery disease, PY = person years, SBP = systolic blood pressure.

Figure S9. Sensitivity analyses with prior CVD subtypes

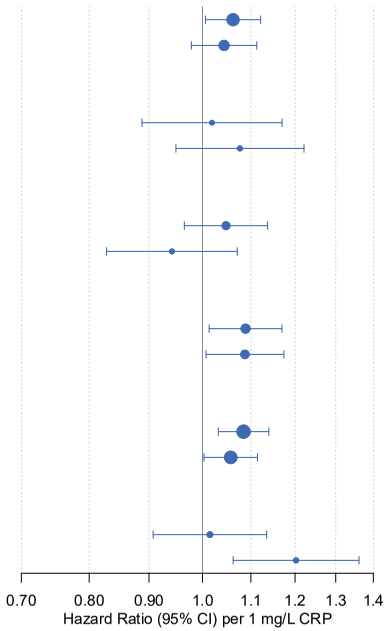
A. Coronary artery disease

Outcome	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)	p for interaction
Recurrent CVD				0.695
Prior myocardial infarction	419/2,352	2.1	1.07 (1.03−1.12)	
Prior coronary revascularization (no MI)	342/2,165	1.6	1.08 (1.03−1.14)	
Non−fatal myocardial infarction				0.753
Prior myocardial infarction	221/2,352	1.1	1.07 (1.01−1.14)	
Prior coronary revascularization (no MI)	170/2,165	0.8	1.04 (0.97−1.12)	
Non−fatal ischemic stroke				0.329
Prior myocardial infarction	78/2,352	0.4	1.14 (1.03−1.25)	
Prior coronary revascularization (no MI)	77/2,165	0.4	1.06 (0.96−1.18)	
Cardiovascular death				0.471
Prior myocardial infarction	180/2,352	0.8	1.11 (1.03−1.18)	
Prior coronary revascularization (no MI)	135/2,165	0.6	1.14 (1.06−1.23)	
All−cause mortality				0.715
Prior myocardial infarction	421/2,352	1.9	1.12 (1.07−1.17)	
Prior coronary revascularization (no MI)	355/2,165	1.6	1.15 (1.09−1.20)	
Major adverse limb event				0.460
Prior myocardial infarction	108/2,352	0.5	1.11 (1.02−1.21)	
Prior coronary revascularization (no MI)	97/2,165	0.4	1.08 (0.99−1.18)	



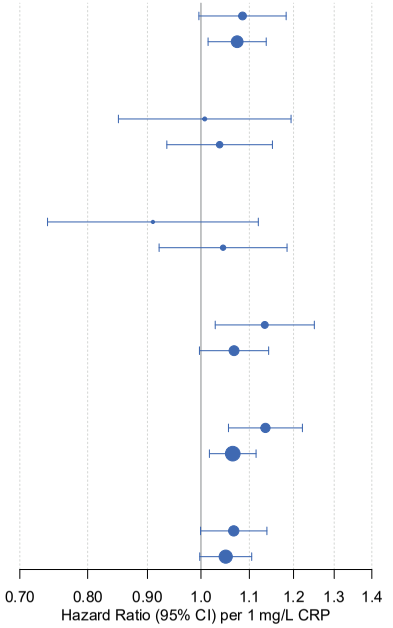
B. Cerebrovascular disease

Outcome	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)	p for interaction
Recurrent CVD				0.865
Prior stroke	257/1,389	2.1	1.06 (1.01−1.12)	
Prior TIA	176/765	2.4	1.04 (0.98−1.11)	
Non−fatal myocardial infarction				0.579
Prior stroke	45/1,389	0.4	1.02 (0.89−1.17)	
Prior TIA	44/765	0.6	1.08 (0.95−1.22)	
Non−fatal ischemic stroke				0.272
Prior stroke	113/1,389	0.9	1.05 (0.96−1.14)	
Prior TIA	59/765	0.8	0.94 (0.83−1.07)	
Cardiovascular death				0.956
Prior stroke	148/1,389	1.1	1.09 (1.01−1.17)	
Prior TIA	114/765	1.4	1.09 (1.01−1.17)	
All−cause mortality				0.782
Prior stroke	309/1,389	2.4	1.08 (1.03−1.14)	
Prior TIA	256/765	3.2	1.06 (1.00−1.11)	
Major adverse limb event				0.078
Prior stroke	61/1,389	0.5	1.01 (0.91−1.13)	
Prior TIA	42/765	0.5	1.20 (1.06−1.36)	



C. Peripheral artery disease

Outcome	Events/Patients	Event rate (events/100 PY)	Hazard Ratio (95% CI)	p for interaction
Recurrent CVD				0.986
Fontaine III/IV or prior lower limb surgery	93/341	2.8	1.09 (1.00–1.18)	
Fontaine II	201/813	2.5	1.07 (1.01–1.14)	
Non−fatal myocardial infarction				0.589
Fontaine III/IV or prior lower limb surgery	24/341	0.7	1.01 (0.85–1.19)	
Fontaine II	66/813	0.8	1.04 (0.94–1.15)	
Non−fatal ischemic stroke				0.663
Fontaine III/IV or prior lower limb surgery	18/341	0.5	0.91 (0.74–1.12)	
Fontaine II	43/813	0.5	1.04 (0.92–1.18)	
Cardiovascular death				0.431
Fontaine III/IV or prior lower limb surgery	72/341	2.1	1.13 (1.03–1.25)	
Fontaine II	145/813	1.7	1.07 (1.00–1.14)	
All−cause mortality				0.455
Fontaine III/IV or prior lower limb surgery	133/341	3.9	1.14 (1.06–1.22)	
Fontaine II	317/813	3.7	1.06 (1.02–1.11)	
Major adverse limb event				0.804
Fontaine III/IV or prior lower limb surgery	141/341	5.9	1.07 (1.00–1.14)	
Fontaine II	273/813	4.3	1.05 (1.00–1.11)	



Hazard ratios (per 1 mg/L CRP) for the association between CRP and outcomes in patients with CAD (A), CeVD (B), and PAD (C), divided into subgroups based on prior CVD subtype. Lower limb surgery includes percutaneous transluminal angioplasty or bypass surgery of the leg, and amputation. Hazard ratios are adjusted for age, sex, history of other CVD locations, smoking status, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR. P-values for the interaction between CRP and prior CVD subtype are provided for each outcome. Following a Bonferroni correction for multiple testing, only p-values <0.008 should be regarded significant.

Abbreviations: AAA = abdominal aortic aneurysm, BMI = body-mass index, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, SBP = systolic blood pressure, TIA = transient ischemic attack.

Chapter 3.

C-reactive protein and risk of incident heart failure in patients with cardiovascular disease

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Abstract

Background
Patients with established cardiovascular disease (CVD) are at high risk of incident heart failure (HF), which may in part reflect the impact of systemic inflammation.

Objective
To determine the association between C-reactive protein (CRP) and incident HF in patients with established CVD.

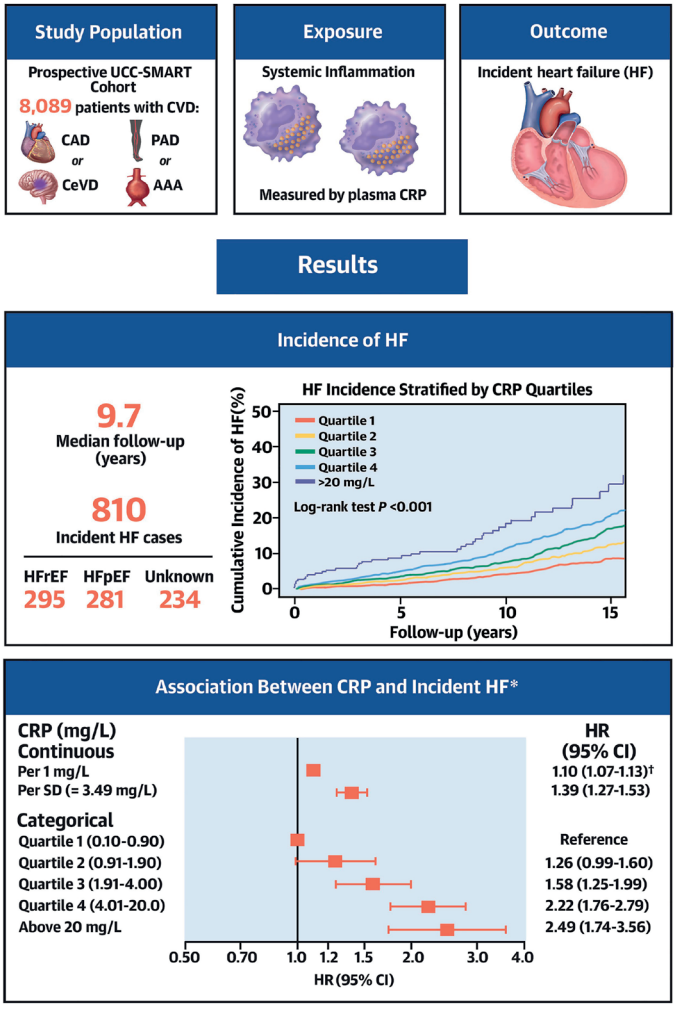
Methods
Patients from the prospective UCC-SMART cohort with established CVD, but without prevalent HF were included (n = 8,089). Incident HF was defined as a first hospitalization for HF. The association between baseline CRP and incident HF was assessed using Cox proportional hazards models adjusted for established risk factors, i.e. age, sex, myocardial infarction, smoking, diabetes mellitus, body-mass index, blood pressure, cholesterol, and kidney function.

Results
During a median follow-up of 9.7 years (interquartile range 5.4-14.1), 810 incident HF cases were observed (incidence rate 1.01/100 person years). Higher CRP was independently associated with an increased risk of incident HF: hazard ratio (HR) per 1 mg/L; 1.10 (95% confidence interval [CI] 1.07-1.13), and for last vs first CRP quartile; 2.22 (95% CI 1.76-2.79). The association was significant for both HF with reduced (HR 1.09; 95% CI 1.04-1.14) and preserved ejection fraction (HR 1.12; 95% CI 1.07-1.18) (p for difference 0.137). Additional adjustment for medication use and interim myocardial infarction did not attenuate the association, and the association remained consistent beyond 15 years after the CRP measurement.

Conclusions
In patients with established CVD, CRP is an independent risk marker of incident HF. These data support ongoing trial efforts to assess whether anti-inflammatory agents can reduce the burden of HF.

Central illustration

CENTRAL ILLUSTRATION: C-Reactive Protein and Risk of Heart Failure in Patients With Established Cardiovascular Disease



Burger PM, et al. J Am Coll Cardiol. 2023;82(5):414-426.

Introduction

Heart failure (HF) is a major global health issue, with a worldwide prevalence estimated at 1-2%.[1] Risk factors of HF commonly recognized and managed in clinical practice include coronary artery disease (CAD), hypertension, diabetes mellitus (DM), and smoking. Besides these traditional risk factors, systemic inflammation has emerged as an important underlying pathophysiology of the HF syndrome.[2] Several population-based studies have shown that high-sensitivity C-reactive protein (CRP) is independently associated with incident HF.[3–9]

These studies were conducted in individuals without a history of cardiovascular disease (CVD). Patients with established CVD have an increased risk of HF, and regularly use drugs such as statins, antiplatelets, and antihypertensive agents, potentially affecting the relation between inflammation and HF. In the Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) which enrolled patients with a prior myocardial infarction (MI), baseline levels of CRP were strongly associated with hospitalization for HF.[10] In this trial, inhibition of interleukin (IL)-1b with canakinumab not only reduced atherothrombotic events, but also reduced HF hospitalizations.[10,11] Further, recent data indicate that sodium/glucose transporter 2 (SGLT2) inhibitors also lower CRP, and that their positive effects on HF hospitalization and mortality may therefore in part be explained by reductions in inflammation.[12] Thus, despite the neutral results of previous trials with anti-inflammatory drugs in prevalent HF, there is still considerable interest in the use of anti-inflammatory therapies to prevent and treat HF.[2] Establishing the relation between low-grade inflammation (measured by CRP) and incident HF in patients with established CVD may reveal the potential for anti-inflammatory therapy to reduce the incidence of HF in this high-risk population.

This study aimed to determine the association between CRP and incident HF in patients with established CVD from a prospective practice-based cohort with long-term follow-up.

Methods

Study population

Patients were from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) study, an ongoing prospective cohort study of patients with established CVD at the University Medical Center Utrecht, the Netherlands. Study details have been described elsewhere.[13] The study was approved by the local Medical Ethics Committee (reference number 22-088), and written informed consent was obtained from all participants. For the current study, all patients with established CVD, i.e. CAD (prior

MI, cardiac arrest, or coronary revascularization), cerebrovascular disease (CeVD; i.e. prior transient ischemic attack, or ischemic or hemorrhagic stroke), peripheral artery disease (PAD; i.e. symptomatic obstruction of distal arteries of the leg with ankle-brachial index ≤0.90, prior percutaneous transluminal angioplasty or bypass surgery of the leg, or amputation), and/or abdominal aortic aneurysm (AAA; i.e. prior abdominal aortic surgery or an abdominal aortic anteroposterior diameter of ≥3 cm), and without a history of hospitalization for HF at baseline, who were enrolled in the cohort between September 1996 and January 2019 were included (n = 8,089). A flowchart of the study enrollment process is provided in Figure S1. Patients were enrolled at least two months after the qualifying CVD event.

Data collection

Medical history, physical examination and laboratory measurements were obtained at baseline based on a standardized screening protocol.[13] From 1996 to 2012, high-sensitivity CRP was measured by immunonephelometry, and from 2013, it was determined in heparin plasma using an AU5811 routine chemistry analyzer. These techniques provide comparable results.[14] Systolic blood pressure (SBP) was measured twice in both arms, and the highest mean of the measurements in one arm was used. Total cholesterol, high-density lipoprotein cholesterol (HDL-c), triglycerides, and creatinine were measured in blood samples collected after an overnight fast. Non-HDL-c was calculated as total cholesterol minus HDL-c. Estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation without race.[15] Smoking status, alcohol consumption, DM, and medication use were self-reported. Missing data (<2.0% for all variables), were imputed by single imputation using predictive mean matching. White blood cell (WBC) counts were not collected as part of the baseline screening, but could be retrieved for patients enrolled after January 2005 (n = 4,155), as from this moment WBC counts were automatically measured in all blood samples analyzed in the laboratory of the UMC Utrecht and stored in a database.

Outcomes

The outcome was incident HF, defined as a first hospitalization for HF. Outcomes were collected through linkage to the national hospitalization registry from Statistics Netherlands, a nationwide registry recording the cause of hospitalization for each hospitalization in the Netherlands. Causes of hospitalization are coded using the International Classification of Diseases (ICD), 9th and 10th revision. Hospitalization for HF was defined as a hospitalization with ICD-9; 428.0-428.4 or 428.9, or ICD-10; I50.1-I50.4 or I50.9. The HF diagnoses were established and the corresponding ICD codes were

registered by clinicians in routine clinical care. In the Netherlands, it is common practice to diagnose HF in accordance with the criteria from the European Society of Cardiology (ESC) guidelines.[16] Outcomes were divided in HF with reduced ejection fraction (HFrEF; i.e. left ventricular ejection fraction [LVEF] ≤50%) and preserved ejection fraction (HFpEF; i.e. LVEF >50%), using echocardiography reports retrieved from medical records. Interim MI and death were collected within the UCC-SMART cohort itself, and were adjudicated by an endpoint committee of three independent physicians. Patients were followed for all outcomes from the time of cohort entry until the predetermined end-of-study date of 1 January 2019 (i.e. most recent date with complete collection and adjudication of outcomes). Follow-up was complete in 94.6% of patients (Figure S1).

Data analyses

Baseline characteristics were described stratified by quartiles of CRP. Kaplan-Meier curves of the cumulative incidence of HF were drawn stratified by quartiles of CRP, and CVD location. Log-rank tests were used to assess differences in HF incidence between subgroups. As CRP concentrations >20 mg/L are often assumed to be associated with an acute inflammatory response, these patients (n = 236) were analyzed as a separate group.[17]

Cause-specific Cox proportional hazards models for the association between CRP and incident HF were derived in all patients with CRP ≤20 mg/L (n = 7,853). Models were progressively adjusted for potential confounders. First, the model was adjusted for age and sex. Then, the model was additionally adjusted for CVD locations, i.e. CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, and established risk factors of HF, i.e. smoking, DM, body-mass index (BMI), SBP, non-HDL-c, and eGFR (main adjustment). In an exploratory model, additional adjustment for alcohol consumption, HDL-c, triglycerides, the use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort was performed. The association was also assessed stratified for HFrEF and HFpEF. In this time-to-first-subtype analysis only first HF hospitalizations were included, thus not progression from one subtype to the other. Whether there was a differential effect of CRP on the risk of HFrEF vs HFpEF was formally tested using the Lunn-McNeil method.[18] Restricted cubic splines revealed no violations of the linearity assumption (p for non-linearity >0.05). The proportional hazards assumption, assessed using Schoenfeld residuals, was not violated. The association between CRP and incident HF was described using cause-specific hazard ratios (HRs) for every 1 mg/L, and 1 standard deviation (SD) increase in CRP, and for CRP quartiles (with CRP >20 mg/L as a separate group).

Next, it was explored whether the association between CRP and incident HF was mediated through the occurrence of an interim MI, by adjusting the model for interim MI as time-

varying covariate. Influence of the competing risk of death (not preceded by HF) was assessed by deriving subdistribution hazard ratios (SHRs) from Fine and Gray models. To support interpretation of these SHRs, Kaplan-Meier curves of the cumulative rates of death were derived, and the association between CRP and (various causes of) death was established using cause-specific Cox proportional hazards models.

Reverse causality was assessed by repeating the analyses after excluding patients who had incident HF within the first 1, 2, 5, 10, and 15 years after inclusion. Consistency of the association between CRP and incident HF over time was assessed by determining the effects of CRP on HF risk within subsequent 5-year time intervals. Effect modification by age, sex, CVD location, smoking, DM, BMI, and use of statins, antiplatelet therapy, and antihypertensive agents was assessed by testing interaction terms of these factors with CRP. The combined effects of the presence of both an elevated CRP concentration and a history of MI, DM, current smoking, or hypertension were assessed by determining the association between combinations of these risk factors and incident HF.

Stability of CRP concentrations over time was assessed by calculating the difference between baseline and follow-up CRP concentration in a subset of patients who revisited for second measurements (n = 1,944). The standardized change (i.e. change divided by the SD of the baseline measurement) in CRP was compared to that in low-density lipoprotein cholesterol (LDL-C) and SBP.

To assess whether the association with incident HF was consistent for other markers of inflammation, the primary analysis was repeated after replacing CRP by WBC counts, and the neutrophil-lymphocyte ratio. Correlations between these measures and CRP were determined using Spearman's correlation tests.

P-values and 95% confidence intervals (CIs) presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible.

Further details of the statistical analysis are provided in the Supplemental Material. All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

Results

Baseline characteristics

In patients with CRP ≤20 mg/L, median CRP concentration was 1.90 mg/L (interquartile range [IQR] 0.90-4.00; distribution shown in Figure S2). The proportions of women, current smokers, and patients with PAD, AAA, DM, and hypertension increased across CRP quartiles, as did BMI, lipid concentrations, and WBC counts (Table 1). Patients in the higher CRP quartiles also less often used a statin and antiplatelet therapy. Characteristics of patients with CRP >20 mg/L were comparable to patients within the third and fourth CRP quartiles below 20 mg/L.

Table 1. Baseline characteristics stratified by quartiles of CRP

Characteristic	**1st Quartile (n = 2,091)**	**2nd Quartile (n = 1,919)**	**3rd Quartile (n = 1,899)**	**4th Quartile (n = 1,944)**	**CRP >20 mg/L (n = 236)**
CRP (mg/L), median (range)	*0.60 (0.10-0.90)*	*1.40 (0.91-1.90)*	*2.74 (1.91-4.00)*	*6.64 (4.01-20.0)*	*31.9 (20.1-247.4)*
Age	59.1±10.2	60.3±10.3	61.4±9.9	60.9±10.5	63.9±10.4
Sex (male)	1,616 (77%)	1,447 (75%)	1,396 (74%)	1,334 (69%)	178 (75%)
Smoking status					
Former	1,028 (49%)	957 (50%)	893 (47%)	828 (43%)	106 (45%)
Current	424 (20%)	507 (26%)	649 (34%)	809 (42%)	89 (38%)
Alcohol (units/week)					
Never drinker	301 (14%)	341 (18%)	343 (18%)	412 (21%)	46 (20%)
<1	204 (10%)	215 (11%)	179 (9%)	196 (10%)	24 (10%)
1-10	1,000 (48%)	827 (43%)	804 (42%)	784 (40%)	88 (37%)
10-20	401 (19%)	326 (17%)	382 (20%)	334 (17%)	52 (22%)
>20	185 (9%)	210 (11%)	191 (10%)	218 (11%)	26 (11%)
CVD locations					
Coronary artery disease	1,364 (65%)	1,262 (66%)	1,176 (62%)	1,026 (53%)	129 (55%)
Prior myocardial infarction	721 (35%)	652 (34%)	621 (33%)	563 (29%)	63 (27%)
Cerebrovascular disease	628 (30%)	533 (28%)	561 (30%)	598 (31%)	72 (31%)
Peripheral artery disease	224 (11%)	260 (14%)	370 (20%)	504 (26%)	68 (29%)
Abdominal aortic aneurysm	90 (4%)	124 (7%)	165 (9%)	258 (13%)	41 (17%)
Hypertension	1,069 (51%)	1,123 (59%)	1,158 (61%)	1,219 (63%)	142 (60%)
Diabetes mellitus	307 (15%)	320 (17%)	307 (16%)	387 (20%)	56 (24%)
Body mass index (kg/m^2)	25.7±**3.4**	25.9±3.7	27.3±4.0	27.7±4.6	27.2±5.1
Systolic blood pressure (mmHg)	137±20	139±20	140±21	142±22	142±23

Characteristic	1st Quartile (n = 2,091)	2nd Quartile (n = 1,919)	3rd Quartile (n = 1,899)	4th Quartile (n = 1,944)	CRP >20 mg/L (n = 236)
Laboratory values					
LDL-cholesterol (mg/dL)	99±36	106±38	113±41	120±43	112±41
HDL-cholesterol (mg/dL)	50±14	48±14	47±14	45±13	43±12
Non-HDL-cholesterol (mg/dL)	123±39	134±42	144±47	153±51	140±46
Triglycerides (mg/dL)	124±85	144±88	161±128	168±152	144±87
eGFR (mL/min/1.73 m^2)	80±16	79±17	76±18	75±20	72±21
Total WBC count ($\times 10^9$/L)[a]	6.2±1.7	6.6±1.7	7.1±1.9	7.8±2.1	8.8±2.7
Neutrophil count ($\times 10^9$/L)[a]	3.5±1.3	3.8±1.3	4.2±1.4	4.7±1.7	5.8±2.2
Lymphocyte count ($\times 10^9$/L)[a]	1.9±0.6	2.0±0.7	2.0±0.7	2.1±0.8	1.9±0.7
Neutrophil-lymphocyte ratio[a]	2.0±0.8	2.1±0.9	2.2±1.0	2.4±1.1	3.1±1.4
Monocyte count ($\times 10^9$/L)[a]	0.52±0.17	0.56±0.16	0.59±0.18	0.63±0.20	0.71±0.24
Medication use					
Statin	1,611 (77%)	1,391 (73%)	1,258 (66%)	1,126 (58%)	118 (50%)
Antiplatelet therapy	1,722 (82%)	1,550 (81%)	1,454 (77%)	1,378 (71%)	156 (66%)
Antihypertensive therapy	1,545 (74%)	1,469 (77%)	1,435 (76%)	1,421 (73%)	173 (73%)

All data in n (%) or mean±SD, unless otherwise specified.

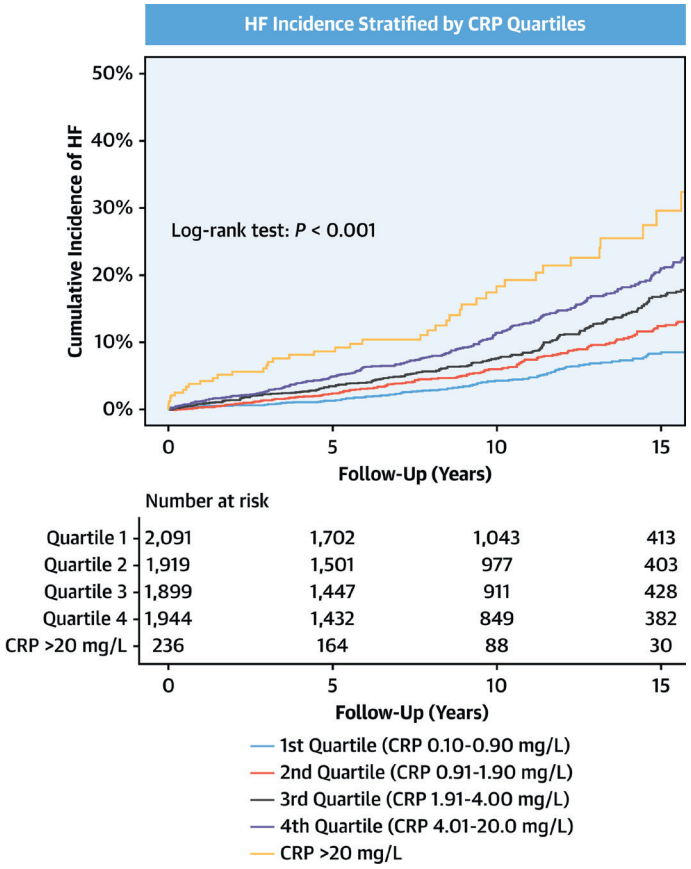
[a] WBC counts were not part of the standard baseline screening. Data presented are based on the 4,155 patients for whom WBC counts were available.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein, PAD = peripheral artery disease, SD = standard deviation, WBC = white blood cell.

HF incidence rates

During a median follow-up of 9.7 years (IQR 5.4-14.1), 768 incident HF cases were observed in patients with CRP ≤20 mg/L (9.8%; incidence rate: 0.98/100 person years [PY]), and 42 cases in patients with CRP >20 mg/L (17.8%; incidence rate: 2.08/100 PY). This included 295 (36.4%) cases of HFrEF, 281 (34.7%) cases of HFpEF, and 234 (28.9%) cases with unknown LVEF. The unadjusted incidence of HF increased across CRP quartiles (p <0.001; Figure 1). The incidence in patients with CRP >20 mg/L exceeded that observed in patients within the highest CRP quartile below 20 mg/L (p = 0.02). HF incidence was lowest in patients with CeVD or CAD without prior MI (p for comparison with other CVD locations: <0.001) (Figure S3). In patients with PAD or AAA, the incidence was comparable to patients with a prior MI (p = 0.58 and p = 0.21 respectively).

Figure 1. HF incidence stratified by CRP quartiles



Cumulative incidence of HF hospitalization stratified by CRP quartiles, with CRP >20 mg/L added as a separate group.

Association between CRP and incident HF

In patients with CRP ≤20 mg/L, higher CRP was significantly associated with an increased risk of incident HF independent of established risk factors (per 1 mg/L increase in CRP: HR 1.10; 95% CI 1.07-1.13) (Table 2 & Central Illustration). A dose-response relationship was observed between CRP in quartiles and incident HF, with an especially high risk for patients in the fourth quartile of CRP (4.01-20.0 mg/L): versus first quartile (0.10-0.90 mg/L); HR 2.22 (95% CI 1.76-2.79). A CRP >20 mg/L was associated with an even higher risk of incident HF (versus first quartile: HR 2.49; 95% CI 1.74-3.56). Additional adjustment for alcohol consumption, HDL-c, triglycerides, use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort did not attenuate the association (Table 2).

Table 2. Cause-specific hazard ratios for the association between CRP and incident HF

	CRP (mg/L), median (range)	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Main adjustment[a], HR (95% CI)	Additional adjustment[b], HR (95% CI)
Continuous							
Per 1 mg/L	1.90 (0.10-20.0)[c]	768/7,853[c]	0.98	1.13 (1.10-1.16)	1.12 (1.09-1.15)	1.10 (1.07-1.13)	1.10 (1.08-1.13)
Per SD (= 3.49 mg/L)	1.90 (0.10-20.0)[c]	768/7,853[c]	0.98	1.53 (1.39-1.68)	1.49 (1.35-1.63)	1.39 (1.27-1.53)	1.40 (1.29-1.55)
Categorical							
Quartile 1	0.60 (0.10-0.90)	118/2,091	0.55	Ref	Ref	Ref	Ref
Quartile 2	1.40 (0.91-1.90)	158/1,919	0.81	1.43 (1.12-1.81)	1.34 (1.06-1.70)	1.26 (0.99-1.60)	1.29 (1.01-1.64)
Quartile 3	2.74 (1.91-4.00)	216/1,899	1.13	1.96 (1.57-2.46)	1.78 (1.42-2.23)	1.58 (1.25-1.99)	1.60 (1.27-2.02)
Quartile 4	6.64 (4.01-20.0)	276/1,944	1.50	2.66 (2.14-3.30)	2.55 (2.05-3.17)	2.22 (1.76-2.79)	2.30 (1.83-2.89)
>20 mg/L	31.9 (20.1-247.4)	42/236	2.08	3.93 (2.76-5.58)	3.17 (2.23-4.52)	2.49 (1.74-3.56)	2.64 (1.84-3.79)

Cause-specific hazard ratios (95% CI) for the association between CRP and incident HF derived from cause-specific Cox proportional hazards models. As CRP concentrations above 20 mg/L are often assumed to be associated with an acute inflammatory response, patients with CRP >20 mg/L (n = 236) were analyzed separately, i.e. they were excluded from the continuous analysis and analyzed as a separate subgroup in the categorical analysis. No corrections for multiple testing were applied.

[a] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.
[b] Main adjustment + alcohol consumption (units/week), HDL-c, triglycerides, use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort.
[c] Only patients with CRP ≤20 mg/L (n = 7,853) were included in the continuous analysis. As CRP concentrations above 20 mg/L are often assumed to be associated with an acute inflammatory response, these patients (n = 236) were excluded from the continuous analysis.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Table 3. Cause-specific hazard ratios for the association between CRP and HF subtypes

			HFrEF		HFpEF		HF unclassified[a]	
	CRP (mg/L), median (range)	**Patients**	**Events**	**HR (95% CI)[b]**	**Events**	**HR (95% CI)[b]**	**Events**	**HR (95% CI)[b]**
Continuous								
Per 1 mg/L	1.90 (0.10-20.0)[c]	7,853[c]	281	1.09 (1.04-1.14)[d]	265	1.12 (1.07-1.18)[d]	222	1.10 (1.04-1.17)
Per SD (= 3.49 mg/L)	1.90 (0.10-20.0)[c]	7,853[c]	281	1.35 (1.15-1.58)	265	1.49 (1.28-1.77)	222	1.40 (1.15-1.71)
Categorical								
Quartile 1	0.60 (0.10-0.90)	2,091	47	Ref	38	Ref	33	Ref
Quartile 2	1.40 (0.91-1.90)	1,919	61	1.19 (0.78-1.81)	53	1.33 (0.87-2.04)	44	1.23 (0.74-2.04)
Quartile 3	2.74 (1.91-4.00)	1,899	76	1.46 (1.01-2.11)	78	1.68 (1.13-2.50)	62	1.59 (1.00-2.53)
Quartile 4	6.64 (4.01-20.0)	1,944	97	2.06 (1.39-3.06)	96	2.37 (1.60-3.52)	83	2.19 (1.39-3.45)
>20 mg/L	31.9 (20.1-247.4)	236	14	2.29 (1.19-4.42)	16	2.62 (1.42-4.83)	12	2.54 (1.26-5.10)

Cause-specific hazard ratios (95% CI) for the association between CRP and HF subtypes, i.e. HFrEF and HFpEF, derived from cause-specific Cox proportional hazards models. This was a time-to-first-subtype analysis, so only first HF hospitalizations were included, while progression from one subtype to the other was not counted as a new event. Cases for which LVEF was unknown were analyzed separately under 'HF unclassified'. As CRP concentrations above 20 mg/L are often assumed to be associated with an acute inflammatory response, patients with CRP >20 mg/L (n = 236) were analyzed separately, i.e. they were excluded from the continuous analysis and analyzed as a separate subgroup in the categorical analysis. No corrections for multiple testing were applied.

[a] Cases for which LVEF was unknown.
[b] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR (main adjustment).
[c] Only patients with CRP ≤20 mg/L (n = 7,853) were included in the continuous analysis. As CRP concentrations above 20 mg/L are often assumed to be associated with an acute inflammatory response, these patients (n = 236) were excluded from the continuous analysis.
[d] Lunn-McNeil method to compare the HR for HFrEF vs HFpEF showed no significant difference: p = 0.137.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Association between CRP and HF subtypes

Higher CRP was significantly associated with an increased risk of both HFrEF (per 1 mg/L: HR 1.09; 95% CI 1.04-1.14), and HFpEF (HR 1.12; 95% CI 1.07-1.18), with no significant difference between the two subtypes (p = 0.137; Table 3). A similar association was found between CRP and unclassified HF cases (HR 1.10; 95% CI 1.04-1.17).

Influence of interim MI

An interim MI was observed in 549 patients (7.0%), of whom 110 (20.0%) developed HF later during follow-up. Higher CRP was independently associated with an increased risk of interim MI (Table S1), but the magnitude of the relationship was smaller as compared to the association between CRP and incident HF. Interim MI strongly increased the risk of subsequent incident HF (HR 2.75; 95% CI 2.24-3.39) (Table S2). However, the association between CRP and incident HF was not attenuated by additional adjustment for interim MI (Table S3).

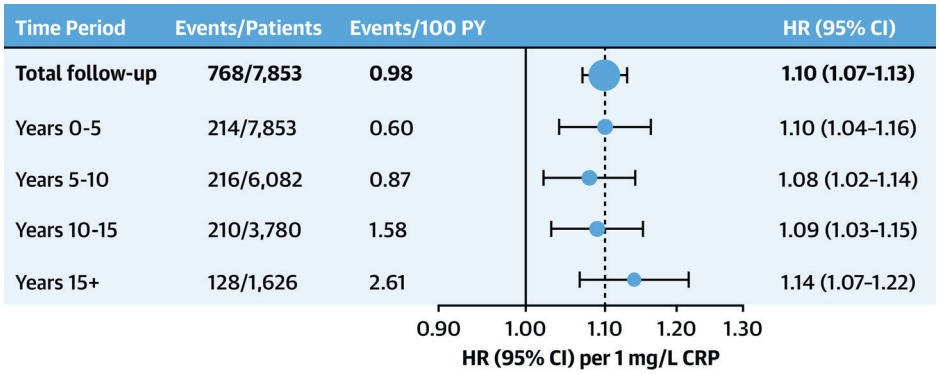
Influence of competing risk of death

A total of 1,991 deaths occurred (incidence rate: 2.60/100 PY), of which 1,584 deaths were not preceded by HF (incidence rate: 1.97/100 PY) (Figure S4). The association between CRP and incident HF was slightly attenuated but remained significant in a model adjusted for competing risk of death (per 1 mg/L: SHR 1.08; 95% CI 1.05-1.11) (Table S4). This attenuation could be explained by the fact that higher CRP was also associated with an increased risk of death due to any cause, and various specific causes (Table S5).

Reverse causality and effect modification

Repeating the analyses after excluding patients who had incident HF within the first 1, 2, 5, 10, and 15 years after inclusion yielded almost identical results (Table S6). The association between CRP and incident HF was consistent over time, and higher baseline CRP remained significantly associated with an increased risk of incident HF even beyond 15 years after the initial measurement (Figure 2). The association between CRP and incident HF was not significantly modified by any of the pre-specified clinical variables (Table S7).

Figure 2. Association between CRP and HF over time



Association between CRP and incident HF within subsequent time intervals. Hazard ratios were adjusted for established risk factors (main adjustment in Table 2).

Combined effects of CRP and established risk factors

A CRP concentration above the median (>1.90 mg/L) increased the risk of incident HF on top of established risk factors (Figure 3). Hazard ratios for the combined presence of CRP above the median with MI (HR 3.69; 95% CI 2.94-4.63), DM (HR 2.99; 95% 2.36-3.78), current smoking (HR 2.31; 95% CI 1.86-2.87), and hypertension (HR 2.06; 95% CI 1.62-2.62), exceeded those of MI (HR 2.39; 95% CI 1.88-3.04), DM (HR 2.19; 95% CI 1.69-2.84), current smoking (HR 1.33; 95% CI 0.99-1.79), and hypertension (HR 1.27; 95% CI 0.99-1.63) alone.

Stability of CRP concentrations over time

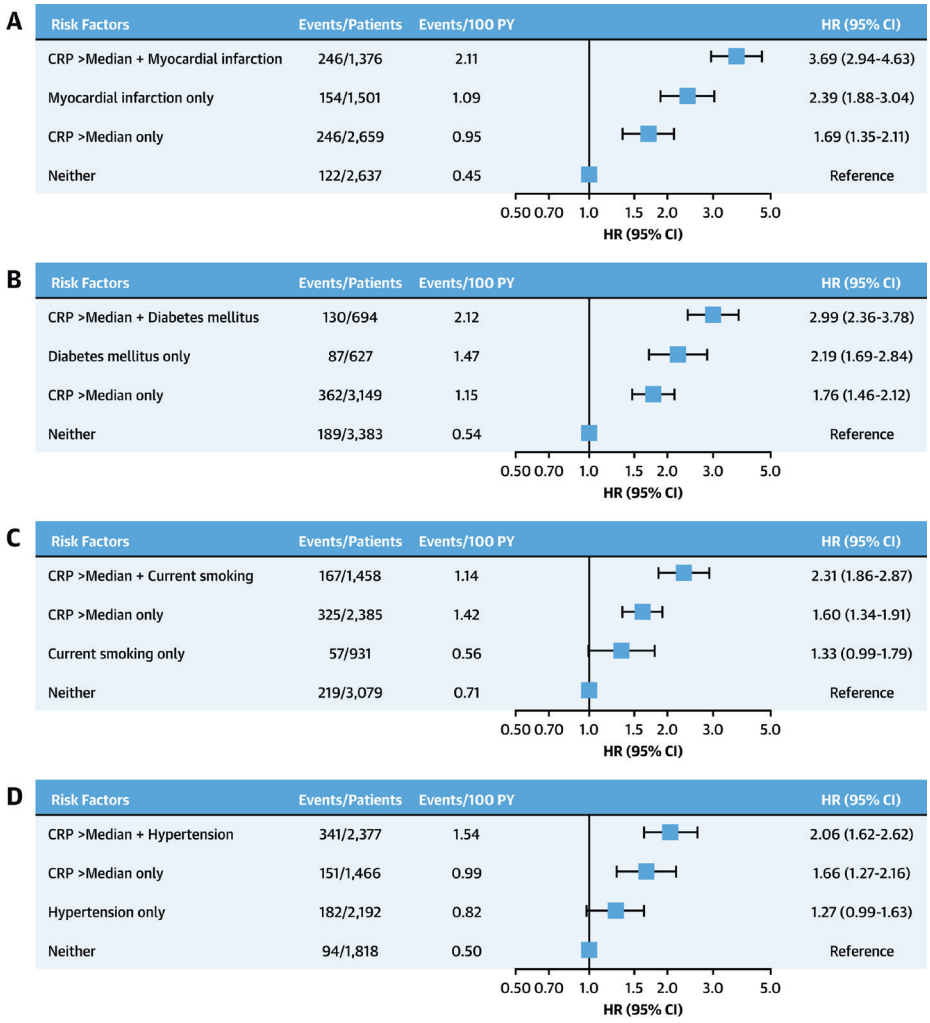
A second measurement of CRP was available for 1,944 (24.0%) patients, with a median time between baseline and second measurement of 10.0 years (IQR 8.6-10.8). Median change in CRP was -0.10 mg/L (IQR -1.00–0.67) (Figure S5). In 76% of patients, CRP had changed by <1 SD. In comparison, after the same time interval, LDL-C and SBP had changed by <1 SD in 67% and 68% of these patients respectively (Figure S6).

Association between WBC counts and incident HF

WBC counts were available for 4,155 (51.4%) patients. There was a significant but weak to moderate correlation between CRP and total WBC count (Spearman's correlation coefficient [ρ] = 0.339), neutrophil-lymphocyte ratio (ρ = 0.203), and several differential WBC counts (Figure S7). Total WBC count was not independently associated with incident HF (Table S8). However, there were significant associations with incident HF for neutrophil count (HR per SD 1.13; 95% CI 1.01-1.27), lymphocyte count (HR per SD 0.88; 95% CI 0.77-0.99),

neutrophil-lymphocyte ratio (HR per SD 1.18; 95% CI 1.08-1.30), and monocyte count (HR per SD 1.16; 95% CI 1.04-1.29). Compared to these measures, CRP was more strongly associated with incident HF in these patients (HR per SD 1.30; 95% CI 1.18-1.43). The associations of WBC counts and the neutrophil-lymphocyte ratio with incident HF were largely independent of CRP and vice versa (Table S9).

Figure 3. Combined effects of CRP and established risk factors on HF risk



Combined effects of a CRP concentration above the median (>1.90 mg/L), and myocardial infarction (A), diabetes mellitus (B), current smoking (C), and hypertension (D) on the risk of incident HF. Hazard ratios were adjusted for established risk factors (main adjustment in Table 2) where appropriate. Myocardial infarction was analyzed as a time-varying covariate.

Discussion

In this prospective observational cohort study of 8,089 patients with established CVD, higher CRP was significantly associated with an increased risk of incident HF, independent of established risk factors, medication use, and interim MI (Central Illustration). The association was significant for both HFrEF and HFpEF, and remained consistent beyond 15 years after the initial CRP measurement.

Several mechanisms may explain the relation between inflammation and incident HF. First, systemic inflammation leads to activation of the renin-angiotensin system and the sympathetic nervous system, contributing to volume expansion, increased peripheral vascular resistance, and myocyte hypertrophy and apoptosis.[19,20] Pro-inflammatory cytokines may also depress myocardial contractility, influence left ventricular remodeling, and lead to pulmonary edema, and endothelial dysfunction.[21,22] In addition, low-grade inflammation may increase the risk of MI, and thereby increase the risk of subsequent HF. But as shown in this study, CRP was associated with incident HF independent of the occurrence of an interim MI. A previous review provided a detailed overview of the role of CRP itself in promoting endothelial dysfunction and atherothrombosis that may contribute to the development of HF.[23] CRP binds to CD32 and CD64 receptors on endothelial cells, triggering a series of proinflammatory pathways. First, CRP reduces endothelial nitric oxide synthase (eNOS) activity, resulting in increased superoxide and decreased NO production, which attenuates vasodilatation. Second, CRP decreases prostacyclin, while inducing plasminogen activator inhibitor-1 (PAI-1), which promotes platelet aggregation. Third, CRP triggers adhesion of monocytes to the endothelium, secretion of other proinflammatory cytokines, and the uptake of oxidized LDL in monocytes leading to foam cell formation. However, whether CRP itself is truly part of the causal pathway between inflammation and incident HF remains uncertain. Elevated CRP may also reflect increased hepatic synthesis under the influence of other, upstream inflammatory markers such as IL-6, and may only be indicative of a generalized inflammatory state antedating HF. Hence, a mendelian randomization study showed that genetic variants related to higher concentrations of CRP are not related to an increased risk of HF.[24] Regardless of the role of CRP in the pathogenesis of HF, this study shows that a single measurement of CRP is strongly associated with incident HF, even beyond 15 years after the initial measurement. This includes CRP concentrations >10 and >20 mg/L, which by clinicians are often assumed to be associated with a temporary inflammatory condition, and therefore often disregarded.[17] The results of this study indicate that all randomly measured CRP concentrations, including very high concentrations (>10/>20 mg/L), are clinically relevant indicators of HF risk that should be fully appreciated.

This study expands on previous studies performed in people without a history of CVD. These population-based studies from Europe and the US have also shown a significant association between CRP and incident HF, but differences in reporting measures complicate a direct comparison.[3–9] In studies that reported the effects of a 1 SD increase in CRP on HF risk, hazard ratios ranged from 1.16 to 1.48, in line with the hazard ratio of 1.39 per 1 SD increase in CRP found in this study.[3,7,8] Only two previous studies distinguished between HFrEF and HFpEF, with contrasting results.[5,7] One study showed that inflammatory markers are more strongly associated with HFpEF.[5] This is in line with the current study, although differences were small and non-significant in this study. In another study CRP was independently associated with HFrEF but not HFpEF.[7] Future studies in which LVEF is systematically assessed in all participants may be considered to evaluate differences in the relation of inflammation with HFrEF vs HFpEF. To our knowledge, the current study is the first to assess the association between CRP and incident HF in a population of patients with various types of CVD, and to evaluate the HF risk associated with very high concentrations of CRP (>20 mg/L).

Establishing the association between CRP and incident HF specifically in patients with established CVD is clinically relevant for multiple reasons. First, low-grade inflammation is very common in patients with CVD. In our study population, 49% had a CRP >2.0 mg/L (a commonly used threshold for low-grade inflammation). In the first place, this is due to the fact that low-grade inflammation is also an established risk factor of atherosclerotic CVD.[25] Secondly, other conditions that may lead to CVD or often coexist together with CVD, such as DM, obesity, and smoking, contribute to low-grade inflammation. Besides the high prevalence of low-grade inflammation, the incidence of HF is also considerably higher in patients with established CVD. The incidence rate observed in our cohort was 1.01/100 PY, as compared to approximately 0.12/100 PY in a Dutch population-based cohort.[26] It is not only patients with CAD who may develop HF, but as shown in this study, patients with non-coronary manifestations of CVD are at high risk of incident HF as well. Moreover, we showed that CRP was associated with incident HF independent of the occurrence of an interim MI. This indicates that strategies focused on the prevention of MI do not necessarily also prevent HF in this population, and that interventions targeted specifically at the prevention of HF may be necessary. Our results indicate that in patients with established CVD, low-grade inflammation (measured by CRP) is a strong and independent risk factor of incident HF. This suggests that interventions targeting inflammation may have the potential to reduce the high risk of HF in this population.

In recent years, clinical trials have demonstrated the efficacy of anti-inflammatory drugs, i.e. canakinumab and low-dose colchicine, in reducing the risk of major adverse cardiovascular events, including myocardial infarction, coronary revascularization, stroke,

and cardiovascular death, in patients with CAD.[11,27,28] In contrast, in patients with prevalent HF various anti-inflammatory agents, i.e. tumor necrosis factor-α inhibitors, IL-1 receptor antagonists, methotrexate, and colchicine did not improve patient functional status nor reduce HF hospitalization or mortality.[2] This may have casted doubts on the potential for anti-inflammatory therapy in the treatment of HF, but these trials were not powered to detect a significant difference in clinical outcomes. Also, anti-inflammatory therapy might be useful in the prevention of HF, though data in this area are limited. Statins have anti-inflammatory effects, and even though trials in prevalent HF yielded neutral results, statins were proven to reduce the risk of a first hospitalization for HF in patients with established CVD or CVD risk factors.[29] A secondary analysis of the CANTOS trial found that treatment with canakinumab was associated with a trend towards a dose-dependent reduction in HF hospitalization, with a non-significant relative risk reduction of 30% in patients without a history of HF on the highest dose of canakinumab (300 mg once every three months).[10] More studies are needed to identify anti-inflammatory and other preventive therapies capable of reducing the high risk of HF in patients with established CVD. For this purpose, we suggest that incident HF could be included as a pre-specified endpoint in future trials in this population. Trials of anti-inflammatory drugs in patients with established CVD powered to detect a difference in HF incidence may be warranted. For example IL-6 inhibition (e.g. with ziltivekimab) may hold promise, and warrants testing in patients with established CVD and/or prevalent HF.[30] Based on the current evidence, intensification of preventive therapy may already be considered in CVD patients with an elevated CRP concentration (e.g. >2.0 mg/L) to reduce the risk of incident HF and other CVD events.

Study strengths and limitations

Strengths of this study include the use of a practice-based cohort with a prospective design, the long follow-up duration, and the low proportions of missing data. Study limitations need to be considered. First of all, this is an observational study, so subject to potential residual confounding. Definitive conclusions on causality cannot be made based on the results of this study. A single measurement of CRP was used, while concentrations might fluctuate during follow-up. However, as shown in the current and in previous studies, CRP concentrations are relatively stable over time.[25,31,32] Also, this study showed that the association between a single measurement of CRP and incident HF is consistent beyond 15 years after the measurement. WBC counts were missing for part of the cohort, and other inflammatory markers such as IL-6 were not measured. Data on auto-inflammatory and infectious diseases that may increase both CRP and HF risk were lacking. But as patients with severe comorbidities were not enrolled in the cohort, and patients with CRP >20 mg/L were analyzed as a separate group, the influence of inflammatory conditions on the results of this study is likely limited. HF outcomes were not adjudicated, but were based on

ICD codes registered by clinicians in routine clinical care. Documentation of ICD codes by clinicians might be imperfect, but a validation study in another Dutch cohort showed that only 3.3% of patients with a presumed HF hospitalization based on ICD codes were misclassified.[33] Also, 71% of HF cases in this study could be confirmed and classified as either HFrEF or HFpEF based on information retrieved from medical records. For 29% of cases, information on LVEF was not available, so these could not be classified. Only in-hospital diagnoses were available, so out-patient diagnoses of HF were missed.

Conclusions

In patients with established CVD, higher CRP is independently associated with an increased long-term risk of incident HF. Future trials may reveal the potential for anti-inflammatory therapy to reduce the high risk of HF in this population.

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Supplementary material

Supplemental Methods

Primary analysis of the association between CRP and incident HF

The association between CRP and incident HF was analyzed using cause-specific Cox proportional hazards models. This means censoring was applied at the time of unrelated death (i.e. death not preceded by HF), or at the end of follow-up.[1] The hazard ratios (HRs) derived from these models and presented in the main analysis should therefore be interpreted as cause-specific HRs, i.e. not adjusted for the competing risk of death. The analysis was a time-to-first-event analysis, i.e. only the patients' first HF hospitalization was included, and recurrent events were disregarded. The models included baseline CRP and an increasing number of potential confounders (also measured once at baseline). The continuous analysis was limited to patients with CRP ≤20 mg/L, as CRP concentrations >20 mg/L are often assumed to be associated with an acute inflammatory response.[2] As an analysis of restricted cubic splines revealed no violations of the linearity assumption (p for non-linearity >0.05), CRP was entered into the models as a linear term. The continuous association between CRP and incident HF was described using cause-specific HRs for every 1 mg/L, and 1 standard deviation (SD) increase in CRP. In addition, a categorical analysis was performed, in which patients with CRP ≤20 mg/L were divided in quartiles based on their CRP concentration, and patients with CRP >20 mg/L were added to the model as a fifth group. Cause-specific HRs for the CRP quartiles, and CRP >20 mg/L as compared to the lowest quartile of CRP (i.e. the reference group) were derived. The proportional hazards assumption, assessed based on scaled Schoenfeld residuals and plots of the HR for CRP over time, was not violated for any of the models, so there was no need to include interactions of CRP with time.

Analysis of the association between CRP and HF subtypes

Similar to the primary analysis, the association between CRP and HF subtypes (i.e. HFrEF and HFpEF) was analyzed using cause-specific Cox proportional hazards models. The analysis was a time-to-first-subtype analysis, meaning that only the first HF subtype was analyzed, i.e. the subtype of HF present at time of the patients' first HF hospitalization. Progression from one subtype to the other (i.e. HFpEF to HFrEF, or the other way around) was not counted as a new event, and not included in the analysis. This means that in the analysis of a specific HF subtype (e.g. HFrEF), censoring was applied at the time of development of a different HF subtype (HFpEF), at the time of unrelated death, or at the end of follow-up. As in the primary analysis, the association between CRP and HF subtypes was described using cause-specific HRs for every 1 mg/L, and 1 SD increase in CRP, and for CRP quartiles (with CRP >20 mg/L added as a separate group). Whether there was a

differential effect of CRP on the risk of HFrEF vs HFpEF was formally tested using the Lunn-McNeil method. A detailed description of this method has been published elsewhere.[3] In summary, the data was duplicated, and a 'status' and 'failure type' variable was created in both duplications. In the first duplication of the data, the 'status' variable was set to 1 for all patients who developed HF (and to 0 for patients who did not develop HF), and the 'failure type' variable was set to 1 for patients who developed HFrEF (and to 0 for patients who developed HFpEF or did not develop HF). In the second duplication of the data, the 'status' variable was set to 0 for all patients, and the 'failure type' variable was set to 1 for patients who developed HFpEF or did not develop HF (and to 0 for patients who developed HFrEF). Then, the two duplications of the data were combined into one dataset. This creates a dataset in which patients who developed HFrEF are censored for HFpEF, patients who developed HFpEF are censored for HFrEF, and patients who did not develop HF are censored for both subtypes. Using this dataset, a Cox proportional hazards model for incident HF (i.e. the 'status' variable) was derived, including an interaction term of CRP (in mg/L) with HF subtype (i.e. the 'failure type' variable) and the main selection of potential confounders. If the interaction term of CRP with HF subtype in this model was significant ($p < 0.05$), this would have indicated that the association between CRP and HFrEF was significantly different from the association between CRP and HFpEF.

Competing risk analysis

To assess the influence of the competing risk of unrelated death (not preceded by HF), a sensitivity analysis was performed in which the association between CRP and incident HF was analyzed using Fine and Gray subdistribution hazard models.[4] In contrast with the primary analysis, not a dichotomous outcome (i.e. HF vs no HF) was entered in the model, but an outcome with three levels: (0) censored (i.e. alive and free of HF at the end of follow-up), (1) HF, and (2) death not preceded by HF. This means patients were only censored if they were alive and free of HF at the end of follow-up, and the competing risk of unrelated death was accounted for. In line with the primary analysis, subdistribution hazard ratios (SHRs) from Fine and Gray models (including the same sets of potential confounders) were derived for every 1 mg/L, and 1 SD increase in CRP, and for CRP quartiles (with CRP >20 mg/L added as a separate group). To support the interpretation and comparison of the cause-specific HRs from the primary analysis and the SHRs from the competing risk analysis, two additional analyses were performed. First, Kaplan-Meier curves were derived showing the cumulative rate of all-cause mortality in the total study population, and the cumulative rates of death preceded by HF (related death) vs death not preceded by HF (unrelated death). In the latter curve all patients were considered at risk of related and unrelated death at the start of follow-up. For death preceded by HF, patients were censored at the time of unrelated death or the end of follow-up. For death not preceded by HF, patients were censored at the time of first HF hospitalization (because after an HF

hospitalization they are no longer at risk of death not preceded by HF) or the end of follow-up. Second, the association between CRP, all-cause death, related vs unrelated death, and various specific causes of death was analyzed using cause-specific Cox proportional hazards models. In the analysis of related death, censoring was applied at the time of unrelated death or the end of follow-up, while in the analysis of unrelated death, censoring was applied at the time of first HF hospitalization or the end of follow-up. In the analyses of specific causes of death, censoring was applied at the time of death due to a different cause or the end of follow-up. All models were adjusted for the main selection of potential confounders, and the association was described using cause-specific HRs for every 1 mg/L increase in CRP.

Table S1. Association between CRP and interim MI

	CRP (mg/L), median (range)	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Main adjustment[a], HR (95% CI)	Additional adjustment[b], HR (95% CI)
Continuous							
Per 1 mg/L	1.90 (0.10-20.0)[c]	549/7,853[c]	0.77	1.04 (1.02-1.07)	1.05 (1.03-1.07)	1.04 (1.02-1.06)	1.03 (1.01-1.06)
Per SD (= 3.49 mg/L)	1.90 (0.10-20.0)[c]	549/7,853[c]	0.77	1.16 (1.08-1.25)	1.17 (1.09-1.26)	1.14 (1.05-1.23)	1.12 (1.04-1.22)
Categorical							
Quartile 1	0.60 (0.10-0.90)	128/2,091	0.67	Ref	Ref	Ref	Ref
Quartile 2	1.40 (0.91-1.90)	113/1,919	0.63	0.94 (0.73-1.21)	0.94 (0.73-1.21)	0.88 (0.68-1.14)	0.85 (0.66-1.10)
Quartile 3	2.74 (1.91-4.00)	140/1,899	0.81	1.19 (0.94-1.52)	1.19 (0.94-1.52)	1.08 (0.84-1.39)	1.04 (0.81-1.34)
Quartile 4	6.64 (4.01-20.0)	168/1,944	1.00	1.48 (1.18-1.86)	1.52 (1.21-1.92)	1.34 (1.04-1.72)	1.26 (0.98-1.62)
>20 mg/L	31.9 (20.1-247.4)	17/236	0.89	1.32 (0.80-2.19)	1.30 (0.78-2.15)	1.16 (0.70-1.94)	1.09 (0.65-1.83)

Hazard ratios (95% CI) for the association between CRP and interim MI. As CRP concentrations above 20 mg/L are usually thought to be associated with an acute inflammatory response, patients with CRP >20 mg/L (n = 236) were analyzed separately, i.e. they were excluded from the continuous analysis and analyzed as a separate subgroup in the categorical analysis. No corrections for multiple testing were applied.

[a] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

[b] Main adjustment + alcohol consumption (units/week), HDL-c, triglycerides, use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort.

[c] Only patients with CRP ≤20 mg/L (n = 7,853) were included in the continuous analysis. As CRP concentrations above 20 mg/L are usually thought to be associated with an acute inflammatory response, these patients (n = 236) were excluded from the continuous analysis.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Table S2. Association between interim MI and incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Main adjustment[a], HR (95% CI)	Additional adjustment[b], HR (95% CI)
Interim MI						
No	658/7,853[c]	0.87	Ref	Ref	Ref	Ref
Yes	110/549	3.51	2.94 (2.39-3.62)	3.01 (2.45-3.70)	2.75 (2.24-3.39)	2.81 (2.28-3.47)

Hazard ratios (95% CI) for the association between interim MI and incident HF in patients with CRP ≤20 mg/L. Interim MI was analyzed as a time-varying covariate, i.e. patients who had an interim MI were analyzed in the group without an interim MI until they had the interim event, after which they were moved to the group with an interim MI for the remainder of follow-up. No corrections for multiple testing were applied.

[a] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

[b] Main adjustment + alcohol consumption (units/week), HDL-c, triglycerides, use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort.

[c] This group includes all patients (n = 7,853) because interim MI is analyzed as a time-varying covariate. At the start of follow-up no patient has an interim MI, and therefore all patients are first included in the group without an interim MI. As soon as patients have an interim MI, they are moved to the group with an interim MI and stay in this group for the remainder of follow-up.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, Ref = reference.

Table S3. Association between CRP and incident HF adjusted for interim MI

	CRP (mg/L), median (range)	Events/ Patients	Event rate (events/ 100 PY)	Main adjustment[a], HR (95% CI)	Main adjustment[a] + interim MI, HR (95% CI)	Additional adjustment[b], HR (95% CI)	Additional adjustment[b] + interim MI, HR (95% CI)
Continuous							
Per 1 mg/L	1.90 (0.10-20.0)[c]	768/7,853[c]	0.98	1.10 (1.07-1.13)	1.10 (1.07-1.12)	1.10 (1.08-1.13)	1.10 (1.07-1.13)
Per SD (= 3.49 mg/L)	1.90 (0.10-20.0)[c]	768/7,853[c]	0.98	1.39 (1.27-1.53)	1.38 (1.26-1.52)	1.40 (1.29-1.55)	1.39 (1.27-1.54)
Categorical							
Quartile 1	0.60 (0.10-0.90)	118/2,091	0.55	Ref	Ref	Ref	Ref
Quartile 2	1.40 (0.91-1.90)	158/1,919	0.81	1.26 (0.99-1.60)	1.25 (0.98-1.59)	1.29 (1.01-1.64)	1.29 (1.01-1.63)
Quartile 3	2.74 (1.91-4.00)	216/1,899	1.13	1.58 (1.25-1.99)	1.57 (1.24-1.96)	1.60 (1.27-2.02)	1.58 (1.25-1.99)
Quartile 4	6.64 (4.01-20.0)	276/1,944	1.50	2.22 (1.76-2.79)	2.20 (1.74-2.76)	2.30 (1.83-2.89)	2.29 (1.82-2.87)
>20 mg/L	31.9 (20.1-247.4)	42/236	2.08	2.49 (1.74-3.56)	2.46 (1.70-3.52)	2.64 (1.84-3.79)	2.60 (1.78-3.72)

Hazard ratios (95% CI) for the association between CRP and incident HF with and without adjustment for interim MI. Interim MI was analyzed as a time-varying covariate, i.e. patients who had an interim MI were analyzed in the group without an interim MI until they had the interim event, after which they were moved to the group with an interim MI for the remainder of follow-up. As CRP concentrations above 20 mg/L are usually thought to be associated with an acute inflammatory response, patients with CRP >20 mg/L (n = 236) were analyzed separately, i.e. they were excluded from the continuous analysis and analyzed as a separate subgroup in the categorical analysis. No corrections for multiple testing were applied.

[a] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

[b] Main adjustment + alcohol consumption (units/week), HDL-c, triglycerides, use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort.

[c] Only patients with CRP ≤20 mg/L (n = 7,853) were included in the continuous analysis. As CRP concentrations above 20 mg/L are usually thought to be associated with an acute inflammatory response, these patients (n = 236) were excluded from the continuous analysis.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Table S4. Subdistribution hazard ratios for the association between CRP and incident HF in competing risk-adjusted models

	CRP (mg/L), median (range)	HF events	Competing events[a]	Unadjusted, SHR (95% CI)	Adjusted for age and sex, SHR (95% CI)	Main adjustment[b], SHR (95% CI)	Additional adjustment[c], SHR (95% CI)
Continuous							
Per 1 mg/L	1.90 (0.10-20.0)[d]	768	1,497	1.11 (1.08-1.14)	1.10 (1.07-1.13)	1.08 (1.05-1.11)	1.08 (1.06-1.11)
Per SD (= 3.49 mg/L)	1.90 (0.10-20.0)[d]	768	1,497	1.44 (1.31-1.58)	1.39 (1.26-1.53)	1.31 (1.18-1.43)	1.32 (1.19-1.45)
Categorical							
Quartile 1	0.60 (0.10-0.90)	118	223	Ref	Ref	Ref	Ref
Quartile 2	1.40 (0.91-1.90)	158	306	1.38 (1.09-1.75)	1.30 (1.03-1.65)	1.24 (0.98-1.58)	1.26 (0.99-1.61)
Quartile 3	2.74 (1.91-4.00)	216	412	1.82 (1.46-2.28)	1.66 (1.33-2.08)	1.50 (1.19-1.89)	1.53 (1.22-1.93)
Quartile 4	6.64 (4.01-20.0)	276	556	2.28 (1.84-2.83)	2.09 (1.69-2.60)	1.88 (1.49-2.36)	1.93 (1.53-2.43)
>20 mg/L	31.9 (20.1-247.4)	42	87	2.96 (2.06-4.24)	2.30 (1.59-3.32)	1.98 (1.36-2.89)	2.07 (1.41-3.04)

Subdistribution hazard ratios (95% CI) for the association between CRP and incident HF derived from Fine and Gray models adjusted for the competing risk of death from any cause (not preceded by HF). No corrections for multiple testing were applied.

[a] Death from any cause, not preceded by HF.

[b] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

[c] Main adjustment + alcohol consumption (units/week), HDL-c, triglycerides, use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort.

[d] Only patients with CRP ≤20 mg/L (n = 7,853) were included in the continuous analysis. As CRP concentrations above 20 mg/L are often assumed to be associated with an acute inflammatory response, these patients (n = 236) were analyzed as a separate group.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, SHR = subdistribution hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Table S5. Association between CRP and death

Cause of death	Events	HR per 1 mg/L[a] (95% CI)
All-cause mortality	**1,874**	**1.10 (1.08-1.13)**
Preceded by HF	377	1.17 (1.12-1.22)
Not preceded by HF	1,497	1.10 (1.07-1.12)
Cardiovascular mortality	**863**	**1.11 (1.08-1.15)**
Myocardial infarction	46	1.12 (0.98-1.27)
Stroke	116	1.03 (0.95-1.13)
Sudden cardiac death	270	1.12 (1.06-1.18)
Heart failure	124	1.14 (1.06-1.24)
AAA rupture	25	1.03 (0.85-1.25)
Other CVD death	282	1.14 (1.08-1.20)
Non-cardiovascular mortality	**877**	**1.10 (1.07-1.13)**
Cancer	564	1.08 (1.04-1.12)
Infection	116	1.15 (1.06-1.24)
Unnatural	34	1.10 (0.95-1.27)
Other non-CVD death	163	1.12 (1.04-1.20)
Unclassified	134	1.13 (1.04-1.21)

Cause-specific hazard ratios (95% CI) derived from cause-specific Cox proportional hazards models for the association between CRP and various causes of death in all patients with CRP ≤20 mg/L (n = 7,853). No corrections for multiple testing were applied.

[a] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR (main adjustment).

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, SBP = systolic blood pressure.

Table S6. Reverse causality assessment

	Total population	Exclude events <1 year	Exclude events <2 years	Exclude events <5 years	Exclude events <10 years	Exclude events <15 years
Events/Patients	768/7,853	715/7,800	673/7,758	554/7,639	338/7,423	128/7,213
HR (95% CI) per 1 mg/L CRP	1.10 (1.07-1.13)	1.09 (1.06-1.12)	1.10 (1.07-1.14)	1.11 (1.07-1.15)	1.12 (1.07-1.17)	1.15 (1.07-1.24)
HR (95% CI) per SD (= 3.49 mg/L)	1.39 (1.27-1.53)	1.36 (1.24-1.49)	1.39 (1.25-1.58)	1.43 (1.26-1.62)	1.48 (1.26-1.73)	1.63 (1.27-2.11)

Hazard ratios per 1 mg/L and per SD CRP in the total population (i.e. all patients with CRP ≤20 mg/L), and after excluding patients who had incident HF within the first 1, 2, 5, 10, and 15 years after inclusion. Hazard ratios were adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR. No corrections for multiple testing were applied.
Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease.

Table S7. Potential effect modifiers in the association between CRP and incident HF

	Events/ Patients	Event rate (events/ 100 PY)	HR per 1 mg/L CRP (95% CI)	p-value for interaction
Age				0.411
<50 years	48/1,257	0.33	1.16 (1.08-1.26)	
50-59 years	163/2,374	0.62	1.10 (1.04-1.17)	
60-69 years	305/2,687	1.20	1.10 (1.05-1.16)	
≥70 years	252/1,535	2.09	1.10 (1.05-1.16)	
Sex				0.140
Male	598/5,793	1.04	1.10 (1.06-1.14)	
Female	170/2,060	0.81	1.09 (1.03-1.16)	
CVD location				0.451
CAD with MI	208/1,956	1.09	1.07 (1.02-1.12)	
CAD without MI	160/1,953	0.78	1.12 (1.06-1.19)	
CeVD	92/1,721	0.53	1.07 (1.00-1.15)	
PAD or AAA	114/1,138	0.94	1.12 (1.05-1.20)	
Polyvascular	194/1,085	2.10	1.10 (1.05-1.16)	
Smoking				0.871
Never	148/1,758	0.87	1.11 (1.05-1.18)	
Former	396/3,706	1.08	1.10 (1.05-1.15)	
Current	224/2,389	0.90	1.10 (1.04-1.16)	
Diabetes mellitus				0.217
No	551/6,532	0.83	1.11 (1.07-1.15)	
Yes	217/1,321	1.80	1.07 (1.01-1.13)	
Body-mass index				0.586
<25 kg/m^2	213/2,615	0.82	1.08 (1.02-1.14)	
25-30 kg/m^2	375/3,761	0.98	1.10 (1.05-1.15)	
≥30 kg/m^2	180/1,477	1.28	1.12 (1.06-1.19)	
Statin				0.256
No	262/2,467	0.97	1.11 (1.06-1.17)	
Yes	506/5,386	0.98	1.09 (1.05-1.14)	
Antiplatelet therapy				0.521
No	197/1,749	1.05	1.11 (1.05-1.17)	
Yes	571/6,104	0.96	1.09 (1.05-1.13)	
Antihypertensive therapy				0.439
No	152/1,983	0.71	1.10 (1.04-1.16)	
Yes	616/5,870	1.08	1.10 (1.06-1.14)	

Hazard ratios (95% CI) for the association between CRP and incident HF in subgroups of age, sex, and CVD location. Hazard ratios were adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR (where appropriate). P-values for the interaction between CRP and the potential effect modifiers are provided. No corrections for multiple testing were applied. Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, SD = standard deviation.

Table S8. Association between white blood cell counts and incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Main adjustment[a], HR (95% CI)	Additional adjustment[b], HR (95% CI)
Total WBC count						
Per SD (= 1.97×10^9/L)	330/4,152[c]	0.90	1.12 (1.01-1.24)	1.21 (1.09-1.35)	1.09 (0.97-1.23)	1.08 (0.96-1.22)
Quartile 1	70/1,039	0.73	Ref	Ref	Ref	Ref
Quartile 2	74/1,044	0.80	1.11 (0.80-1.54)	1.04 (0.75-1.44)	0.90 (0.65-1.25)	0.89 (0.64-1.24)
Quartile 3	92/1,035	1.02	1.43 (1.05-1.95)	1.40 (1.02-1.90)	1.09 (0.79-1.50)	1.06 (0.77-1.46)
Quartile 4	95/1,037	1.08	1.54 (1.13-2.10)	1.74 (1.27-2.37)	1.28 (0.92-1.77)	1.25 (0.90-1.74)
Neutrophil count						
Per SD (= 1.51×10^9/L)	330/4,152[c]	0.90	1.17 (1.06-1.29)	1.22 (1.10-1.35)	1.13 (1.01-1.27)	1.12 (1.00-1.26)
Quartile 1	65/1,048	0.67	Ref	Ref	Ref	Ref
Quartile 2	71/1,033	0.77	1.15 (0.82-1.61)	1.09 (0.78-1.53)	0.99 (0.70-1.39)	0.99 (0.71-1.40)
Quartile 3	92/1,035	1.02	1.55 (1.13-2.13)	1.38 (1.01-1.90)	1.13 (0.82-1.55)	1.13 (0.81-1.56)
Quartile 4	103/1,038	1.17	1.79 (1.31-2.44)	1.80 (1.32-2.46)	1.36 (0.99-1.88)	1.37 (0.99-1.90)
Lymphocyte count						
Per SD (= 0.69×10^9/L)	330/4,147[c]	0.90	0.82 (0.72-0.92)	0.98 (0.86-1.10)	0.88 (0.77-0.99)	0.86 (0.76-0.98)
Quartile 1	103/1,039	1.14	Ref	Ref	Ref	Ref
Quartile 2	77/1,055	0.82	0.72 (0.53-0.96)	0.86 (0.64-1.15)	0.81 (0.60-1.10)	0.80 (0.59-1.07)
Quartile 3	81/1,022	0.88	0.77 (0.57-1.02)	1.02 (0.76-1.37)	0.86 (0.64-1.16)	0.84 (0.62-1.13)
Quartile 4	70/1,035	0.77	0.68 (0.50-0.92)	1.08 (0.79-1.47)	0.88 (0.64-1.21)	0.84 (0.61-1.16)
Neutrophil-lymphocyte ratio						
Per SD (= 0.97)	330/4,136[c]	0.90	1.35 (1.23-1.47)	1.21 (1.10-1.32)	1.18 (1.08-1.30)	1.19 (1.09-1.31)
Quartile 1	55/1,038	0.58	Ref	Ref	Ref	Ref
Quartile 2	71/1,038	0.76	1.32 (0.93-1.87)	1.22 (0.86-1.73)	1.11 (0.78-1.58)	1.13 (0.79-1.61)
Quartile 3	93/1,037	1.01	1.77 (1.27-2.47)	1.47 (1.05-2.06)	1.40 (1.00-1.96)	1.44 (1.03-2.01)
Quartile 4	112/1,037	1.28	2.26 (1.64-3.12)	1.66 (1.20-2.31)	1.52 (1.09-2.12)	1.56 (1.12-2.18)

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Main adjustment[a], HR (95% CI)	Additional adjustment[b], HR (95% CI)
Monocyte count						
Per SD (= 0.19×10^9/L)	331/4,152[c]	0.90	1.28 (1.16-1.40)	1.22 (1.10-1.35)	1.16 (1.04-1.29)	1.15 (1.03-1.28)
Quartile 1	61/1,075	0.61	Ref	Ref	Ref	Ref
Quartile 2	81/1,010	0.89	1.50 (1.08-2.09)	1.32 (0.95-1.84)	1.26 (0.90-1.77)	1.25 (0.89-1.75)
Quartile 3	82/1,004	0.93	1.58 (1.14-2.20)	1.38 (0.99-1.93)	1.20 (0.86-1.68)	1.19 (0.85-1.67)
Quartile 4	107/1,065	1.20	2.09 (1.52-2.86)	1.75 (1.27-2.41)	1.46 (1.06-2.03)	1.43 (1.03-1.99)

Cause-specific hazard ratios (95% CI) for the association between white blood cell counts and incident HF derived from cause-specific Cox proportional hazards models. White blood cell counts were not part of the standard baseline screening. Data presented are based on the 4,155 patients for whom WBC counts were available. No corrections for multiple testing were applied.
Quartiles, median (range): Total WBC count (×10^9/L): Quartile 1, 4.9 (1.4-5.5); Quartile 2, 6.1 (5.5-6.6); Quartile 3, 7.2 (6.6-7.9); Quartile 4, 9.0 (7.9-40.1); Neutrophil count (×10^9/L): Quartile 1, 2.6 (0.8-3.0); Quartile 2, 3.4 (3.0-3.8); Quartile 3, 4.2 (3.8-4.7); Quartile 4, 5.6 (4.7-26.1); Lymphocyte count (×10^9/L): Quartile 1, 1.3 (0.4-1.5); Quartile 2, 1.7 (1.5-1.9); Quartile 3, 2.1 (1.9-2.4); Quartile 4, 2.8 (2.4-35.2); Neutrophil-lymphocyte ratio: Quartile 1, 1.2 (0.1-1.5); Quartile 2, 1.7 (1.5-2.0); Quartile 3, 2.3 (2.0-2.6); Quartile 4, 3.2 (2.6-16.0); Monocyte count (×10^9/L): Quartile 1, 0.38 (0.08-0.44); Quartile 2, 0.50 (0.45-0.54); Quartile 3, 0.60 (0.55-0.66); Quartile 4, 0.77 (0.67-2.73).
[a] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.
[b] Main adjustment + alcohol consumption (units/week), HDL-c, triglycerides, use of statins, antiplatelet therapy, and antihypertensive agents, and year of inclusion in the cohort.
[c] Patients with missing values (for total WBC count, n = 0; neutrophil count, n = 1; lymphocyte count, n = 4; NLR, n = 5; monocyte count, n = 1) were excluded. In the continuous analysis, additionally patients with very high values (total WBC count >20×10^9/L, n = 3; neutrophil count >15×10^9/L, n = 2; lymphocyte count >8×10^9/L, n = 4; NLR >8, n = 14; monocyte count >2×10^9/L, n = 2) were excluded to reduce the effects of outliers.
Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, NLR = neutrophil-lymphocyte ratio, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation, WBC = white blood cell.

Table S9. Independent associations of CRP and white blood cell counts with incident HF

	Events/ Patients	Main adjustment[a], HR (95% CI)	Main adjustment[a] + CRP, HR (95% CI)	Main adjustment[a] + NLR, HR (95% CI)
C-reactive protein (per SD = 3.36 mg/L)	317/4,055[b]	1.30 (1.18-1.43)	-	1.26 (1.14-1.39)
Total WBC count (per SD = 1.97×10^9/L)	330/4,152[c]	1.09 (0.97-1.23)	1.07 (0.95-1.20)	-
Neutrophil count (per SD = 1.51×10^9/L)	330/4,152[c]	1.13 (1.01-1.27)	1.10 (0.98-1.24)	-
Lymphocyte count (per SD = 0.69×10^9/L)	330/4,147[c]	0.88 (0.77-0.99)	0.88 (0.78-1.00)	-
Neutrophil-lymphocyte ratio (per SD = 0.97)	330/4,136[c]	1.18 (1.08-1.30)	1.16 (1.05-1.28)	-
Monocyte count (per SD = 0.19×10^9/L)	331/4,152[c]	1.16 (1.04-1.29)	1.13 (1.02-1.26)	-

Cause-specific hazard ratios (95% CI) derived from cause-specific Cox proportional hazards models for the association between CRP and incident HF adjusted for neutrophil-lymphocyte ratio (NLR), and for the association between white blood cell counts and incident HF adjusted for CRP. White blood cell counts were not part of the standard baseline screening. Data presented are based on the 4,155 patients for whom WBC counts were available. No corrections for multiple testing were applied.

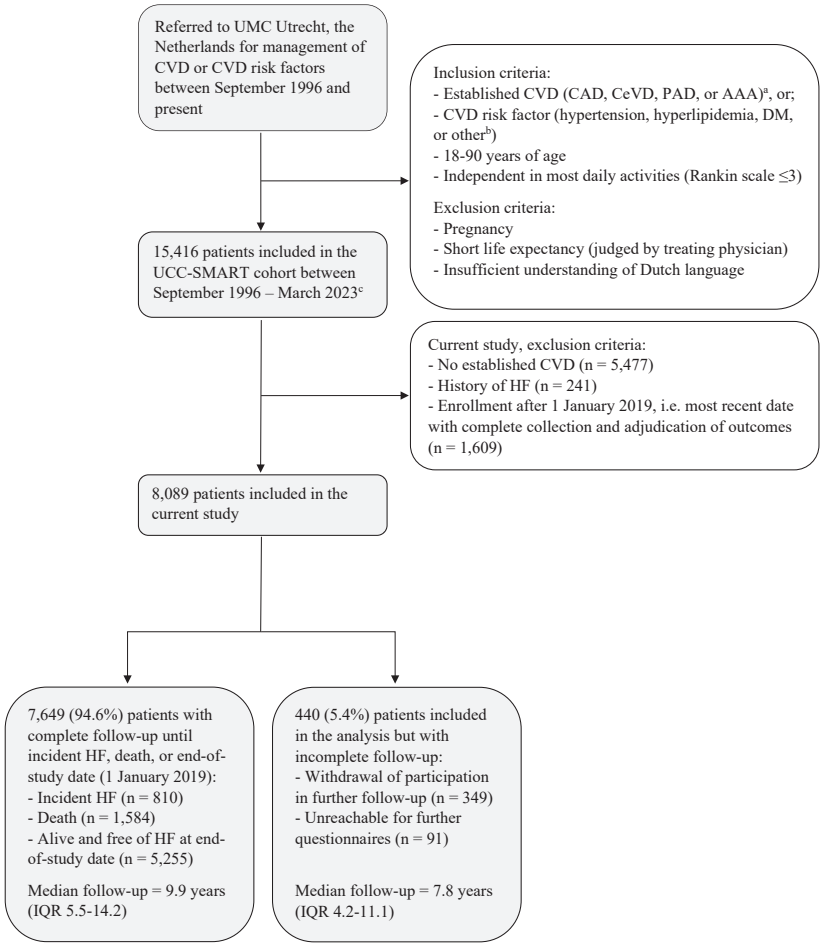
[a] Adjusted for age, sex, CAD with prior MI, CAD without prior MI, CeVD, PAD, AAA, smoking, diabetes mellitus, BMI, SBP, non-HDL-c, and eGFR.

[b] The analysis was limited to patients with available WBC counts to allow adjustment for NLR. Patients with CRP >20 mg/L (n = 100) were excluded.

[c] Patients with missing values (for total WBC count, n = 0; neutrophil count, n = 1; lymphocyte count, n = 4; NLR, n = 5; monocyte count, n = 1) were excluded. In addition, patients with very high values (total WBC count $>20\times10^9$/L, n = 3; neutrophil count $>15\times10^9$/L, n = 2; lymphocyte count $>8\times10^9$/L, n = 4; NLR >8, n = 14; monocyte count $>2\times10^9$/L, n = 2) were excluded to reduce the effects of outliers.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, NLR = neutrophil-lymphocyte ratio, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation, WBC = white blood cell.

Figure S1. Flowchart of study enrollment



Flowchart of enrollment in the UCC-SMART cohort, and the current study. A detailed description of the UCC-SMART study and its protocol has been published elsewhere.[5]

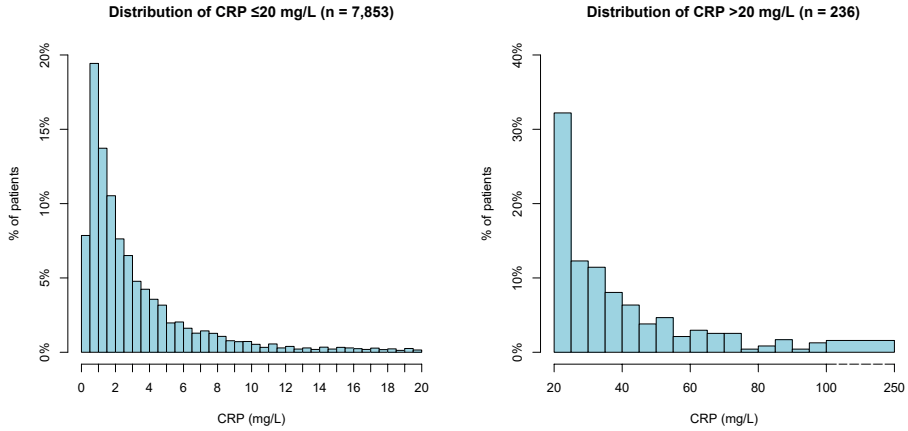
[a] Established CVD was defined as a history of myocardial infarction, coronary revascularization (PCI or CABG), cerebral infarction, transient ischemic attack, subarachnoid hemorrhage, peripheral artery disease of the lower limbs (Fontaine II-IV), prior percutaneous transluminal angioplasty or bypass surgery of the leg, amputation, abdominal aortic aneurysm (anterior-posterior diameter ≥3 cm), or abdominal aortic surgery.

[b] Other qualifying CVD risk factors are renal insufficiency, HIV infection, family history of CVD, and hypertensive pregnancy complications.

[c] UCC-SMART is an ongoing cohort study, with continuous follow-up, and without a prespecified end date. The number of patients included in the cohort between September 1996 (start of the study) and 1 March 2023 is presented.

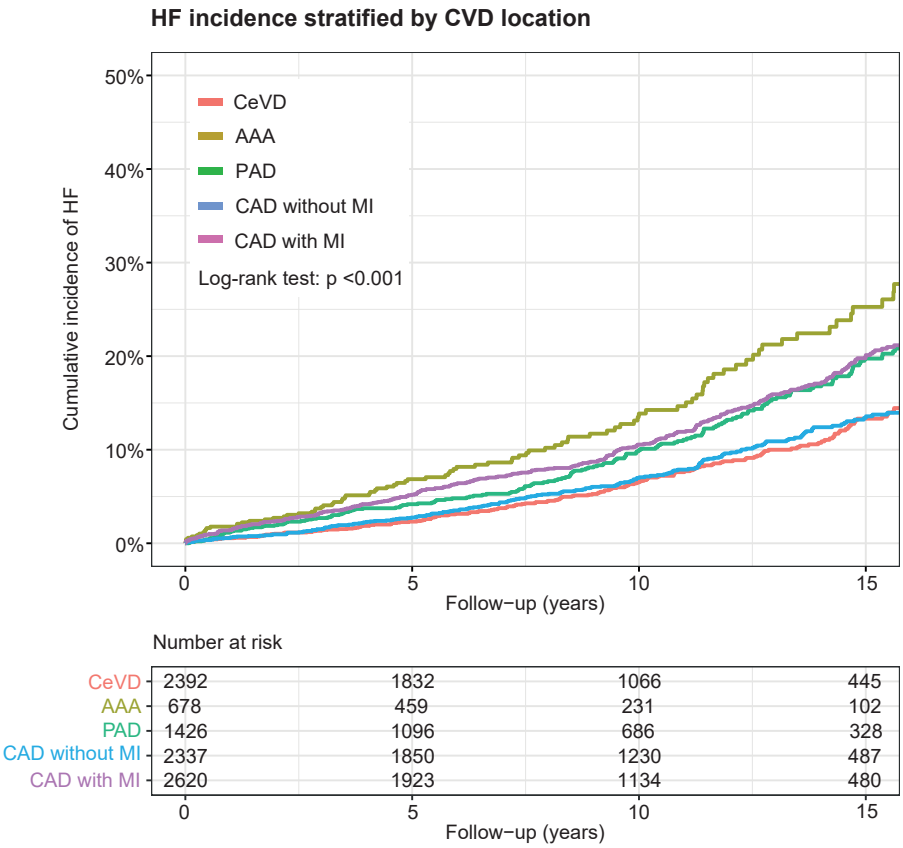
Abbreviations: AAA = abdominal aortic aneurysm, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CeVD = cerebrovascular disease, CVD = cardiovascular disease, DM = diabetes mellitus, HF = heart failure, HIV = human immunodeficiency virus, IQR = interquartile range, PAD = peripheral artery disease, PCI = percutaneous coronary intervention, UCC-SMART = Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease.

Figure S2. Distribution of CRP in the study population



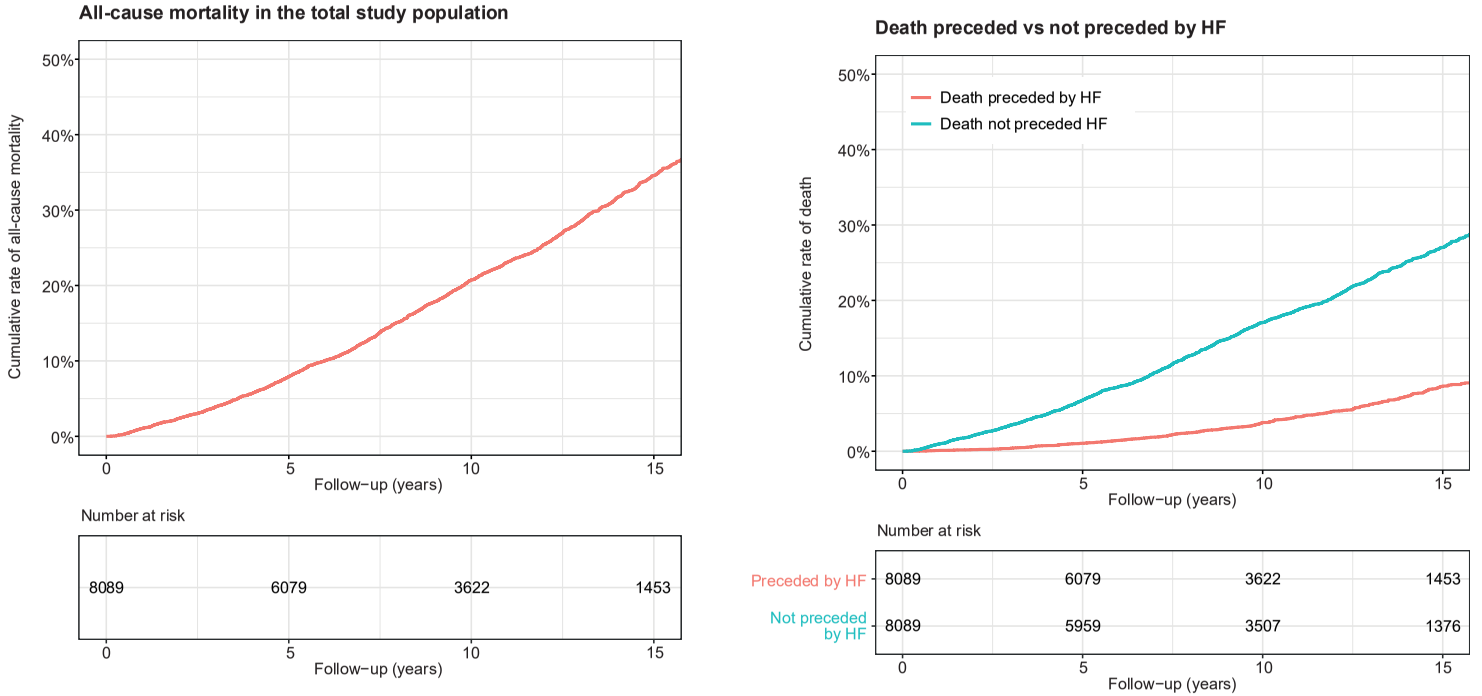
Distribution of CRP in patients with CRP ≤20 mg/L (A), and CRP >20 mg/L (B).
Abbreviations: CRP = C-reactive protein.

Figure S3. Kaplan-Meier curve of the incidence of HF stratified by CVD location



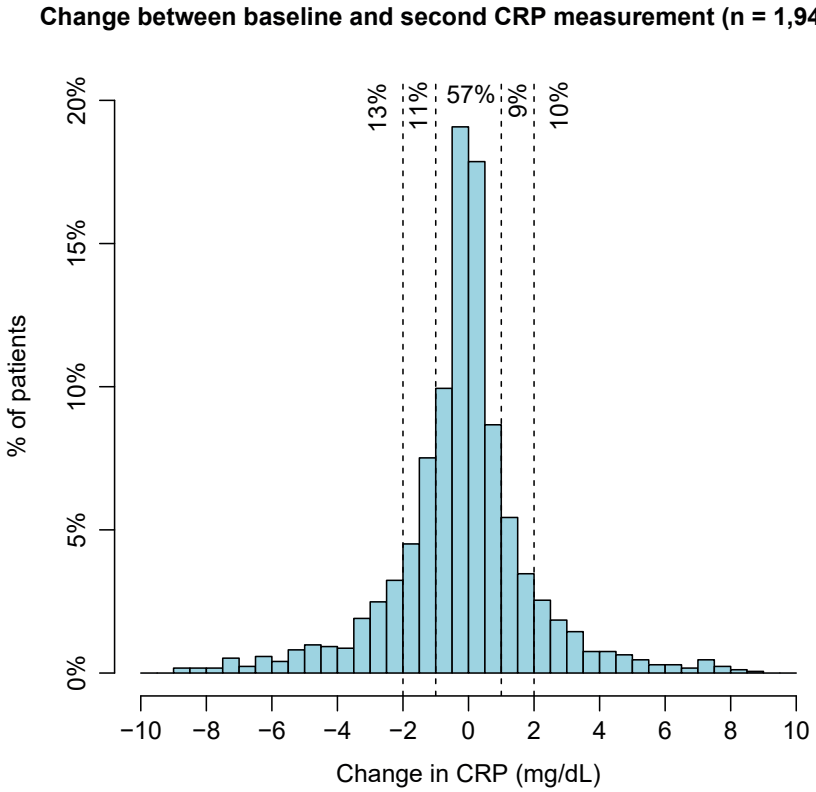
Cumulative incidence of HF hospitalization stratified by CVD location. The subgroups are non-exclusive, i.e. patients with multiple CVD locations are included in all applicable subgroups.
Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CVD = cardiovascular disease, HF = heart failure, MI = myocardial infarction, PAD = peripheral artery disease.

Figure S4. Kaplan-Meier curves of the cumulative rates of death



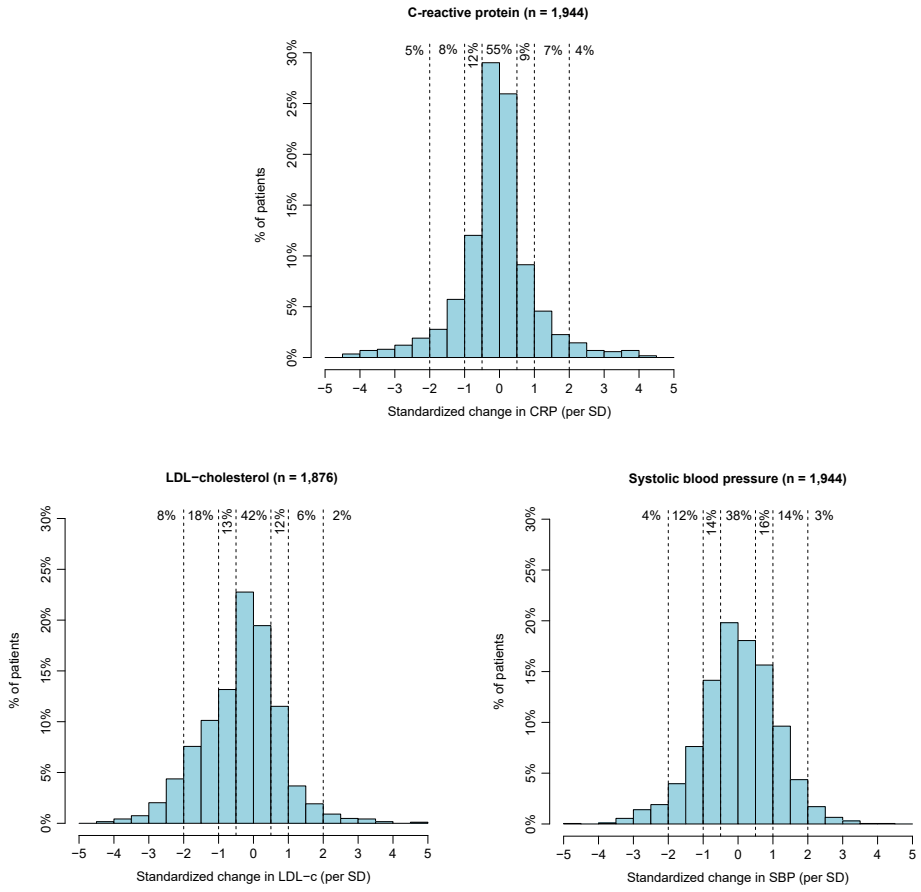
Kaplan-Meier curves of the cumulative rate of all-cause mortality (A), and the cumulative rates of death preceded and not preceded by HF (B) in the total study population (n = 8,089). The numbers at risk during follow-up are lower for death not preceded by HF, as patients who are hospitalized for HF are no longer at risk of death not preceded by HF, and are censored for this outcome at the time of the HF hospitalization.
Abbreviations: HF = heart failure.

Figure S5. Distribution of the change between baseline and second CRP measurement



Histogram showing the distribution of the change in CRP concentration between the baseline and second measurement in the subset of patients (n = 1,944) who revisited for second measurements a median of 10.0 years (IQR 8.6-10.8) after the baseline screening.
Abbreviations: CRP = C-reactive protein, IQR = interquartile range.

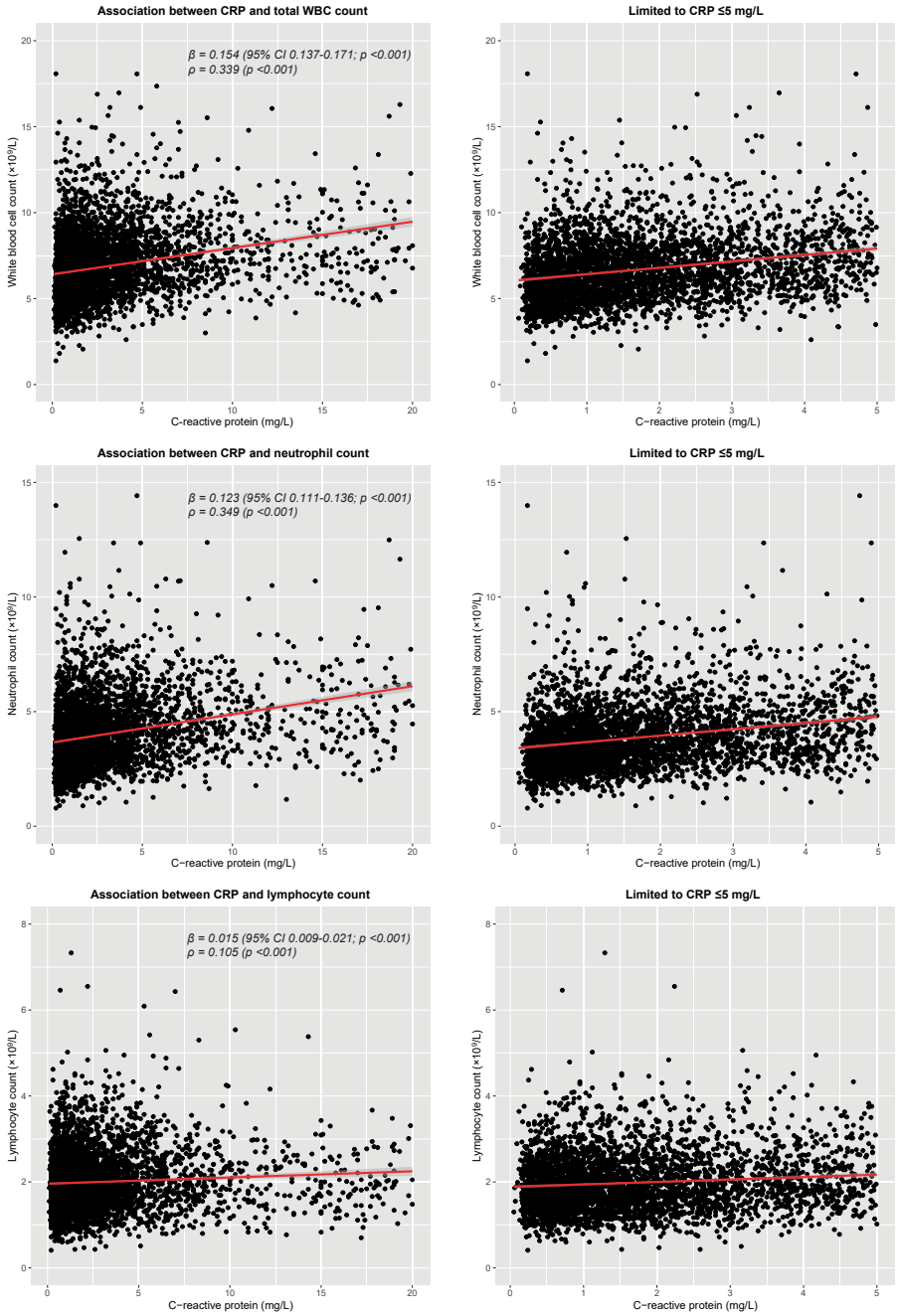
Figure S6. Standardized change over time in CRP vs LDL-c and SBP

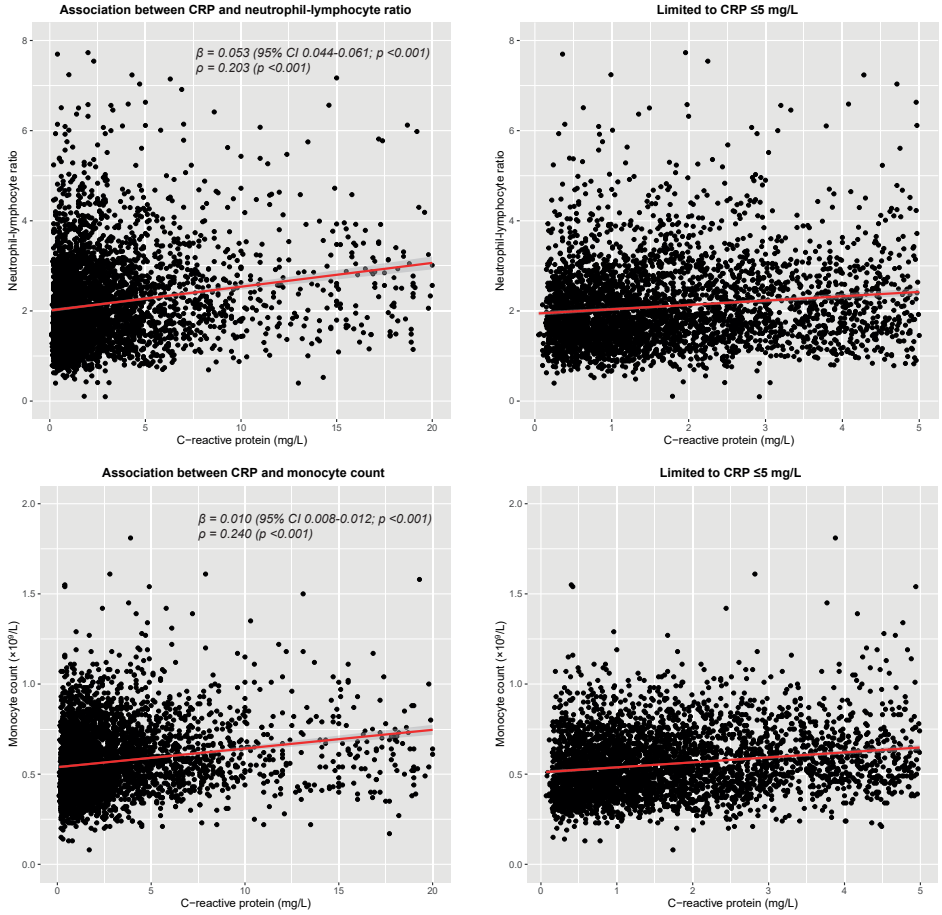


Histograms showing the distribution of the standardized change (i.e. change divided by the SD of the baseline measurement) between the baseline and second measurement of CRP, LDL-c, and SBP, in the subset of patients (n = 1,944) who revisited for second measurements a median of 10.0 years (IQR 8.6-10.8) after the baseline screening. LDL-c, at baseline or second visit, was not available for 68 patients, so for LDL-c the analysis was limited to the 1,876 patients with available measurements at both time points.

Abbreviations: CRP = C-reactive protein, IQR = interquartile range, LDL-c = low-density lipoprotein cholesterol, SBP = systolic blood pressure, SD = standard deviation.

Figure S7. Association between CRP and white blood cell counts





Scatterplots of the association between CRP and total WBC count, differential WBC counts, and neutrophil-lymphocyte ratio (NLR) in patients with available WBC counts (n = 4,155). The β represents the increase in WBC count/NLR for every 1 mg/L increase in CRP, i.e. the beta coefficient derived from a linear model regressing WBC count/NLR on CRP. The red line represents the regression line derived from this same model.
The ρ is the Spearman's correlation coefficient for the correlation between WBC count/NLR and CRP. For viewing purposes, all plots are also shown for CRP ≤5 mg/L.
Abbreviations: CRP = C-reactive protein, NLR = neutrophil-lymphocyte ratio, WBC = white blood cell.

Supplemental References

1. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation*. 2016;133(6):601-609. doi:10.1161/CIRCULATIONAHA.115.017719
2. Ridker PM, Cook N. Clinical Usefulness of Very High and Very Low Levels of C-Reactive Protein Across the Full Range of Framingham Risk Scores. *Circulation*. 2004;109(16):1955-1959. doi:10.1161/01.CIR.0000125690.80303.A8
3. Lunn M, McNeil D. Applying Cox Regression to Competing Risks. *Biometrics*. 1995;51(2):524-532. doi:10.2307/2532940
4. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144
5. Castelijns MC, Helmink MAG, Hageman SHJ, et al. Cohort profile: the Utrecht Cardiovascular Cohort–Second Manifestations of Arterial Disease (UCC-SMART) Study–an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands. *BMJ Open*. 2023;13(2):e066952. doi:10.1136/bmjopen-2022-066952

Chapter 3.1.

Reply: C-reactive protein and heart failure in patients with established cardiovascular disease: evidence from the UK Biobank

Pascal M. Burger, Frank L.J. Visseren, Jannick A.N. Dorresteijn

J Am Coll Cardiol. 2023;82(20):e193.

We appreciate the interest of Dr Morze and Dr Rynkiewicz in our paper, and read with great interest their letter including the results of a replication analysis in the UK Biobank.[1,2] The results of this analysis largely confirm our findings in the UCC-SMART cohort. Among patients with a history of cardiovascular disease (CVD) in the UK Biobank, as in our study, higher C-reactive protein (CRP) was independently associated with an increased risk of incident heart failure (HF), and the analysis with CRP quartiles showed a clear dose-response relationship. This means that now two independent studies, comprising of 35,233 participants and 4,941 HF cases, have shown that CRP is an independent risk marker of incident HF in patients with established CVD. This supports the involvement of systemic inflammation in HF pathogenesis, and the potential for anti-inflammatory therapies to prevent HF in these patients.

The modest difference in effect sizes between the two cohorts may have several explanations. As suggested, it may be related to differences in participant selection. The UK Biobank is a community-based cohort in the UK in which CVD patients were selected based on a prior hospitalization for CVD, whereas UCC-SMART is a referral-based cohort in the Netherlands selecting patients based on a clinical diagnosis of CVD. This may have led to differences in patient characteristics, such as type and severity of CVD, that could modify the association between CRP and HF, although we found no evidence of effect modification by these and other factors in our study.[1] Secondly, it may be attributed to the assay used to measure CRP (analyzer type, high-sensitive vs standard assay), the timing of the measurement (chronic phase and stable on medication, or more acute setting), or the fact that the boundaries of the CRP quartiles were lower in the UK Biobank. Also, there were some differences in the factors adjusted for in the analyses, e.g. CVD location and ethnicity. Finally, there may be differences in the threshold for HF hospitalization, or the registration of ICD codes between the Netherlands and the UK. Future studies could replicate the analyses in other populations, and assess factors related to a stronger or weaker association of CRP with incident HF.

References

1. Burger PM, Koudstaal S, Mosterd A, et al. C-Reactive Protein and Risk of Incident Heart Failure in Patients With Cardiovascular Disease. *J Am Coll Cardiol*. 2023;82(5):414-426. doi:10.1016/j.jacc.2023.05.035
2. Morze J, Rynkiewicz A. C-Reactive Protein and Heart Failure in Patients with Established Cardiovascular Disease: Evidence from the UK Biobank. *J Am Coll Cardiol*. 2023;82(20):e191-e192. doi:10.1016/j.jacc.2023.08.052

Chapter 4.

Metabolic syndrome and risk of incident heart failure in non-diabetic patients with established cardiovascular disease

Pascal M. Burger, Stefan Koudstaal, Jannick A.N. Dorresteijn, Gianluigi Savarese, Manon G. van der Meer, Gert J. de Borst, Arend Mosterd, Frank L.J. Visseren, on behalf of the UCC-SMART study group

Int J Cardiol. 2023;379:66-75.

Abstract

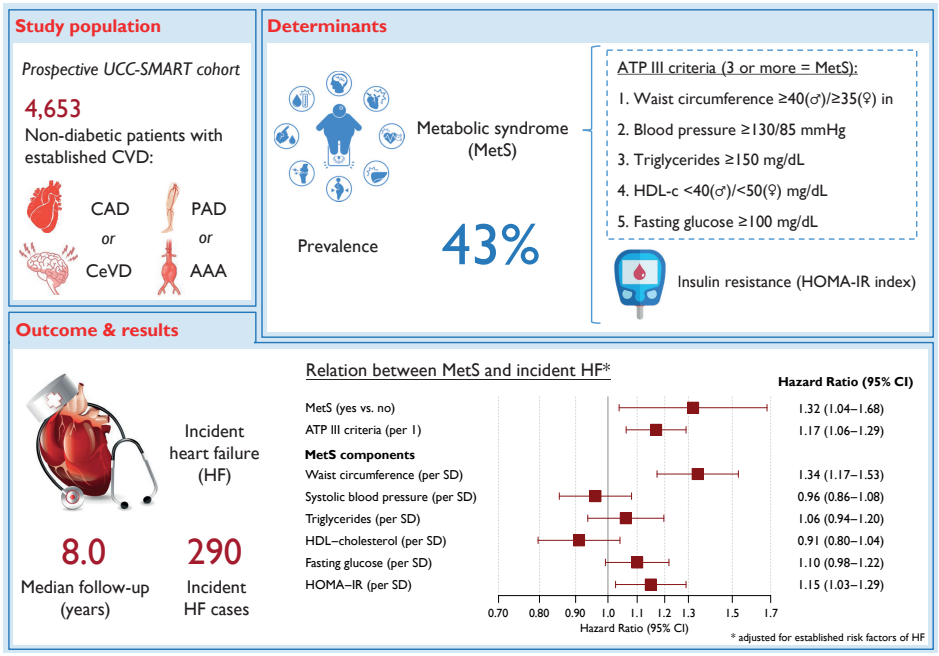
Background
In patients with established cardiovascular disease (CVD), the relation between metabolic syndrome (MetS) and incident heart failure (HF) in the absence of diabetes mellitus (DM) is largely unknown. This study assessed this relation in non-diabetic patients with established CVD.

Methods
Patients from the prospective UCC-SMART cohort with established CVD, but without DM or HF at baseline were included (n = 4,653). MetS was defined according to the Adult Treatment Panel III criteria. Insulin resistance was quantified using the homeostasis model of insulin resistance (HOMA-IR). The outcome was a first hospitalization for HF. Relations were assessed using Cox proportional hazards models adjusted for established risk factors: age, sex, prior myocardial infarction (MI), smoking, cholesterol, and kidney function.

Results
During a median follow-up of 8.0 years, 290 cases of incident HF were observed (0.81/100 person years). MetS was significantly related to an increased risk of incident HF independent of established risk factors (hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.04-1.68, HR per criterion 1.17; 95% CI 1.06-1.29), as was HOMA-IR (HR per standard deviation [SD] 1.15; 95% CI 1.03-1.29). Of the individual MetS components, only higher waist circumference independently increased the risk of HF (HR per SD 1.34; 95% CI 1.17-1.53). Relations were independent of the occurrence of interim DM and MI, and were not significantly different for HF with reduced vs preserved ejection fraction.

Conclusion
In CVD patients without a current diagnosis of DM, MetS and insulin resistance increase the risk of incident HF independent of established risk factors.

Graphical abstract



Introduction

Obesity is an increasing global health issue, with nearly a third of the world's population now classified as overweight or obese.[1] At the same time, there has been an emerging heart failure (HF) epidemic. The current worldwide prevalence of HF in the general adult population is estimated to be 1-2%.[2] The rising number of patients with HF is thought to be related to the growing burden of obesity-related diseases. Several factors have been identified as potential links between obesity and HF. Diabetes mellitus (DM) is an established and widely recognized risk factor of incident HF.[3] But in individuals without DM, other less commonly appreciated metabolic risk factors such as abdominal obesity, hypertension, lipid disturbances, and impaired glucose metabolism (clustered as part of the metabolic syndrome [MetS]) might also contribute to an elevated risk of HF.[4]

MetS and insulin resistance increase the risk of incident HF in apparently healthy people and individuals with DM.[5–13] In non-diabetic patients with established cardiovascular disease (CVD), i.e. coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral artery disease (PAD), or abdominal aortic aneurysm (AAA), metabolic risk factors have been shown to be strongly related to atherosclerotic CVD events, but their relation with incident HF is largely unknown.[14,15] This while the incidence of HF in these patients is considerably higher than in the general population, and interventions targeting (components of) the MetS may therefore be more (cost-)effective.[16,17] Establishing the relation between metabolic risk factors and incident HF in patients with established CVD may reveal potential treatment targets to reduce the incidence of HF in this high-risk population.

This study aimed to determine the relation between MetS (and its components), insulin resistance, and the risk of incident HF in CVD patients without a current diagnosis of DM.

Methods

Study population

Patients were from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) study, an ongoing prospective cohort study of patients with established CVD at the University Medical Centre Utrecht, the Netherlands. A detailed description of the study protocol has been published elsewhere.[18] The Medical Ethics Committee approved the study, and all participants gave their written informed consent. For the current study, all patients with established CVD, i.e. CAD (prior myocardial infarction [MI], cardiac arrest, or coronary revascularization), CeVD (prior transient ischemic attack, or ischemic or hemorrhagic stroke), PAD (symptomatic obstruction of

distal arteries of the leg with ankle-brachial index ≤0.90, prior percutaneous transluminal angioplasty or bypass surgery of the leg, or amputation), and/or AAA (prior abdominal aortic surgery or an abdominal aortic anteroposterior diameter of ≥3 cm), without a history of HF, and without DM at baseline (self-reported diagnosis, use of anti-diabetic medication, or fasting glucose ≥126 mg/dL at screening), who were enrolled in the cohort between July 2003 and January 2019 were included (n = 4,653). Patients were enrolled in the cohort at least two months after the qualifying CVD event.

Data collection

Information on medical history, and physical examination and laboratory measurements were obtained at baseline based on a standardized screening protocol.[18] Waist circumference was measured halfway between the lower rib and the iliac crest. Hip circumference was measured at the largest circumference around the buttocks. Visceral and total abdominal fat were measured by ultrasonography. Systolic blood pressure (SBP) was measured twice in both arms, and the highest mean of the measurements in one arm was used. Total cholesterol, high-density lipoprotein cholesterol (HDL-c), triglycerides, creatinine, plasma glucose, and plasma insulin were measured in blood samples collected after an overnight fast. Non-HDL-c was calculated as total cholesterol minus HDL-c. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Smoking and medication use were self-reported. Missing data (<3.0% for all variables) were imputed by single imputation using predictive mean matching.

MetS was defined according to the Adult Treatment Panel (ATP) III criteria.[19] MetS was considered present in patients meeting at least three of the following criteria: waist circumference ≥40 inches (≥102 cm) in men and ≥35 inches (≥88 cm) in women, SBP ≥130 mmHg or DBP ≥85 mmHg, triglycerides ≥150 mg/dL (≥1.7 mmol/L), HDL-c <40 mg/dL (<1.04 mmol/L) in men and <50 mg/dL (<1.29 mmol/L) in women, and fasting glucose ≥100 mg/dL (≥5.6 mmol/L). Patients with a history of hypertension who were currently on antihypertensive drug treatment were considered to meet the criterion for elevated blood pressure.

Insulin resistance was quantified using the homeostasis model of insulin resistance (HOMA-IR): HOMA-IR = fasting glucose (mmol/L) × fasting insulin (mIU/L) / 22.5.[20] HOMA-IR correlates well with more direct, but complicated and expensive measurements of insulin resistance, i.e. the euglycemic clamp technique, and therefore provides a reliable and feasible method for estimating insulin resistance in large epidemiological studies.[21] In a sensitivity analysis, HOMA-IR was replaced by other measures of insulin resistance,

i.e. the quantitative insulin sensitivity check index (QUICKI = 1/(log(insulin [mIU/L] × glucose [mg/dL]))), and the triglyceride-glucose index (TyG = ln(triglycerides [mg/dL] × glucose [mg/dL] / 2)).[22]

Outcomes

The outcome of interest was incident HF, which was defined as a first hospitalization for HF. Outcomes were retrieved through linkage of UCC-SMART data to the national hospitalization registry from Statistics Netherlands. This registry continuously collects causes of hospitalization for all hospitalizations in the Netherlands. Cause of hospitalization is coded using the International Classification of Diseases (ICD), 9th (1995-2012) and 10th revision (2013-present). Hospitalization for HF was defined as any hospitalization with ICD-9 codes 428.0-428.4 or 428.9, or ICD-10 codes I50.1-I50.4 or I50.9. Outcomes were divided in HF with reduced ejection fraction (HFrEF; i.e. left ventricular ejection fraction [LVEF] ≤50%) and preserved ejection fraction (HFpEF; i.e. LVEF >50%), using echocardiography reports retrieved from medical records. MI and DM were assessed as interim outcomes (i.e. outcomes occurring during follow-up but before an HF event). These outcomes were available in the UCC-SMART cohort, and were based on hospital and general practitioner's data, and adjudicated by three independent physicians.

Data analyses

Baseline characteristics were presented stratified by number of MetS criteria, and HOMA-IR quartiles. Kaplan-Meier curves for incident HF were plotted stratified by number of MetS criteria, HOMA-IR quartiles, and CVD location.

Cox proportional hazards models were derived to assess the relation of MetS and HOMA-IR with incident HF. MetS was analyzed as a dichotomous variable (based on the ATP III definition), and in terms of the number of MetS criteria (both categorically and continuously). The relations of HOMA-IR and the individual MetS components with incident HF were analyzed continuously (per SD increase) and in quartiles. HOMA-IR was winsorized at the 1st and 99th percentile to limit the effect of outliers. The models were progressively adjusted for potential confounders. First, models were adjusted for age and sex. Then, models were additionally adjusted for established risk factors of HF, i.e. smoking, non-HDL-c, and eGFR, including CVD locations, i.e. CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA. Finally, to assess whether the effect of one metabolic risk factor on the risk of incident HF was mediated by another, models were additionally adjusted for all metabolic risk factors. The analyses were also performed stratified for HFrEF and HFpEF. Whether there was a differential effect of metabolic risk factors on the risk of HFrEF

vs HFpEF was formally tested using the Lunn-McNeil method.[23] The proportional hazards assumption, assessed using Schoenfeld residuals, was not violated. Visual inspection of restricted cubic splines revealed no violations of the linearity assumption, except for SBP. A series of sensitivity analyses evaluating the influence of antihypertensive therapy, history of hypertension, and blood pressure cut points was performed to further explore the relation between hypertension and incident HF.

Influence of medication use was evaluated in an exploratory model adjusted for baseline use of statins, antiplatelet therapy, and antihypertensive agents. Mediation through the occurrence of DM or MI during follow-up was assessed by adjusting the model for interim DM and MI as time-varying covariates. To assess the effects of metabolic risk factors in complete absence of DM (both at baseline and during follow-up), a sensitivity analysis was performed in which patients with interim DM were excluded. Reverse causality was assessed by repeating the analyses after excluding patients who had incident HF within the first 1, 2, and 5 years of follow-up. Effect modification by age, sex, and CVD location was evaluated by testing interaction terms of these factors with metabolic risk factors, and by performing stratified analyses. In a sensitivity analysis, the relation of QUICKI and TyG with incident HF was assessed and compared to the main analysis with HOMA-IR. The effects of waist circumference were compared to other measures of obesity by replacing it by body-mass index (BMI), waist-to-hip ratio, visceral fat, and contribution of visceral fat to total abdominal fat. The combined effects of the presence of both metabolic and established risk factors were assessed by determining the effects of combinations of MetS with prior MI and/or current smoking, on the risk of incident HF.

All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

Results

Baseline characteristics

In the total study population, 1,979 patients (42.5%) had MetS, and median HOMA-IR was 2.4 (interquartile range [IQR] 1.6-3.6). Baseline characteristics are presented stratified by number of MetS criteria in Table 1, and HOMA-IR quartiles in Table S1. Levels of HOMA-IR and other measures of insulin resistance, the individual MetS components, and BMI increased with an increasing number of MetS criteria, while age, sex, smoking status, and statin and antiplatelet use remained relatively stable. Similar trends were observed across HOMA-IR quartiles.

Table 1. Baseline characteristics stratified by number of metabolic syndrome criteria

	No metabolic syndrome, n = 2,674 (57%)		Metabolic syndrome, n = 1,979 (43%)	
Characteristic	**0-1 ATP III criteria, n = 1,283 (28%)**	**2 ATP III criteria, n = 1,391 (30%)**	**3 ATP III criteria, n = 1,106 (24%)**	**4-5 ATP III criteria, n = 873 (19%)**
Age (years)	58.2±11.0	60.7±10.2	61.1±9.9	59.9±9.7
Sex (male)	885 (69%)	1,033 (74%)	795 (72%)	634 (73%)
Smoking status				
Former	580 (45%)	662 (48%)	532 (48%)	405 (46%)
Current	354 (28%)	364 (26%)	310 (28%)	283 (32%)
CVD locations				
Coronary artery disease	734 (57%)	883 (64%)	729 (66%)	596 (68%)
Prior myocardial infarction	407 (32%)	438 (32%)	375 (34%)	334 (38%)
Cerebrovascular disease	452 (35%)	421 (30%)	325 (29%)	222 (25%)
Peripheral artery disease	152 (12%)	168 (12%)	141 (13%)	138 (16%)
Abdominal aortic aneurysm	73 (6%)	78 (6%)	86 (8%)	80 (9%)
History of hypertension	420 (33%)	761 (55%)	710 (64%)	637 (73%)
Body-mass index (kg/m^2)	24.4±2.8	25.9±3.2	28.1±3.9	29.9±4.0
Metabolic syndrome				
Waist circumference (inch)	34.3±3.9	36.2±4.0	39.0±4.3	41.3±4.0
Systolic blood pressure (mmHg)	130±19	139±20	139±19	142±19
Diastolic blood pressure (mmHg)	78±11	82±11	82±11	84±11
Triglycerides (mg/dL)	89±35	106±53	151±97	204±106
HDL-cholesterol (mg/dL)	54±15	50±14	46±12	39±8
Fasting glucose (mg/dL)	95±7	105±11	106±12	112±13
Insulin resistance				
Fasting insulin (mU/L), median (IQR)	7.0 (5.0-9.7)	8.6 (6.0-12.0)	11.0 (8.0-16.0)	14.0 (10.0-20.0)
HOMA-IR, median (IQR)	1.6 (1.1-2.3)	2.2 (1.6-3.0)	2.9 (2.0-4.2)	3.9 (2.7-5.8)
HOMA-IR ≥2.0, n (%)[a]	414 (32%)	802 (58%)	832 (75%)	787 (90%)
HOMA-IR ≥2.5, n (%)[a]	247 (19%)	530 (38%)	661 (60%)	697 (80%)
QUICKI, median (IQR)	0.36 (0.34-0.38)	0.34 (0.32-0.36)	0.33 (0.31-0.34)	0.31 (0.30-0.33)
TyG, median (IQR)	8.3 (8.1-8.6)	8.5 (8.3-8.8)	8.8 (8.5-9.1)	9.2 (9.0-9.5)
Other laboratory values				
CRP (mg/L), median (IQR)	1.2 (0.6-2.8)	1.6 (0.8-3.2)	2.1 (1.1-4.2)	2.6 (1.3-5.3)
LDL-cholesterol (mg/dL)	101±35	102±36	104±39	106±40
Non-HDL-cholesterol (mg/dL)	116±35	120±39	131±42	143±44
eGFR (mL/min/1.73 m^2)	81±16	78±17	78±17	77±18

Characteristic	No metabolic syndrome, n = 2,674 (57%)		Metabolic syndrome, n = 1,979 (43%)	
	0-1 ATP III criteria, n = 1,283 (28%)	2 ATP III criteria, n = 1,391 (30%)	3 ATP III criteria, n = 1,106 (24%)	4-5 ATP III criteria, n = 873 (19%)
Medication use				
Statin	943 (74%)	1,090 (78%)	881 (80%)	671 (77%)
Antiplatelet therapy	1,040 (81%)	1,164 (84%)	920 (83%)	718 (82%)
Antihypertensive agent	836 (65%)	1,065 (77%)	913 (83%)	741 (85%)

All data in n (%) or mean±SD, unless otherwise specified.

[a] Commonly used thresholds for insulin resistance.

Abbreviations: ATP = Adult Treatment Panel, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HOMA-IR = homeostasis model of insulin resistance, IQR = interquartile range, LDL = low-density lipoprotein, MetS = metabolic syndrome, QUICKI = quantitative insulin sensitivity check index, SD = standard deviation, TyG = triglyceride-glucose index.

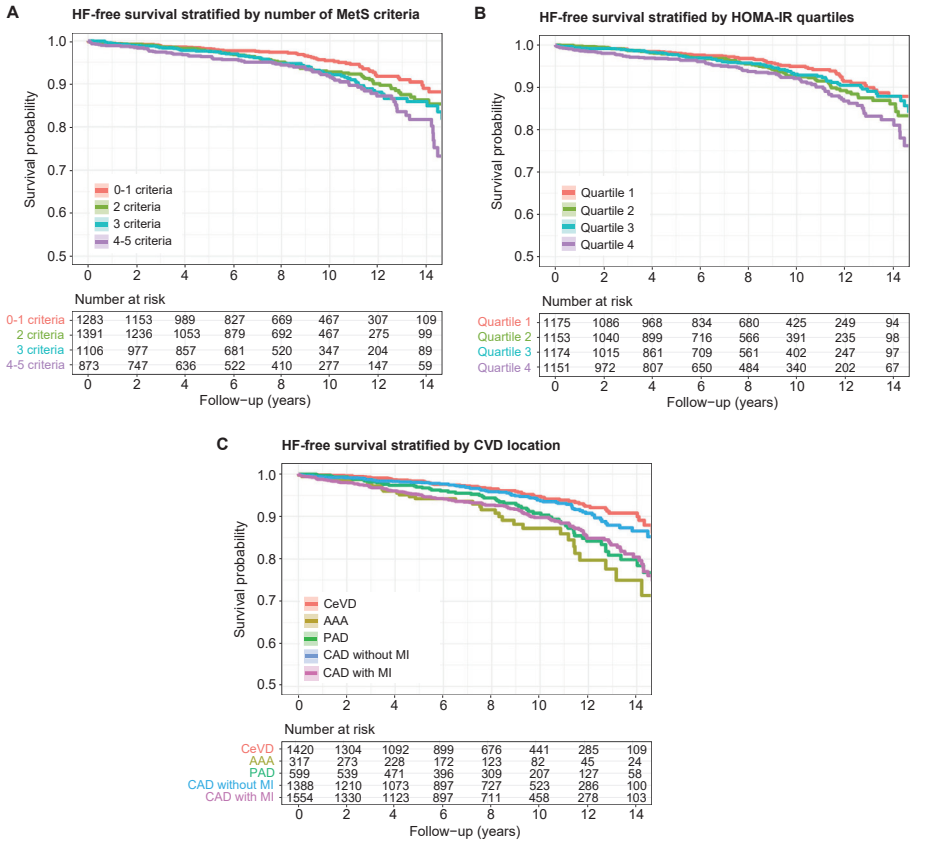
Incidence of HF

During a median follow-up of 8.0 years (IQR 4.3-11.4) incident HF was observed in 290 patients (6.2%; event rate: 0.81 / 100 person years). This included 114 (39.3%) cases of HFrEF, 102 (35.2%) cases of HFpEF, and 74 (25.5%) cases with unknown LVEF. The crude incidence of HF was higher in patients with compared to without MetS (0.98 vs. 0.69 / 100 person years), and increased with an increasing number of MetS criteria (Figure 1A). A similar trend was observed across HOMA-IR quartiles, but the incidence in the second and third quartiles was almost equal (Figure 1B). HF incidence was lowest in patients with CeVD, followed by patients with CAD without prior MI (Figure 1C). The incidence in patients with PAD and AAA was comparable to patients with a prior MI.

Relation of MetS and HOMA-IR with incident HF

MetS was significantly related to an increased risk of incident HF, independent of established risk factors (hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.04-1.68) (Table 2). There was a significant continuous relation between the number of MetS criteria and incident HF (HR per 1 criterion 1.17; 95% CI 1.06-1.29), with an especially high relative risk for patients with 4-5 criteria (HR vs. 0-1 criteria 1.69; 95% CI 1.18-2.41). Higher HOMA-IR was also significantly related to an increased risk of incident HF independent of established risk factors (HR per SD [= 1.91] increase 1.15; 95% CI 1.03-1.29). Especially values within the highest quartile of HOMA-IR (>3.6) were associated with a high relative risk (HR vs. lowest quartile 1.55; 95% CI 1.11-2.17). Additional adjustment for medication use hardly changed the results (Table S2).

Figure 1. Kaplan-Meier curves for incident HF



Unadjusted HF-free survival stratified by number of metabolic syndrome criteria (A), HOMA-IR quartiles (B), and CVD location (C). Quartiles of HOMA-IR, median (range): Quartile 1, 1.18 (0.39-1.58); Quartile 2, 1.96 (1.59-2.36); Quartile 3, 2.88 (2.37-3.64); Quartile 4, 4.95 (3.65-30.80).

The relation between MetS and incident HF was attenuated and no longer statistically significant after additional adjustment for HOMA-IR, indicating that the effect of MetS on the risk of HF is partially mediated by increases in insulin resistance (Table 2). However, the relation of the number of MetS criteria and the presence of 4-5 criteria with incident HF remained significant, implying that metabolic disturbances also contribute to an elevated risk of HF through other pathways than insulin resistance. The relation between HOMA-IR and incident HF was almost completely attenuated by adjustment for waist circumference, SBP, triglycerides, and HDL-c, indicating that the effect of insulin resistance on HF risk is largely mediated by changes in these components of the MetS.

Table 2. Relation of metabolic syndrome and HOMA-IR with incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Metabolic syndrome						
ATP III definition	290/4,653	0.81	1.46 (1.16-1.83)	1.39 (1.11-1.75)	1.32 (1.04-1.68)	1.21 (0.93-1.57)
No. of criteria						
Continuous (per 1 criterion)	290/4,653	0.81	1.22 (1.11-1.33)	1.20 (1.09-1.32)	1.17 (1.06-1.29)	1.13 (1.01-1.27)
Continuous (per SD = 1.25 criteria)	290/4,653	0.81	1.28 (1.14-1.43)	1.26 (1.12-1.42)	1.21 (1.07-1.37)	1.17 (1.02-1.34)
0-1	60/1,283	0.58	Ref	Ref	Ref	Ref
2	85/1,391	0.79	1.40 (1.00-1.94)	1.19 (0.85-1.69)	1.14 (0.82-1.59)	1.10 (0.78-1.54)
3	74/1,106	0.88	1.57 (1.12-2.21)	1.30 (0.92-1.83)	1.25 (0.88-1.77)	1.16 (0.80-1.67)
4-5	71/873	1.10	1.97 (1.40-2.78)	1.89 (1.34-2.66)	1.69 (1.18-2.41)	1.51 (1.02-2.26)
Insulin resistance						
HOMA-IR						
Continuous (per 1 unit)	290/4,653	0.81	1.10 (1.04-1.16)	1.10 (1.04-1.16)	1.08 (1.02-1.14)	1.02 (0.96-1.10)
Continuous (per SD = 1.91 units)	290/4,653	0.81	1.19 (1.07-1.33)	1.20 (1.07-1.33)	1.15 (1.03-1.29)	1.05 (0.92-1.19)
Quartile 1	60/1,175	0.61	Ref	Ref	Ref	Ref
Quartile 2	75/1,153	0.83	1.34 (0.96-1.88)	1.27 (0.91-1.79)	1.29 (0.92-1.81)	1.15 (0.81-1.63)
Quartile 3	68/1,174	0.76	1.21 (0.85-1.71)	1.20 (0.85-1.69)	1.09 (0.77-1.56)	0.91 (0.63-1.32)
Quartile 4	87/1,151	1.07	1.80 (1.29-2.50)	1.68 (1.21-2.34)	1.55 (1.11-2.17)	1.15 (0.78-1.69)

Hazard ratios (95% CI) for the relation of metabolic syndrome and HOMA-IR with incident HF.

Quartiles of HOMA-IR, median (range): Quartile 1, 1.18 (0.39-1.58); Quartile 2, 1.96 (1.59-2.36); Quartile 3, 2.88 (2.37-3.64); Quartile 4, 4.95 (3.65-30.80).

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.
[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR (only in the analyses with metabolic syndrome and its criteria), or waist circumference, systolic blood pressure, triglycerides, and HDL-c (only in the analyses with HOMA-IR). The analyses with HOMA-IR were not adjusted for fasting glucose, as fasting glucose is in the HOMA-IR formula.

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, No. = number, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Individual components of the MetS

The ATP III criteria for high waist circumference, high triglycerides, and low HDL-c were significantly related to an increased risk of incident HF when adjusted for age and sex (Table 3). These components and fasting glucose also had a significant continuous relation with HF adjusted for age and sex. Only waist circumference remained significantly related to incident HF after adjustment for established risk factors (HR per SD [= 4.7 inches/12.0 cm] increase 1.34; 95% CI 1.17-1.53). Especially a waist circumference in the highest quartile (>40.9 inches [>104 cm] for men, and >37.4 inches [>95 cm] for women) was related to an increased risk (HR vs. lowest quartile 2.10; 95% CI 1.49-2.97). After adjustment for the other MetS components and HOMA-IR, the relation between waist circumference and incident HF was only marginally attenuated, suggesting that waist circumference increases the risk of HF independent of other metabolic risk factors. The full model containing all established and metabolic risk factors is presented in Table S3.

Blood pressure was not related to incident HF based on the ATP III criterion, nor when the relation between SBP and HF was assessed linearly (Table 3). However, restricted cubic splines revealed a non-linear relation between SBP and incident HF, with both low (<130 mmHg) and high (>160 mmHg) levels of SBP related to an increased risk of HF (Figure S1A). A similar shape was observed for other measures of blood pressure (Figure S1B-D). Alternative indicators of hypertension were related to an increased risk of incident HF, i.e. history of hypertension (HR 1.33; 95% CI 1.04-1.70), and number of antihypertensive drugs used at baseline (HR per one drug 1.26; 95% CI 1.12-1.42), as was SBP dichotomized at a threshold of 160 mmHg (HR 1.33; 95% CI 1.00-1.77) (Table S4). There was a trend towards an increased risk of HF with higher levels of SBP and DBP in patients without antihypertensive therapy at baseline, and patients with SBP ≥120 mmHg, while opposite trends were observed in patients with antihypertensive therapy or SBP <120 mmHg (Table S5).

Relation between metabolic risk factors and HF subtypes

There was a trend towards a relation between MetS, higher HOMA-IR, and an increased risk of both HFrEF and HFpEF (Table 4; individual MetS components in Table S6). Every additional MetS criterion significantly increased the risk of HFrEF (HR 1.16; 95% CI 1.00-1.35), and HFpEF (HR 1.18; 95% CI 1.00-1.39). Overall, effect sizes were greater for HFpEF as compared to HFrEF (except for triglycerides and HDL-c), but differences were not significant (Lunn-McNeil tests: $p > 0.05$). Similar results were obtained for unclassified HF cases.

Table 3. Relation between individual components of the metabolic syndrome and incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Waist circumference						
ATP III criterion, ≥40/≥35 inches (M/F)	290/4,653	0.81	1.68 (1.34-2.12)	1.70 (1.35-2.15)	1.60 (1.27-2.03)	1.52 (1.18-1.95)
Continuous (per SD = 4.7 inches)	290/4,653	0.81	1.41 (1.26-1.58)	1.38 (1.21-1.57)	1.34 (1.17-1.53)	1.31 (1.13-1.52)
Quartile 1	50/1,189	0.53	Ref	Ref	Ref	Ref
Quartile 2	73/1,248	0.73	1.35 (0.94-1.93)	1.19 (0.83-1.71)	1.16 (0.81-1.66)	1.14 (0.79-1.64)
Quartile 3	69/1,145	0.78	1.46 (1.02-2.11)	1.30 (0.90-1.87)	1.22 (0.85-1.76)	1.18 (0.80-1.72)
Quartile 4	98/1,071	1.26	2.45 (1.74-3.44)	2.27 (1.61-3.19)	2.10 (1.49-2.97)	1.98 (1.36-2.88)
Blood pressure						
ATP III criterion, ≥130/≥85 mmHg	290/4,653	0.81	1.18 (0.88-1.60)	0.88 (0.65-1.19)	0.94 (0.69-1.27)	0.85 (0.62-1.16)
Continuous, SBP (per SD = 20 mmHg)	290/4,653	0.81	1.15 (1.03-1.28)	0.96 (0.85-1.07)	0.96 (0.86-1.08)	0.95 (0.84-1.06)
Quartile 1	71/1,198	0.82	Ref	Ref	Ref	Ref
Quartile 2	53/1,153	0.62	0.75 (0.53-1.07)	0.67 (0.47-0.96)	0.70 (0.49-1.00)	0.68 (0.48-0.97)
Quartile 3	78/1,181	0.83	0.94 (0.68-1.29)	0.72 (0.52-1.00)	0.76 (0.55-1.06)	0.72 (0.51-0.99)
Quartile 4	88/1,121	0.93	1.04 (0.76-1.43)	0.62 (0.45-0.85)	0.65 (0.47-0.90)	0.62 (0.45-0.87)
Triglycerides						
ATP III criterion, ≥150 mg/dL	290/4,653	0.81	1.12 (0.87-1.44)	1.33 (1.04-1.72)	1.21 (0.91-1.61)	1.08 (0.80-1.46)
Continuous (per SD = 87 mg/dL)	290/4,653	0.81	1.03 (0.92-1.14)	1.11 (1.00-1.22)	1.06 (0.94-1.20)	1.00 (0.87-1.16)
Quartile 1	69/1,232	0.73	Ref	Ref	Ref	Ref
Quartile 2	75/1,134	0.86	1.11 (0.80-1.54)	1.11 (0.80-1.54)	1.01 (0.73-1.41)	0.95 (0.68-1.33)
Quartile 3	66/1,124	0.75	0.93 (0.67-1.31)	1.01 (0.72-1.42)	0.90 (0.63-1.28)	0.78 (0.54-1.12)
Quartile 4	80/1,163	0.88	1.09 (0.79-1.51)	1.36 (0.98-1.89)	1.15 (0.79-1.66)	0.93 (0.62-1.40)

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
HDL-cholesterol						
ATP III criterion, <40/<50 mg/dL (M/F)	290/4,653	0.81	1.20 (0.95-1.53)	1.39 (1.09-1.77)	1.26 (0.99-1.61)	1.14 (0.88-1.47)
Continuous (per SD = 14 mg/dL)	290/4,653	0.81	0.88 (0.78-0.99)	0.85 (0.74-0.97)	0.91 (0.80-1.04)	0.98 (0.85-1.13)
Quartile 1	84/1,198	0.90	Ref	Ref	Ref	Ref
Quartile 2	64/1,174	0.72	0.81 (0.58-1.11)	0.75 (0.54-1.04)	0.81 (0.58-1.12)	0.88 (0.63-1.22)
Quartile 3	64/1,128	0.74	0.80 (0.58-1.11)	0.70 (0.50-0.97)	0.78 (0.56-1.09)	0.86 (0.61-1.20)
Quartile 4	78/1,150	0.85	0.91 (0.67-1.24)	0.72 (0.53-0.98)	0.85 (0.62-1.17)	1.03 (0.73-1.44)
Fasting glucose						
ATP III criterion, ≥100 mg/dL	290/4,653	0.81	1.48 (1.17-1.88)	1.15 (0.90-1.47)	1.12 (0.88-1.43)	1.02 (0.80-1.31)
Continuous (per SD = 12 mg/dL)	290/4,653	0.81	1.26 (1.14-1.39)	1.12 (1.01-1.25)	1.10 (0.98-1.22)	1.04 (0.93-1.17)
Quartile 1	69/1,226	0.66	Ref	Ref	Ref	Ref
Quartile 2	69/1,337	0.66	1.06 (0.76-1.48)	0.88 (0.63-1.23)	0.89 (0.64-1.25)	0.84 (0.60-1.17)
Quartile 3	66/1,041	0.85	1.41 (1.01-1.98)	1.05 (0.74-1.47)	0.99 (0.71-1.39)	0.90 (0.64-1.27)
Quartile 4	86/1,049	1.16	1.97 (1.44-2.71)	1.37 (0.99-1.89)	1.29 (0.93-1.78)	1.10 (0.79-1.54)

Hazard ratios (95% CI) for the relation of the individual components of the metabolic syndrome with incident HF. Waist circumference and HDL-c quartiles are sex-specific (e.g. the highest waist circumference quartile includes the 25% of men with the highest waist circumference and the 25% of women with the highest waist circumference).

Quartiles, median (range): Waist circumference (M/F, inch): Quartile 1, 34 (25-35) / 29 (23-31); Quartile 2, 37 (36-38) / 33 (32-34); Quartile 3, 40 (39-41) / 36 (35-37); Quartile 4, 43 (42-63) / 40 (38-55); SBP (mmHg): Quartile 1, 116 (85-123); Quartile 2, 130 (124-134); Quartile 3, 140 (135-148); Quartile 4, 160 (149-227); Triglycerides (mg/dL): Quartile 1, 69 (18-80); Quartile 2, 97 (81-106); Quartile 3, 126 (107-157); Quartile 4, 204 (158-1311); HDL-c (M/F, mg/dL): Quartile 1, 34 (6-38) / 41 (19-47); Quartile 2, 41 (39-44) / 51 (48-55); Quartile 3, 48 (45-52) / 60 (56-66); Quartile 4, 60 (53-135) / 75 (67-152); Fasting glucose (mg/dL): Quartile 1, 92 (54-95); Quartile 2, 100 (96-103); Quartile 3, 107 (104-110); Quartile 4, 117 (111-125).

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.
[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus all other components of the metabolic syndrome and HOMA-IR. The analyses with fasting glucose were not adjusted for HOMA-IR, as the HOMA-IR formula includes fasting glucose.

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, F = female, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, M = male, MI = myocardial infarction, PY = person years, Ref = reference, SD = standard deviation.

Table 4. Relation of metabolic syndrome and HOMA-IR with HF subtypes

	HFrEF (n = 114 [39.3%])		HFpEF (n = 102 [35.2%])		HF unclassified[a] (n = 74 [25.5%])	
	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)
Metabolic syndrome						
ATP III definition	1.28 (0.87-1.89)[d]	1.19 (0.78-1.82)	1.35 (0.90-2.03)[d]	1.24 (0.79-1.95)	1.33 (0.82-2.15)	1.21 (0.71-2.05)
No. of criteria						
Continuous (per 1 criterion)	1.16 (1.00-1.35)[d]	1.12 (0.94-1.33)	1.18 (1.00-1.39)[d]	1.14 (0.93-1.39)	1.17 (0.96-1.43)	1.14 (0.91-1.42)
Continuous (per SD = 1.25 criteria)	1.20 (1.00-1.46)	1.15 (0.93-1.43)	1.23 (1.00-1.51)	1.18 (0.91-1.51)	1.22 (0.95-1.56)	1.18 (0.89-1.55)
Insulin resistance						
HOMA-IR						
Continuous (per 1 unit)	1.06 (0.97-1.16)	1.01 (0.90-1.13)	1.10 (1.00-1.21)	1.04 (0.93-1.17)	1.09 (0.96-1.23)	1.02 (0.88-1.19)
Continuous (per SD = 1.91 units)	1.12 (0.94-1.33)[d]	1.02 (0.82-1.26)	1.20 (1.00-1.44)[d]	1.08 (0.87-1.35)	1.18 (0.92-1.48)	1.04 (0.78-1.39)

Hazard ratios (95% CI) for the relation of metabolic syndrome and HOMA-IR with HF subtypes.

[a] Cases for which LVEF was unknown.
[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.
[c] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR (only in the analyses with metabolic syndrome and its criteria), or waist circumference, systolic blood pressure, triglycerides, and HDL-c (only in the analyses with HOMA-IR). The analyses with HOMA-IR were not adjusted for fasting glucose, as fasting glucose is in the HOMA-IR formula.
[d] Hazard ratios compared for HFrEF vs HFpEF using the Lunn-McNeil method. This showed no significant differences (p >0.05).

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, No. = number, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Influence of interim MI and DM

Interim MI and DM were observed in 237 patients (event rate: 0.67 / 100 person years) and 316 patients (event rate: 0.92 / 100 person years) respectively, of whom 31 (13.1%) and 23 (7.3%) patients went on to have incident HF later during follow-up. Adjusted for established risk factors, MetS and HOMA-IR were not significantly related to interim MI, but very strongly related to interim DM (Table S7). Interim MI significantly increased the risk of subsequent incident HF (HR 2.55; 95% CI 1.74-3.74), while interim DM did not (Table S8). Adjustment for interim MI and DM hardly altered the relation of MetS and HOMA-IR with incident HF (Table S9). Results also remained largely unchanged after excluding patients with interim DM (Table S10).

Other measures of insulin resistance and obesity

Replacing HOMA-IR by QUICKI and TyG yielded largely comparable results, although the relation between these other measures of insulin resistance and incident HF was no longer significant after adjustment for established risk factors (Table S11). Waist-to-hip ratio, visceral fat, and contribution of visceral to total abdominal fat all had similar relations with incident HF as waist circumference (Table S12). Waist circumference and the other measures of abdominal obesity were more strongly related to incident HF than BMI.

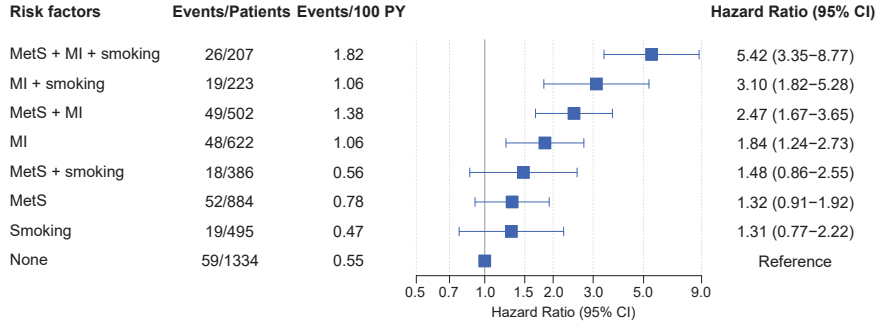
Reverse causality and effect modification

Repeating the analyses after excluding patients who had incident HF within the first 1, 2, and 5 years of follow-up yielded largely consistent results (Table S13). The relation between HOMA-IR and incident HF was slightly attenuated by excluding patients with an event in the first year. The relation between metabolic risk factors and incident HF was not significantly modified by age, sex, or CVD location (Table S14). There was a non-significant trend towards a stronger effect of MetS and HOMA-IR in women as compared to men.

Combined effects of metabolic and established risk factors

MetS increased the risk of incident HF on top of established risk factors, i.e. prior MI and current smoking (Figure 2). The combined presence of all three risk factors was associated with the highest relative risk of incident HF (compared to none of the three risk factors: HR 5.42; 95% CI 3.35-8.78), exceeding relative risks associated with prior MI alone (HR 1.84; 95% CI 1.24-2.73), current smoking alone (HR 1.31; 95% CI 0.77-2.22), and the combination of prior MI and current smoking (HR 3.10; 95% CI 1.82-5.28).

Figure 2. Combined effects of MetS and established risk factors on HF risk



Hazard ratios (95% CI) for the combined effects of metabolic syndrome, MI, and current smoking on the risk of incident HF. Hazard ratios are adjusted for age, sex, non-HDL-c, eGFR, CAD without MI, CeVD, PAD, and AAA. The reference group includes non-smoking patients without metabolic syndrome and without a prior MI. When a risk factor is not included in the description of the subgroup, it means the risk factor is absent (e.g. 'MetS + smoking' indicates current smokers with the metabolic syndrome, but without a prior MI).

Discussion

In this study of 4,653 CVD patients without a current diagnosis of DM, MetS and insulin resistance (measured by HOMA-IR) were related to an increased risk of incident HF independent of established risk factors. Effects mostly appeared to be greater for HFpEF as compared to HFrEF, but differences were not significant. The relation between insulin resistance and incident HF was largely mediated through changes in the MetS components, while the degree of metabolic disturbances in the context of the MetS also increased the risk of HF independent of insulin resistance. Of the individual components, abdominal obesity appeared to be the major driver of HF risk.

Several mechanisms may explain the relation between MetS, insulin resistance, and incident HF. First of all, in the setting of insulin resistance, the myocardium uses more free fatty acids instead of glucose, which increases vulnerability to pressure overload and ischemia.[24] Second, insulin may act as a growth factor, leading to increased myocardial mass and reduced cardiac output.[25] Dysfunctional adipose tissue causes sodium retention, activation of the sympathetic nervous system, and an increased response to angiotensin II, which contribute to volume expansion, increased peripheral vascular resistance, and myocardial hypertrophy and fibrosis.[26,27] Independent of insulin resistance, MetS may lead to incident HF through hypertension.[5] However, in the current study there was no significant continuous relation between SBP and incident HF. This is likely explained by the study population consisting of patients with established CVD, in whom the relation

between SBP and HF appears to be non-linear, with both low and high levels of SBP related to an increased risk. A low SBP may be related to a higher risk of HF because it can be an early sign of systolic dysfunction leading up to HF, which may be common in a population in which 63% of patients had a history of CAD. Also, 54% had a history of hypertension, and 76% used at least one antihypertensive drug. Therefore, a low SBP may also be indicative of the use of (multiple) antihypertensive drugs, which may reflect a history of (severe) hypertension and/or a high presumed risk of CVD events. As shown in this study, a history of hypertension and a larger number of antihypertensive drugs at baseline were both related to an increased risk of HF. Moreover, antihypertensive therapy and patients' adherence to this therapy may change during follow-up, potentially diluting the relation between baseline SBP and outcomes. Finally, blood pressure was based on office measurements, which may not represent the average blood pressure during the day. Another explanation of how MetS may lead to incident HF independent of insulin resistance, is through its association with inflammation. It has been shown that inflammatory markers such as CRP, IL-6, and TNF-α are associated with progressive systolic dysfunction and cardiac remodelling.[28] Finally, MetS and insulin resistance may lead to MI or DM, which then increase the risk of subsequent HF. But as shown in this study, metabolic risk factors are related to incident HF independent of interim MI and DM.

The results of this study extend prior work in people without a history of CVD. In line with the current study, previous population-based studies in America and Europe have shown that MetS is related to an increased risk of incident HF independent of established risk factors, with hazard ratios ranging from 1.32 to 1.74.[10–12] As in the current study, abdominal obesity was strongly related to HF.[5,7,10,11,13] But in contrast with the current findings in patients with CVD, hypertension, low HDL-cholesterol, and high triglycerides were also identified as independent risk factors in some studies.[7,10–13] This difference might be explained by the fact that most patients with established CVD are treated with blood pressure- and lipid-lowering medication, potentially distorting the relation between these modifiable risk factors and incident HF. Previous studies have also demonstrated that insulin resistance is independently related to incident HF in people without a history of CVD.[6–8,13] But differences in the measures used to quantify insulin resistance complicate a direct comparison. One previous study assessed the relation between metabolic risk factors and the risk of HFrEF vs HFpEF.[13] In line with the current study, HOMA-IR and waist circumference were more strongly related to HFpEF, and lipids to HFrEF, although differences were larger and significant for HOMA-IR in the previous study. To our knowledge, no previous studies assessed the relation between metabolic risk factors and incident HF in patients with established CVD.

When evaluating metabolic risk factors and the risk of incident HF, a distinction between individuals with and without a history of CVD might be important for several reasons. First of all, many previous studies have demonstrated an obesity paradox in patients with established CVD, with the overweight having a better prognosis than their leaner counterparts.[29] This has casted doubts over the potential benefits of weight loss in this population. Second, the prevalence of MetS is considerably higher in patients with established CVD (42.5% in our cohort) as compared to the general population (7.0-26.9% in Western countries based on the ATP III definition).[30] The median HOMA-IR of 2.4 in our cohort, indicates that almost half/more than half of all patients with established CVD meet commonly used thresholds for insulin resistance (HOMA-IR ≥2.0/≥2.5).[6,20] At the same time, the incidence of HF is also considerably higher in patients with established CVD, with an event rate of 0.81 per 100 person years in our cohort as compared to approximately 0.12 per 100 person years in a Dutch population-based cohort.[31] As shown in this study, not only patients with a prior MI or other manifestations of CAD, but also patients with non-coronary vascular disease are at high risk of HF. The prognosis associated with HF is poor with 5-year mortality rates exceeding 50%, and it imposes a huge economic burden estimated at a global expenditure of over $100 billion per year.[32] Besides HF, previous studies have shown that MetS and insulin resistance also increase the risk of other major adverse cardiovascular events in patients with established CVD.[14,15] This illustrates the scale and importance of both metabolic disturbances and the risk of HF in patients with a history of CVD, and highlights the need for interventions targeting these metabolic risk factors to reduce HF risk, especially in these high-risk patients.

In contrast with the obesity paradox observed in previous studies in patients with established CVD, abdominal obesity was the major driver of HF risk in the current study. Waist circumference was strongly related to incident HF independent of established and other metabolic risk factors. This suggests that weight loss might be an effective way to lower the risk of HF in these patients. Weight loss naturally reduces abdominal obesity, and also has positive effects on the other components of the MetS and insulin resistance. A meta-analysis of four cohort studies of patients with CAD has shown that intentional weight loss through lifestyle interventions reduced the risk of major adverse cardiovascular events by 33%.[33] Previous studies have also demonstrated that weight loss decreases left ventricular mass and lowers arterial and cardiac filling pressures, and may therefore reduce the risk of incident HF as well.[34] Randomized clinical trials assessing the effects of weight loss interventions (e.g. dietary interventions or exercise programs) on the risk of incident HF (and other CVD events) in patients with established CVD may be warranted. In addition, we propose that incident HF should be among the outcomes routinely presented in all future trials in this population, in an attempt to identify new therapies that can reduce the

high risk of HF in these patients. Based on current knowledge, intensification of preventive therapy in CVD patients with MetS and/or insulin resistance may already be considered.

Strengths of this study are the practice-based cohort with prospective design, long follow-up, and low proportions of missing data. Study limitations should be considered. This is an observational study, thus subject to possible residual confounding. Insulin resistance was quantified by HOMA-IR instead of the euglycemic clamp technique, usually considered as the gold standard. However, HOMA-IR correlates well with clamp-measured insulin resistance and is more suitable for large epidemiological studies.[21] Echocardiography was not part of the baseline screening, so data on LVEF and other parameters of systolic and diastolic function at study entry were not available. Therefore, the influence of baseline cardiac function on the study results could not be assessed. HF outcomes were based on ICD codes. Registration of ICD codes by clinicians in routine clinical care might be imperfect, but a previous study in another Dutch cohort found that only 3.3% of patients with a presumed HF hospitalization based on ICD codes were misclassified.[35] Also, 74% of HF cases in this study could be confirmed and classified as either HFrEF or HFpEF based on echocardiography reports retrieved from medical records. For 26% of cases, information on LVEF was not available, so these remained unclassified. As outcomes were based on hospitalizations only, out-patient diagnoses of HF were missed. Specifically, the number of HFpEF cases may be underestimated, as HFpEF less frequently leads to hospitalization.

In conclusion, this study showed that in CVD patients without a current diagnosis of DM, MetS and insulin resistance are independent risk factors of incident HF. Abdominal obesity was identified as a major driver of HF risk, supporting the importance of weight loss in this population.

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Supplementary material

Table S1. Baseline characteristics stratified by HOMA-IR quartiles

	Quartile 1 (n = 1,175)	Quartile 2 (n = 1,153)	Quartile 3 (n = 1,174)	Quartile 4 (n = 1,151)
HOMA-IR, median (range)	*1.18 (0.39-1.58)*	*1.96 (1.59-2.36)*	*2.88 (2.37-3.64)*	*4.95 (3.65-30.80)*
Age (years)	59.6±10.7	59.9±10.4	60.3±9.9	59.9±10.2
Sex (male)	803 (68%)	810 (70%)	840 (72%)	894 (78%)
Smoking status				
Former	495 (42%)	538 (47%)	565 (48%)	581 (51%)
Current	371 (32%)	317 (28%)	306 (26%)	317 (28%)
CVD location				
Coronary artery disease	671 (57%)	701 (61%)	765 (65%)	805 (70%)
Prior myocardial infarction	325 (28%)	355 (31%)	420 (36%)	454 (39%)
Cerebrovascular disease	387 (33%)	370 (32%)	466 (31%)	297 (26%)
Peripheral artery disease	170 (15%)	133 (12%)	146 (12%)	150 (13%)
Abdominal aortic aneurysm	79 (7%)	86 (8%)	64 (6%)	88 (8%)
History of hypertension	529 (45%)	611 (53%)	636 (54%)	752 (65%)
Body mass index (kg/m^2)	24.5±3.1	25.8±3.2	27.2±3.4	29.5±4.3
Metabolic syndrome				
MetS (ATP III definition)	187 (16%)	354 (31%)	579 (49%)	859 (75%)
No. of ATP III criteria	1.5±1.0	2.0±1.1	2.5±1.1	3.3±1.1
Waist circumference (inch)	34.6±4.3	36.2±4.0	37.8±4.0	40.6±4.7
Systolic blood pressure (mmHg)	136±20	136±19	137±20	139±19
Diastolic blood pressure (mmHg)	80±11	81±11	81±11	82±12
Triglycerides (mg/dL)	106±62	115±80	142±89	168±97
HDL-cholesterol (mg/dL)	54±15	50±14	46±12	43±11
Fasting glucose (mg/dL)	97±9	101±9	105±11	112±14
Insulin resistance				
Fasting insulin (mU/L), median (IQR)	5.0 (4.0-6.0)	8.0 (7.0-8.8)	11.0 (10.0-13.0)	18.0 (16.0-23.0)
QUICKI, median (IQR)	0.37 (0.36-0.39)	0.34 (0.34-0.35)	0.33 (0.32-0.33)	0.30 (0.29-0.31)
TyG index, median (IQR)	8.4 (8.1-8.7)	8.5 (8.3-8.8)	8.7 (8.4-9.1)	9.0 (8.6-9.3)
Other laboratory values				
CRP (mg/L), median (IQR)	1.4 (0.7-3.1)	1.6 (0.8-3.7)	1.8 (0.9-3.8)	2.1 (1.1-4.4)
LDL-cholesterol (mg/dL)	100±35	103±37	101±36	101±35
Non-HDL-cholesterol (mg/dL)	124±39	125±42	128±43	131±43
eGFR (mL/min/1.73 m^2)	80±16	79±16	78±17	78±18
Medication use				
Statin	832 (71%)	879 (76%)	929 (79%)	945 (82%)
Antiplatelet therapy	923 (79%)	945 (82%)	984 (84%)	990 (86%)
Antihypertensive agent	796 (68%)	851 (74%)	921 (78%)	987 (86%)

All data in n (%) or mean±SD, unless otherwise specified.
Abbreviations: ATP = Adult Treatment Panel, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HOMA-IR = homeostasis model of insulin resistance, IQR = interquartile range, LDL = low-density lipoprotein, MetS = metabolic syndrome, No. = number, QUICKI = quantitative insulin sensitivity check index, SD = standard deviation, TyG = triglyceride-glucose index.

Table S2. Relation between metabolic risk factors and incident HF adjusted for medication use

	Events/ Patients	Event rate (events/ 100 PY)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for established risk factors + medication[b], HR (95% CI)
Metabolic syndrome				
ATP III definition	290/4,653	0.81	1.32 (1.04-1.68)	1.32 (1.04-1.68)
Continuous (per 1 criterion)	290/4,653	0.81	1.17 (1.06-1.29)	1.17 (1.06-1.29)
Individual components				
Waist circumference (per SD = 4.7 inches)	290/4,653	0.81	1.34 (1.17-1.53)	1.35 (1.18-1.54)
Systolic blood pressure (per SD = 20 mmHg)	290/4,653	0.81	0.96 (0.86-1.08)	0.96 (0.86-1.08)
Triglycerides (per SD = 87 mg/dL)	290/4,653	0.81	1.06 (0.94-1.20)	1.06 (0.93-1.20)
HDL-cholesterol (per SD = 14 mg/dL)	290/4,653	0.81	0.91 (0.80-1.04)	0.91 (0.80-1.04)
Fasting glucose (per SD = 12 mg/dL)	290/4,653	0.81	1.10 (0.98-1.22)	1.10 (0.98-1.22)
Insulin resistance				
HOMA-IR (per SD = 1.91 units)	290/4,653	0.81	1.15 (1.03-1.29)	1.15 (1.03-1.29)

Hazard ratios (95% CI) for the relation between metabolic risk factors and incident HF, adjusted for established risk factors and additionally adjusted for baseline use of statins, antiplatelet therapy, and antihypertensive agents.

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus baseline use of statins, antiplatelet therapy, and antihypertensive agents.

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, SD = standard deviation.

Table S3. Full model for the relation of established and metabolic risk factors with incident HF

	HR (95% CI)	p value
CVD locations		
Prior MI	2.60 (1.82-3.72)	<0.001
Interim MI[a]	2.55 (1.74-3.74)	<0.001
Coronary artery disease without MI	1.51 (1.02-2.25)	0.042
Cerebrovascular disease	1.42 (1.02-1.97)	0.036
Peripheral artery disease	2.39 (1.72-3.33)	<0.001
Abdominal aortic aneurysm	1.34 (0.91-1.96)	0.138
Established risk factors		
Age (per SD = 10 years)	2.38 (1.99-2.84)	<0.001
Sex (male)	1.16 (0.84-1.62)	0.372
Former smoking	0.96 (0.70-1.31)	0.807
Current smoking	1.51 (1.05-2.15)	0.025
Non-HDL-cholesterol (per SD = 41 mg/dL)	0.96 (0.83-1.11)	0.590
eGFR (per SD = 17 mL/min/1.73 m^2)	0.89 (0.77-1.03)	0.112
Metabolic risk factors		
Waist circumference (per SD = 4.7 inches)	1.33 (1.15-1.54)	<0.001
Systolic blood pressure (per SD = 20 mmHg)	0.94 (0.84-1.06)	0.309
Triglycerides (per SD = 87 mg/dL)	1.00 (0.87-1.16)	0.998
HDL-cholesterol (per SD = 14 mg/dL)	1.00 (0.87-1.15)	0.955
Fasting glucose (per SD = 12 mg/dL)	1.04 (0.93-1.17)[b]	0.495
HOMA-IR (per SD = 1.91 units)	1.04 (0.91-1.19)[b]	0.575

Hazard ratios (95% CI) for the relation of established and metabolic risk factors with incident HF from a model containing all factors.
[a] Interim MI was analyzed as a time-varying covariate, i.e. patients who had an interim MI were analyzed as patients without an interim MI until they had the interim MI, after which they were analyzed as patients with an interim MI for the remainder of follow-up.
[b] As the HOMA-IR formula includes fasting glucose, the HR for fasting glucose was derived from a model containing all factors except HOMA-IR, and the HR for HOMA-IR was derived from a model containing all factors except fasting glucose.
Abbreviations: CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, SD = standard deviation.

Table S4. Relation between different measures of hypertension and incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for established risk factors + other measures of hypertension[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)
History of hypertension					
No	103/2,125	0.61	Ref	Ref	Ref
Yes	187/2,528	0.98	1.33 (1.04-1.70)	1.24 (0.92-1.66)	1.25 (0.97-1.60)
No. of antihypertensive drugs					
Continuous (per 1 drug)	290/4,653	0.81	1.26 (1.12-1.42)	1.21 (1.07-1.38)	1.21 (1.07-1.36)
None	48/1,101	0.53	Ref	Ref	Ref
1	71/1,450	0.59	0.74 (0.50-1.09)	0.68 (0.46-1.02)	0.68 (0.46-1.01)
2	99/1,338	1.00	1.17 (0.80-1.71)	1.04 (0.69-1.55)	1.05 (0.72-1.55)
3 or more	72/764	1.41	1.61 (1.07-2.41)	1.37 (0.88-2.14)	1.40 (0.93-2.12)
Systolic blood pressure					
Continuous (per 20 mmHg)	290/4,653	0.81	0.96 (0.86-1.08)	0.92 (0.81-1.05)	0.95 (0.84-1.06)
>130 mmHg	185/2,754	0.83	0.75 (0.58-0.96)	0.69 (0.53-0.89)	0.72 (0.56-0.92)
>140 mmHg	126/1,688	0.90	0.82 (0.65-1.04)	0.76 (0.59-0.97)	0.80 (0.63-1.02)
>150 mmHg	82/1,007	0.97	0.86 (0.66-1.12)	0.76 (0.57-1.01)	0.86 (0.66-1.12)
>160 mmHg	64/533	1.42	1.33 (1.00-1.77)	1.28 (0.94-1.74)	1.32 (0.99-1.76)
>170 mmHg	41/294	1.67	1.37 (0.98-1.93)	1.32 (0.93-1.88)	1.32 (0.93-1.85)
Diastolic blood pressure					
Continuous (per 10 mmHg)	290/4,653	0.81	0.97 (0.88-1.08)	0.95 (0.85-1.06)	0.95 (0.86-1.06)
>85 mmHg	94/1,464	0.76	0.92 (0.72-1.18)	0.87 (0.67-1.12)	0.88 (0.69-1.13)
>90 mmHg	59/837	0.82	1.01 (0.76-1.35)	0.96 (0.71-1.31)	0.97 (0.73-1.30)
>95 mmHg	39/492	0.91	1.17 (0.83-1.65)	1.12 (0.78-1.60)	1.14 (0.81-1.61)
>100 mmHg	20/248	0.95	1.04 (0.65-1.64)	0.98 (0.61-1.57)	1.00 (0.63-1.58)

Hazard ratios (95% CI) for the relation between different measures of hypertension and incident HF. For the cut points of systolic and diastolic blood pressure, events/patients and event rates are displayed for the subgroup above the cut point, and hazard ratios are shown for above vs below the cut point.

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus history of hypertension, number of antihypertensive drugs, and systolic blood pressure where appropriate.

[c] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus waist circumference, triglycerides, HDL-c, and HOMA-IR.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years.

Table S5. Relation between blood pressure and incident HF in subgroups of antihypertensive therapy and SBP level

Subgroup	Events/ Patients	Event rate (events/ 100 PY)	Systolic blood pressure (per 20 mmHg)		Diastolic blood pressure (per 10 mmHg)	
			Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Antihypertensive therapy						
No	48/1,098	0.54	1.19 (0.89-1.58)	1.24 (0.92-1.67)	1.08 (0.84-1.38)	1.05 (0.82-1.35)
Yes	242/3,555	0.90	0.91 (0.80-1.04)	0.89 (0.78-1.02)	0.95 (0.85-1.07)	0.93 (0.83-1.05)
Systolic blood pressure						
<120 mmHg	52/920	0.80	0.48 (0.21-1.08)	0.43 (0.19-0.98)	1.01 (0.67-1.53)	0.99 (0.65-1.49)
≥120 mmHg	238/3,733	0.81	1.05 (0.92-1.21)	1.05 (0.92-1.21)	1.02 (0.91-1.15)	1.01 (0.90-1.14)

Hazard ratios (95% CI) for the relation of systolic and diastolic blood pressure with incident HF, in patients with and without antihypertensive therapy at baseline, and patients with a systolic blood pressure above and below 120 mmHg.

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus waist circumference, triglycerides, HDL-c, and HOMA-IR.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years.

Table S6. Relation between individual components of the metabolic syndrome and HF subtypes

	HFrEF (n = 114 [39.3%])		HFpEF (n = 102 [35.2%])		HF unclassified[a] (n = 74 [25.5%])	
	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)
Waist circumference						
ATP III criterion, ≥40/≥35 inches (M/F)	1.51 (1.03-2.22)	1.45 (0.96-2.19)	1.67 (1.12-2.49)	1.58 (1.03-2.43)	1.61 (1.00-2.59)	1.53 (0.93-2.53)
Continuous (per SD = 4.7 inches)	1.29 (1.06-1.57)[d]	1.27 (1.02-1.58)	1.38 (1.11-1.71)[d]	1.35 (1.05-1.73)	1.34 (1.03-1.75)	1.32 (0.98-1.78)
Blood pressure						
ATP III criterion, ≥130/≥85 mmHg	0.86 (0.55-1.34)	0.75 (0.48-1.18)	1.04 (0.60-1.79)	1.01 (0.58-1.76)	0.93 (0.47-1.83)	0.81 (0.41-1.61)
Continuous, SBP (per SD = 20 mmHg)	0.88 (0.73-1.06)[d]	0.86 (0.71-1.04)	1.05 (0.87-1.26)[d]	1.04 (0.86-1.26)	0.96 (0.77-1.20)	0.94 (0.75-1.17)
Triglycerides						
ATP III criterion, ≥150 mg/dL	1.26 (0.80-1.99)	1.12 (0.69-1.81)	1.19 (0.74-1.91)	1.07 (0.64-1.78)	1.19 (0.68-2.09)	1.06 (0.58-1.94)
Continuous (per SD = 87 mg/dL)	1.10 (0.91-1.32)[d]	1.04 (0.84-1.28)	1.05 (0.85-1.30)[d]	1.00 (0.75-1.33)	1.04 (0.77-1.40)	0.99 (0.71-1.38)
HDL-cholesterol						
ATP III criterion, <40/<50 mg/dL (M/F)	1.30 (0.88-1.91)	1.19 (0.79-1.79)	1.24 (0.81-1.90)	1.11 (0.71-1.74)	1.25 (0.77-2.04)	1.12 (0.67-1.86)
Continuous (per SD = 14 mg/dL)	0.88 (0.71-1.08)[d]	0.94 (0.75-1.18)	0.93 (0.75-1.15)[d]	0.99 (0.79-1.25)	0.92 (0.70-1.20)	0.99 (0.74-1.32)
Fasting glucose						
ATP III criterion, ≥100 mg/dL	1.10 (0.74-1.63)	1.01 (0.67-1.51)	1.15 (0.76-1.73)	1.04 (0.69-1.58)	1.12 (0.69-1.82)	1.03 (0.63-1.69)
Continuous (per SD = 12 mg/dL)	1.09 (0.92-1.30)[d]	1.03 (0.86-1.24)	1.12 (0.94-1.33)[d]	1.05 (0.87-1.26)	1.11 (0.87-1.42)	1.04 (0.80-1.35)

Hazard ratios (95% CI) for the relation between the individual components of the metabolic syndrome and HF subtypes.

[a] Cases for which LVEF was unknown.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[c] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus all other components of the metabolic syndrome and HOMA-IR. The analyses with fasting glucose were not adjusted for HOMA-IR, as the HOMA-IR formula includes fasting glucose.

[d] Hazard ratios compared for HFrEF vs HFpEF using the Lunn-McNeil method. This showed no significant differences (p >0.05).

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, No. = number, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Table S7A. Relation of metabolic syndrome and HOMA-IR with interim MI

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Metabolic syndrome						
ATP III definition	237/4,653	0.67	1.42 (1.10-1.83)	1.40 (1.09-1.81)	1.21 (0.93-1.57)	1.24 (0.93-1.65)
No. of criteria						
Continuous (per 1 criterion)	237/4,653	0.67	1.15 (1.04-1.28)	1.15 (1.04-1.27)	1.06 (0.96-1.18)	1.08 (0.95-1.21)
Continuous (per SD = 1.25 criteria)	237/4,653	0.67	1.20 (1.05-1.36)	1.19 (1.05-1.35)	1.08 (0.95-1.23)	1.10 (0.94-1.27)
0-1	47/1,283	0.46	Ref	Ref	Ref	Ref
2	72/1,391	0.68	1.47 (1.02-2.12)	1.41 (0.97-2.04)	1.30 (0.90-1.89)	1.32 (0.91-1.92)
3	69/1,106	0.84	1.82 (1.26-2.64)	1.76 (1.21-2.56)	1.54 (1.06-2.25)	1.58 (1.07-2.35)
4-5	49/873	0.77	1.67 (1.12-2.49)	1.63 (1.09-2.43)	1.24 (0.82-1.88)	1.29 (0.82-2.04)
Insulin resistance						
HOMA-IR						
Continuous (per 1 unit)	237/4,653	0.67	1.05 (0.98-1.12)	1.04 (0.98-1.11)	1.01 (0.94-1.08)	1.02 (0.95-1.11)
Continuous (per SD = 1.91 units)	237/4,653	0.67	1.09 (0.97-1.24)	1.08 (0.95-1.22)	1.01 (0.89-1.15)	1.05 (0.91-1.21)
Quartile 1	53/1,175	0.55	Ref	Ref	Ref	Ref
Quartile 2	56/1,153	0.63	1.14 (0.78-1.66)	1.13 (0.77-1.64)	1.07 (0.73-1.56)	1.10 (0.75-1.62)
Quartile 3	68/1,174	0.78	1.40 (0.98-2.01)	1.38 (0.97-1.98)	1.24 (0.86-1.78)	1.30 (0.89-1.91)
Quartile 4	60/1,151	0.76	1.37 (0.95-1.98)	1.31 (0.91-1.90)	1.10 (0.76-1.61)	1.23 (0.81-1.89)

Hazard ratios (95% CI) for the relation of metabolic syndrome and HOMA-IR with interim MI.
Quartiles of HOMA-IR, median (range): Quartile 1, 1.18 (0.39-1.58); Quartile 2, 1.96 (1.59-2.36); Quartile 3, 2.88 (2.37-3.64); Quartile 4, 4.95 (3.65-30.80).
[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.
[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR (only in the analyses with metabolic syndrome and its criteria), or waist circumference, systolic blood pressure, triglycerides, and HDL-c (only in the analyses with HOMA-IR). The analyses with HOMA-IR were not adjusted for fasting glucose, as fasting glucose is in the HOMA-IR formula.
Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, No. = number, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Table S7B. Relation of metabolic syndrome and HOMA-IR with interim DM

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Metabolic syndrome						
ATP III definition	316/4,653	0.92	4.46 (3.47-5.75)	4.46 (3.46-5.74)	4.23 (3.27-5.48)	2.76 (2.09-3.64)
No. of criteria						
Continuous (per 1 criterion)	316/4,653	0.92	1.91 (1.74-2.09)	1.91 (1.74-2.09)	1.90 (1.72-2.09)	1.57 (1.41-1.75)
Continuous (per SD = 1.25 criteria)	316/4,653	0.92	2.25 (2.01-2.52)	2.25 (2.01-2.52)	2.23 (1.98-2.51)	1.76 (1.54-2.02)
0-1	25/1,283	0.24	Ref	Ref	Ref	Ref
2	56/1,391	0.56	2.19 (1.36-3.50)	2.16 (1.35-3.46)	2.09 (1.30-3.35)	1.77 (1.10-2.84)
3	97/1,106	0.98	5.02 (3.23-7.79)	4.98 (3.20-7.73)	4.78 (3.07-7.46)	3.29 (2.09-5.18)
4-5	138/873	2.02	10.18 (6.65-15.60)	10.11 (6.60-15.49)	9.57 (6.19-14.79)	5.24 (3.30-8.32)
Insulin resistance						
HOMA-IR						
Continuous (per 1 unit)	316/4,653	0.92	1.37 (1.31-1.42)	1.37 (1.31-1.42)	1.36 (1.30-1.41)	1.25 (1.19-1.31)
Continuous (per SD = 1.91 units)	316/4,653	0.92	1.81 (1.68-1.96)	1.81 (1.68-1.95)	1.79 (1.66-1.94)	1.53 (1.40-1.69)
Quartile 1	20/1,175	0.21	Ref	Ref	Ref	Ref
Quartile 2	46/1,153	0.52	2.55 (1.51-4.31)	2.54 (1.50-4.30)	2.56 (1.51-4.32)	2.12 (1.25-3.60)
Quartile 3	88/1,174	1.03	5.06 (3.12-8.23)	5.05 (3.11-8.20)	5.02 (3.08-8.16)	3.59 (2.18-5.90)
Quartile 4	162/1,151	2.22	11.07 (6.96-17.62)	10.98 (6.89-17.48)	10.71 (6.71-17.09)	6.20 (3.77-10.19)

Hazard ratios (95% CI) for the relation of metabolic syndrome and HOMA-IR with interim DM.
Quartiles of HOMA-IR, median (range): Quartile 1, 1.18 (0.39-1.58); Quartile 2, 1.96 (1.59-2.36); Quartile 3, 2.88 (2.37-3.64); Quartile 4, 4.95 (3.65-30.80).
[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.
[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR (only in the analyses with metabolic syndrome and its criteria), or waist circumference, systolic blood pressure, triglycerides, and HDL-c (only in the analyses with HOMA-IR). The analyses with HOMA-IR were not adjusted for fasting glucose, as fasting glucose is in the HOMA-IR formula.
Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, No. = number, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.

Table S8. Relation of interim MI and DM with incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Interim MI						
No	259/4,653[c]	0.74	Ref	Ref	Ref	Ref
Yes	31/237	2.93	2.89 (1.98-4.22)	2.69 (1.84-3.94)	2.46 (1.68-3.60)	2.55 (1.74-3.74)
Interim DM						
No	267/4,653[c]	0.78	Ref	Ref	Ref	Ref
Yes	23/316	1.42	1.25 (0.81-1.92)	1.24 (0.81-1.92)	1.23 (0.79-1.90)	1.05 (0.67-1.65)

Hazard ratios (95% CI) for the relation of interim MI and DM with incident HF. Interim MI and DM were analyzed as time-varying covariates, i.e. patients with an interim event were analyzed in the group without an interim event until they had the interim event, after which they were moved to the group with an interim event for the remainder of follow-up.

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR, waist circumference, systolic blood pressure, triglycerides, and HDL-c. The analyses were not adjusted for fasting glucose, as fasting glucose is in the HOMA-IR formula.

[c] This group includes all patients (n = 4,653) because interim MI and DM are analyzed as time-varying covariates. At the start of follow-up no patient has an interim MI or DM, and therefore all patients are first included in the group without an interim event. As soon as patients have an interim event, they are moved to the group with an interim event and stay in this group for the remainder of follow-up.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, Ref = reference.

Table S9. Relation of metabolic syndrome and HOMA-IR with incident HF adjusted for interim MI and DM

	Events/ Patients	Event rate (events/ 100 PY)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for established risk factors[a] + interim MI, HR (95% CI)	Adjusted for established risk factors[a] + interim DM, HR (95% CI)
Metabolic syndrome					
ATP III definition	290/4,653	0.81	1.32 (1.04-1.68)	1.31 (1.03-1.66)	1.30 (1.02-1.66)
Continuous (per 1 criterion)	290/4,653	0.81	1.17 (1.06-1.29)	1.16 (1.05-1.28)	1.16 (1.05-1.29)
Individual components					
Waist circumference (per SD = 4.7 inches)	290/4,653	0.81	1.34 (1.17-1.53)	1.35 (1.19-1.54)	1.33 (1.17-1.52)
Systolic blood pressure (per SD = 20 mmHg)	290/4,653	0.81	0.96 (0.86-1.08)	0.96 (0.85-1.07)	0.96 (0.86-1.08)
Triglycerides (per SD = 87 mg/dL)	290/4,653	0.81	1.06 (0.94-1.20)	1.06 (0.93-1.20)	1.05 (0.93-1.19)
HDL-cholesterol (per SD = 14 mg/dL)	290/4,653	0.81	0.91 (0.80-1.04)	0.92 (0.81-1.05)	0.92 (0.80-1.04)
Fasting glucose (per SD = 12 mg/dL)	290/4,653	0.81	1.10 (0.98-1.22)	1.10 (0.98-1.22)	1.09 (0.97-1.22)
Insulin resistance					
HOMA-IR (per SD = 1.91 units)	290/4,653	0.81	1.15 (1.03-1.29)	1.15 (1.03-1.28)	1.15 (1.02-1.28)

Hazard ratios (95% CI) for the relation of the metabolic syndrome, the individual components of the metabolic syndrome, and HOMA-IR with incident HF adjusted for interim MI and DM. Interim MI and DM were analyzed as time-varying covariates, i.e. patients with an interim event were analyzed in the group without an interim event until they had the interim event, after which they were moved to the group with an interim event for the remainder of follow-up.

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, SD = standard deviation.

Table S10. Relation of metabolic syndrome and HOMA-IR with incident HF in patients without interim DM

	Total population			Patients without interim DM		
	Events/ Patients	**Adjusted for established risk factors[a], HR (95% CI)**	**Adjusted for metabolic risk factors[b], HR (95% CI)**	**Events/ Patients**	**Adjusted for established risk factors[a], HR (95% CI)**	**Adjusted for metabolic risk factors[b], HR (95% CI)**
Metabolic syndrome						
ATP III definition	290/4,653	1.32 (1.04-1.68)	1.21 (0.93-1.57)	267/4,337	1.32 (1.03-1.69)	1.19 (0.90-1.55)
Continuous (per 1 criterion)	290/4,653	1.17 (1.06-1.29)	1.13 (1.01-1.27)	267/4,337	1.17 (1.06-1.30)	1.13 (1.00-1.27)
Individual components						
Waist circumference (per SD = 4.7 inches)	290/4,653	1.34 (1.17-1.53)	1.31 (1.13-1.52)	267/4,337	1.36 (1.18-1.56)	1.31 (1.13-1.53)
Systolic blood pressure (per SD = 20 mmHg)	290/4,653	0.96 (0.86-1.08)	0.95 (0.84-1.06)	267/4,337	0.94 (0.84-1.06)	0.92 (0.82-1.04)
Triglycerides (per SD = 87 mg/dL)	290/4,653	1.06 (0.94-1.20)	1.00 (0.87-1.16)	267/4,337	1.04 (0.91-1.19)	0.97 (0.83-1.14)
HDL-cholesterol (per SD = 14 mg/dL)	290/4,653	0.91 (0.80-1.04)	0.98 (0.85-1.13)	267/4,337	0.90 (0.79-1.03)	0.97 (0.84-1.12)
Fasting glucose (per SD = 12 mg/dL)	290/4,653	1.10 (0.98-1.22)	1.04 (0.93-1.17)	267/4,337	1.12 (0.99-1.27)	1.07 (0.94-1.22)
Insulin resistance						
HOMA-IR (per SD = 1.91 units)	290/4,653	1.15 (1.03-1.29)	1.05 (0.92-1.19)	267/4,337	1.19 (1.05-1.34)	1.09 (0.95-1.25)

Hazard ratios (95% CI) for the relation of the metabolic syndrome, the individual components of the metabolic syndrome, and HOMA-IR with incident HF in patients without interim DM as compared to the total population (including patients with interim DM).

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR, waist circumference, systolic blood pressure, triglycerides, and HDL-c where appropriate.

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, SD = standard deviation.

Table S11. Relation between various measures of insulin resistance and incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
HOMA-IR						
Continuous (per SD = 1.91 units)	290/4,653	0.81	1.19 (1.07-1.33)	1.20 (1.07-1.33)	1.15 (1.03-1.29)	1.05 (0.92-1.19)
Quartile 1	60/1,175	0.61	Ref	Ref	Ref	Ref
Quartile 2	75/1,153	0.83	1.34 (0.96-1.88)	1.27 (0.91-1.79)	1.29 (0.92-1.81)	1.15 (0.81-1.63)
Quartile 3	68/1,174	0.76	1.21 (0.85-1.71)	1.20 (0.85-1.69)	1.09 (0.77-1.56)	0.91 (0.63-1.32)
Quartile 4	87/1,151	1.07	1.80 (1.29-2.50)	1.68 (1.21-2.34)	1.55 (1.11-2.17)	1.15 (0.78-1.69)
QUICKI						
Continuous (per SD = 0.032 units)	290/4,653	0.81	1.17 (1.04-1.32)	1.16 (1.02-1.31)	1.11 (0.98-1.26)	0.97 (0.84-1.12)
Quartile 1	60/1,160	0.62	Ref	Ref	Ref	Ref
Quartile 2	75/1,148	0.83	1.34 (0.95-1.88)	1.28 (0.91-1.80)	1.30 (0.92-1.83)	1.16 (0.82-1.64)
Quartile 3	67/1,179	0.74	1.17 (0.83-1.66)	1.16 (0.82-1.64)	1.06 (0.74-1.51)	0.87 (0.60-1.26)
Quartile 4	88/1,166	1.07	1.78 (1.28-2.47)	1.66 (1.19-2.30)	1.53 (1.09-2.14)	1.12 (0.77-1.65)
TyG						
Continuous (per SD = 0.54 units)	290/4,653	0.81	1.08 (0.97-1.22)	1.15 (1.02-1.30)	1.08 (0.94-1.25)	0.99 (0.85-1.16)
Quartile 1	65/1,170	0.71	Ref	Ref	Ref	Ref
Quartile 2	74/1,158	0.81	1.10 (0.79-1.53)	1.09 (0.78-1.52)	1.01 (0.72-1.42)	0.94 (0.66-1.32)
Quartile 3	65/1,162	0.73	0.98 (0.70-1.38)	0.99 (0.70-1.40)	0.89 (0.62-1.27)	0.76 (0.52-1.10)
Quartile 4	86/1,163	0.98	1.28 (0.92-1.76)	1.48 (1.07-2.05)	1.27 (0.88-1.84)	1.02 (0.68-1.53)

Hazard ratios (95% CI) for the relation of HOMA-IR, QUICKI, and TyG with incident HF. An increase in HOMA-IR and TyG represents an increase in insulin resistance, while an increase in QUICKI represents a decrease in insulin resistance. To facilitate a comparison of the various measures, the results for QUICKI are shown per SD decrease and the ranking of the quartiles is reversed (i.e. Quartile 1 includes patients with the highest QUICKI and Quartile 4 patients with the lowest QUICKI).

Quartiles, median (range): HOMA-IR: Quartile 1, 1.18 (0.39-1.58); Quartile 2, 1.96 (1.59-2.36); Quartile 3, 2.88 (2.37-3.64); Quartile 4, 4.95 (3.65-30.80); QUICKI: Quartile 1, 0.374 (0.357-0.455); Quartile 2, 0.345 (0.336-0.357); Quartile 3, 0.326 (0.316-0.336); Quartile 4, 0.303 (0.244-0.316); TyG: Quartile 1, 8.1 (6.9-8.3); Quartile 2, 8.5 (8.3-8.6); Quartile 3, 8.8 (8.6-9.0); Quartile 4, 9.3 (9.0-11.3).

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus waist circumference, systolic blood pressure, triglycerides (not in the analyses with TyG), and HDL-c. The analyses were not adjusted for fasting glucose, as fasting glucose is included in the HOMA-IR, QUICKI, and TyG formulas.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, QUICKI = quantitative insulin sensitivity check index, Ref = reference, SD = standard deviation, TyG = triglyceride-glucose index.

Table S12. Relation between various measures of obesity and incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Waist circumference						
Continuous (per SD = 4.7 inches)	290/4,653	0.81	1.41 (1.26-1.58)	1.38 (1.21-1.57)	1.34 (1.17-1.53)	1.31 (1.13-1.52)
Body-mass index						
Continuous (per SD = 4.0 kg/m^2)	290/4,653	0.81	1.13 (1.01-1.26)	1.23 (1.08-1.39)	1.22 (1.08-1.38)	1.18 (1.03-1.36)
Waist-to-hip ratio						
Continuous (per SD = 0.081 units)	290/4,653	0.81	1.56 (1.39-1.76)	1.48 (1.29-1.71)	1.38 (1.19-1.59)	1.34 (1.15-1.57)
Visceral fat						
Continuous (per SD = 0.96 inches)	290/4,653	0.81	1.39 (1.25-1.55)	1.33 (1.19-1.50)	1.28 (1.14-1.45)	1.26 (1.11-1.44)
Visceral/total fat %						
Continuous (per SD = 9.2%)	290/4,653	0.81	1.54 (1.35-1.75)	1.36 (1.17-1.56)	1.31 (1.13-1.52)	1.30 (1.12-1.51)

Hazard ratios (95% CI) for the relation of waist circumference, BMI, waist-to-hip ratio, visceral fat, and contribution of visceral to total abdominal fat (visceral/total fat %) with incident HF.

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR, systolic blood pressure, triglycerides, and HDL-c. The analyses were not adjusted for fasting glucose, as fasting glucose is included in the HOMA-IR formula.

Abbreviations: AAA = abdominal aortic aneurysm, BMI = body-mass index, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, SD = standard deviation.

Table S13. Reverse causality assessment

	Total population, HR (95% CI)	Exclude events <1 year, HR (95% CI)	Exclude events <2 years, HR (95% CI)	Exclude events <5 years, HR (95% CI)
Events/Patients	290/4,653	260/4,623	244/4,607	189/4,552
Metabolic syndrome				
ATP III definition	1.32 (1.04-1.68)	1.30 (1.01-1.68)	1.29 (0.99-1.68)	1.35 (1.00-1.82)
No. of criteria (per 1 criterion)	1.17 (1.06-1.29)	1.17 (1.05-1.30)	1.17 (1.05-1.30)	1.18 (1.04-1.33)
Waist circumference (per SD = 4.7 inches)	1.34 (1.17-1.53)	1.35 (1.17-1.55)	1.34 (1.16-1.55)	1.37 (1.16-1.61)
Systolic blood pressure (per SD = 20 mmHg)	0.96 (0.86-1.08)	1.02 (0.91-1.15)	1.00 (0.89-1.13)	0.99 (0.86-1.14)
Triglycerides (per SD = 87 mg/dL)	1.06 (0.94-1.20)	1.03 (0.90-1.18)	1.04 (0.90-1.19)	1.10 (0.96-1.27)
HDL-cholesterol (per SD = 14 mg/dL)	0.91 (0.80-1.04)	0.92 (0.81-1.06)	0.90 (0.78-1.03)	0.87 (0.74-1.02)
Fasting glucose (per SD = 12 mg/dL)	1.10 (0.98-1.22)	1.06 (0.94-1.20)	1.05 (0.92-1.19)	1.05 (0.91-1.21)
Insulin resistance				
HOMA-IR (per SD = 1.91 units)	1.15 (1.03-1.29)	1.10 (0.97-1.24)	1.08 (0.95-1.23)	1.11 (0.95-1.29)

Hazard ratios (95% CI) for the relation between metabolic risk factors and incident HF in the total population, and after excluding patients who had incident HF within the first 1, 2, and 5 years after inclusion. All estimates were adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, SD = standard deviation.

Table S14A. Potential effect modifiers in the relation of metabolic syndrome and HOMA-IR with incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Metabolic syndrome (ATP III definition), HR (95% CI)	Metabolic syndrome (per 1 criterion), HR (95% CI)	HOMA-IR (per SD = 1.91 units), HR (95% CI)
Age					
p-value for interaction			0.204	0.114	0.322
<50 years	17/794	0.26	1.33 (0.47-3.76)	1.30 (0.90-1.89)	1.22 (0.82-1.82)
50-59 years	46/1,412	0.39	1.37 (0.75-2.53)	1.22 (0.96-1.55)	1.19 (0.89-1.58)
60-69 years	123/1,602	1.03	1.65 (1.14-2.39)	1.22 (1.05-1.42)	1.13 (0.95-1.34)
≥70 years	104/845	1.82	1.00 (0.67-1.51)	1.04 (0.86-1.24)	1.17 (0.96-1.43)
Sex					
p-value for interaction			0.385	0.792	0.279
Male	231/3,347	0.90	1.22 (0.93-1.60)	1.15 (1.03-1.28)	1.11 (0.98-1.25)
Female	59/1,306	0.57	1.81 (1.04-3.15)	1.26 (1.00-1.58)	1.32 (1.02-1.71)
CVD location					
p-value for interaction			0.447	0.376	0.070
CAD with MI	95/1,268	1.02	1.76 (1.14-2.70)	1.24 (1.05-1.47)	1.32 (1.11-1.57)
CAD without MI	65/1,212	0.67	1.09 (0.66-1.78)	1.04 (0.84-1.30)	1.16 (0.93-1.45)
CeVD	28/1,118	0.31	1.34 (0.62-2.92)	1.32 (0.95-1.82)	1.44 (0.96-2.17)
PAD or AAA	32/527	0.75	0.80 (0.37-1.69)	0.97 (0.70-1.34)	0.64 (0.36-1.12)
Polyvascular	70/528	1.90	1.28 (0.78-2.09)	1.19 (0.97-1.47)	0.99 (0.78-1.26)

Hazard ratios (95% CI) for the relation of metabolic syndrome and HOMA-IR with incident HF in subgroups of age, sex, and CVD location. Hazard ratios were adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA where appropriate. P-values for the interaction between metabolic risk factors and the potential effect modifiers are provided. Following a Bonferroni correction for multiple testing, only p-values <0.006 should be regarded significant.

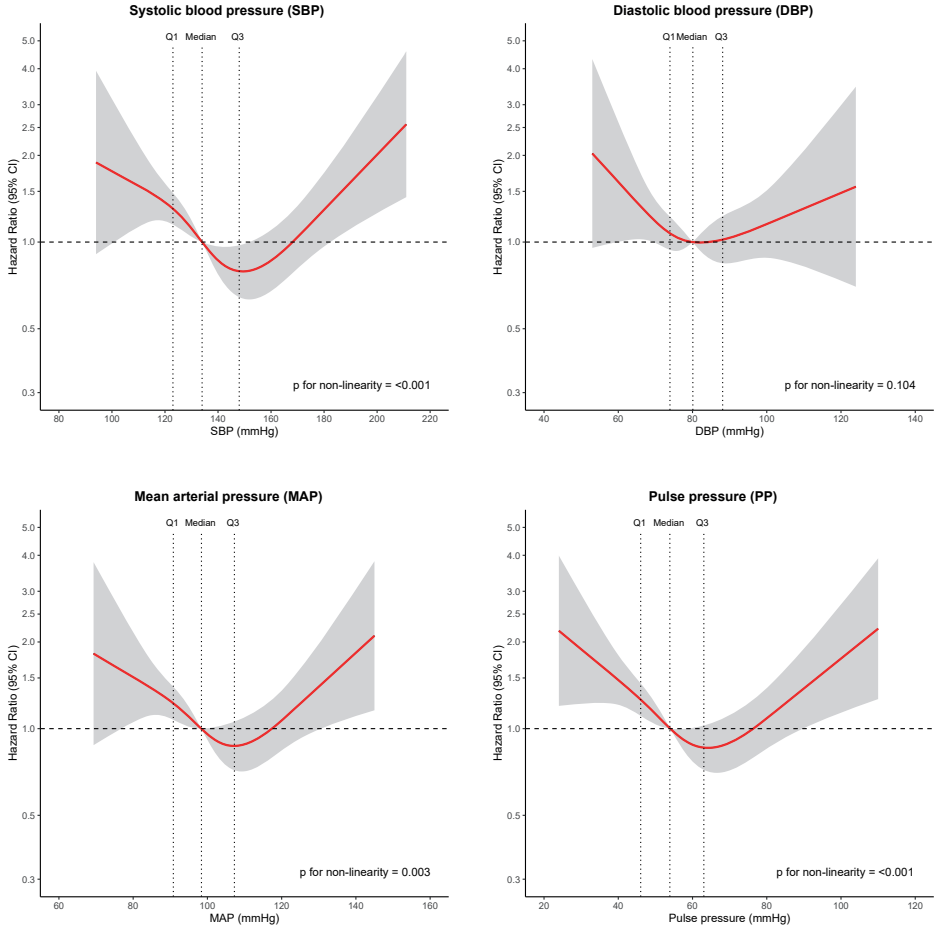
Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, SD = standard deviation.

Table S14B. Potential effect modifiers in the relation of metabolic syndrome components with incident HF

	Events/ Patients	Event rate (events/ 100 PY)	Waist circumference (per SD = 4.7 inches), HR (95% CI)	Systolic blood pressure (per SD = 20 mmHg), HR (95% CI)	Triglycerides (per SD = 87 mg/dL), HR (95% CI)	HDL-c (per SD = 14 mg/dL), HR (95% CI)	Fasting glucose (per SD = 12 mg/dL), HR (95% CI)
Age							
p-value for interaction			0.215	0.179	0.098	0.753	0.657
<50 years	17/794	0.26	1.14 (0.69-1.89)	1.31 (0.76-2.26)	1.05 (0.82-1.34)	0.91 (0.52-1.58)	0.72 (0.37-1.42)
50-59 years	46/1,412	0.39	1.48 (1.08-2.03)	1.06 (0.77-1.45)	0.97 (0.72-1.31)	1.07 (0.75-1.52)	1.32 (1.00-1.75)
60-69 years	123/1,602	1.03	1.57 (1.28-1.93)	0.93 (0.78-1.12)	1.02 (0.82-1.26)	0.85 (0.69-1.04)	1.12 (0.95-1.32)
≥70 years	104/845	1.82	1.08 (0.85-1.37)	0.97 (0.81-1.16)	1.19 (0.89-1.58)	0.91 (0.74-1.12)	1.08 (0.90-1.31)
Sex							
p-value for interaction			0.483	0.409	0.488	0.587	0.089
Male	231/3,347	0.90	1.29 (1.10-1.50)	0.96 (0.84-1.09)	1.06 (0.91-1.23)	0.96 (0.82-1.12)	1.04 (0.92-1.18)
Female	59/1,306	0.57	1.48 (1.13-1.95)	0.94 (0.75-1.18)	1.06 (0.83-1.35)	0.78 (0.61-1.00)	1.35 (1.07-1.71)
CVD location							
p-value for interaction			0.064	0.573	0.060	0.641	0.735
CAD with MI	95/1,268	1.02	1.64 (1.31-2.04)	0.90 (0.73-1.10)	1.21 (1.01-1.46)	0.95 (0.73-1.23)	1.20 (0.99-1.45)
CAD without MI	65/1,212	0.67	1.32 (0.99-1.75)	0.97 (0.76-1.24)	1.08 (0.81-1.45)	0.84 (0.63-1.13)	1.04 (0.84-1.29)
CeVD	28/1,118	0.31	1.21 (0.79-1.87)	1.08 (0.74-1.58)	1.41 (1.11-1.80)	0.74 (0.50-1.09)	0.88 (0.57-1.37)
PAD or AAA	32/527	0.75	0.98 (0.67-1.44)	1.28 (0.91-1.81)	0.60 (0.33-1.10)	0.95 (0.71-1.29)	1.25 (0.86-1.81)
Polyvascular	70/528	1.90	1.23 (0.92-1.64)	0.91 (0.72-1.16)	0.89 (0.66-1.21)	0.99 (0.77-1.28)	1.02 (0.81-1.30)

Hazard ratios (95% CI) for the relation of the individual components of the metabolic syndrome with incident HF in subgroups of age, sex, and CVD location. Hazard ratios were adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA where appropriate. P-values for the interaction between metabolic risk factors and the potential effect modifiers are provided. Following a Bonferroni correction for multiple testing, only p-values <0.003 should be regarded significant. Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years, SD = standard deviation.

Figure S1. Continuous relation between measures of blood pressure and incident HF



Hazard ratios for the continuous relation between various measures of blood pressure and incident HF, based on restricted cubic splines. Models were adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA. MAP was calculated using the formula: MAP = (2*DBP + SBP)/3. PP was calculated as SBP – DBP. The vertical dashed lines represent the 25th percentile (Q1), median, and 75th percentile (Q3) of the blood pressure measurement in the study population. Shaded areas represent 95% confidence intervals.

Part II.

Individualized prediction of risk and treatment effects

Chapter 5.

Personalized lifetime prediction of survival and treatment benefit in patients with heart failure with reduced ejection fraction: the LIFE-HF model

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Abstract

Aims

Although trials have proven the group-level effectiveness of various therapies for heart failure with reduced ejection fraction (HFrEF), important differences in absolute effectiveness exist between individuals. We developed and validated the LIFEtime-perspective for Heart Failure (LIFE-HF) model for the prediction of individual (lifetime) risk and treatment benefit in patients with HFrEF.

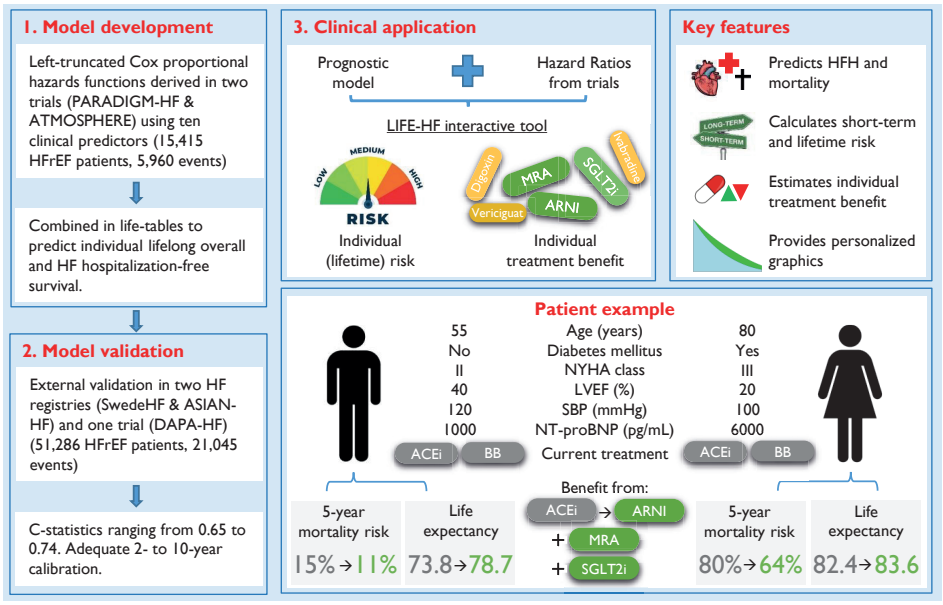
Methods and results

Cox proportional hazards functions with age as the time scale were developed in the PARADIGM-HF and ATMOSPHERE trials (n = 15,415). Outcomes were cardiovascular death, HF hospitalization or cardiovascular death, and non-cardiovascular mortality. Predictors were age, sex, New York Heart Association class, prior HF hospitalization, diabetes mellitus, extracardiac vascular disease, systolic blood pressure, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, and glomerular filtration rate. The functions were combined in life-tables to predict individual overall and HF hospitalization-free survival. External validation was performed in the SwedeHF registry, ASIAN-HF registry, and DAPA-HF trial (n = 51,286). Calibration of 2- to 10-year risk was adequate, and c-statistics were 0.65-0.74. An interactive tool was developed combining the model with hazard ratios from trials to allow estimation of an individual's (lifetime) risk and treatment benefit in clinical practice. Applying the tool to the development cohort, combined treatment with a mineralocorticoid receptor antagonist (MRA), sodium/glucose cotransporter 2 (SGLT2) inhibitor, and angiotensin receptor–neprilysin inhibitor (ARNI) was estimated to afford a median of 2.5 (interquartile range [IQR] 1.7-3.7) and 3.7 (IQR 2.4-5.5) additional years of overall and HF hospitalization-free survival respectively.

Conclusion

The LIFE-HF model enables estimation of lifelong overall and HF hospitalization-free survival, and (lifetime) treatment benefit for individual patients with HFrEF. It could serve as a tool to improve the management of HFrEF by facilitating personalized medicine and shared decision-making.

Graphical abstract



Introduction

Patients with heart failure with reduced ejection fraction (HFrEF) are at high risk of morbidity and mortality, with 5-year mortality rates as high as 43-75%.[1] This is despite considerable progress in the development of new treatments. Besides conventional therapy consisting of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), and a beta-blocker, international guidelines identify three drug classes with a class I recommendation: mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), and sodium/glucose cotransporter 2 (SGLT2) inhibitors.[2,3] However, the use of these therapies in clinical practice remains suboptimal.[4–7]

A recent analysis suggested that optimal guideline-recommended pharmacological therapy could afford, on average, considerable gains in lifetime survival for patients with HFrEF.[8] However, the absolute effectiveness of therapy varies greatly between individuals, depending on a patient's baseline risk and remaining life expectancy.[9,10] Although many prediction models exist for patients with HFrEF, estimating the 1- to 5-year risk of hospitalization and mortality, no models are available to predict individual lifetime risk and treatment benefit.[11–15] As HFrEF is a chronic disease and therapies are usually continued lifelong, lifetime estimates of an individual's risk and anticipated benefit from treatment are important. In other populations, i.e. primary and secondary prevention of atherosclerotic CVD, models combining lifetime risk predictions with hazard ratios from trials to estimate an individual's risk, life expectancy, and absolute treatment benefit, are one of the foundations of the 2021 European Society of Cardiology (ESC) CVD Prevention Guidelines.[16–19] A similar tool for patients with HFrEF could improve their management by facilitating personalized medicine and shared decision-making.

The primary objective of this study was to develop and externally validate the LIFEtime-perspective for Heart Failure (LIFE-HF) model for personalized lifetime prediction of overall and HF hospitalization-free survival in patients with HFrEF. The secondary objective was to illustrate how the LIFE-HF model can be combined with hazard ratios from trials to predict benefit from guideline-recommended therapies for individual patients.

Methods

Study populations

The derivation cohort included all patients from the PARADIGM-HF (n = 8,399) and ATMOSPHERE (n = 7,016) trials (combined n = 15,415). External validation was performed in the SwedeHF registry (n = 42,063), ASIAN-HF registry (n = 4,479), and DAPA-HF trial (n = 4,744). The choice of derivation cohort was based on the proportions of missing data in the

studies (very low in PARADIGM-HF and ATMOSPHERE but higher in the registries; Table S1). Study details have been described elsewhere and the eligibility criteria are summarised in Table S2.[20–24] All patients had a left ventricular ejection fraction (LVEF) ≤40% at study entry, following the definition of HFrEF in international guidelines.[2,3] Patients remained in the study population regardless of subsequent changes in LVEF. All participants provided informed consent and the studies were approved by local institutional review boards. Missing data were handled by single imputation in the trials and multiple imputation in the registries. If variables were missing for all patients in a validation cohort, population medians (from the derivation cohort) were used (Methods S1).[25]

Outcomes

Outcomes of interest were: 1) overall survival, and 2) HF hospitalization-free survival. These outcomes were predicted by respectively combining functions for cardiovascular (CV) death, and first hospitalization for HF or CV death, with a function for non-CV mortality. Outcome definitions are described in Table S3.

Predictors

Based on existing risk scores and availability in the derivation cohort, 24 candidate predictors were selected (Table S4).[11–15] All candidate predictors were entered in a Cox proportional hazards function for first hospitalization for HF or CV death (as this endpoint represents both hospitalization and mortality), derived in the derivation cohort (Methods S2). Backward selection was performed based on the Akaike Information Criterion (AIC). All independent predictors were selected for the development of an extended model. To facilitate uptake in clinical practice, the core model was reduced to the ten strongest predictors (with the highest chi-square statistics). This selection of predictors was presented to a panel of HF experts. The final selection of predictors for the core model was based on their feedback. The same predictors were used for all outcomes. Randomized treatments (i.e. sacubitril/valsartan, aliskiren, and aliskiren/enalapril combination therapy) were forced into the model using offset terms and the hazard ratios from the original trial reports.[20,21] Non-randomized treatments were not considered as candidate predictors, as their prognostic effect largely depends on their indication, which may vary over time and across regions.

Model development

Using data from the 15,415 patients in PARADIGM-HF and ATMOSPHERE, cause-specific Cox proportional hazards functions including the previously selected predictors were derived for: 1) CV death, 2) first hospitalization for HF or CV death, and 3) non-CV mortality. These functions allow the use of age as time scale (i.e. left truncation), meaning that participants contribute from their age at study entry to their age at end of follow-up.[10] This enables estimation of age-specific baseline survivals used to make predictions beyond the follow-up duration of the original cohorts (Methods S3). Continuous predictors were winsorized at the 1st and 99th percentile, and quadratic or logarithmic transformations were included if they substantially improved model fit. There was no evidence for interaction of predictors with age based on visual inspection of plotted Schoenfeld residuals. To reduce optimism, shrinkage was applied to model coefficients using ridge regression (Methods S4). The model was adjusted for geographical differences in baseline risk (Methods S5). Model assumptions are described in Table S5.

Prediction of individual risk and life expectancy

Individual predictions were based on life-tables.[10,17–19] Overall survival was predicted by combining the function for CV death with the function for non-CV death. For each patient, the risk of CV death (a_t) and the risk of non-CV death (b_t) were estimated for each 3-month age interval from the patient's age at baseline up to the maximum age of 95 years. A survival probability (p_t) was obtained for each interval ($p_t = 1 - a_t - b_t$). Cumulative survival probabilities (e_t) were calculated by multiplying the survival probabilities of consecutive intervals (e.g. for a 60-year-old: $e_{t=95} = p_{t=60} * p_{t=60.25} * \ldots * p_{t=94.5} * p_{t=94.75}$). Likewise, HF hospitalization-free survival was predicted by combining the function for first hospitalization for HF or CV death with the function for non-CV death. These predictions form an individual life-table for each patient, from which estimates can be derived for the any-year risk of CV death, first hospitalization for HF or CV death, non-CV mortality, all-cause mortality (i.e. 1 minus overall survival), and first hospitalization for HF or all-cause mortality (i.e. 1 minus HF hospitalization-free survival). Overall and HF hospitalization-free life expectancy were defined as the age where the cumulative overall/HF hospitalization-free survival probability in the life-table equalled 0.50 (i.e. the median life expectancy for a group of patients with identical characteristics). A detailed description of the methodology is provided in Methods S6, with an example of a life-table presented in Table S6.

Model validation

Internal validity was assessed using Harrell's c-statistic for discrimination, and calibration plots of the predicted vs. observed 2-year risk for all outcomes. Additionally, validation was performed in subgroups of MRA and digoxin users and non-users (i.e. therapies of interest already prescribed in a considerable proportion of the derivation cohort at baseline), patients with and without device therapies, patients with an LVEF of 36-40% (as eligibility criteria largely precluded their inclusion in the derivation cohort), and stratified by sex and race. External validation was performed in SwedeHF (5-year risks), ASIAN-HF (3-year risks), and DAPA-HF (2-year risks). In SwedeHF, the model was additionally validated over a 10-year period for all-cause mortality. In DAPA-HF, the model was also validated separately in the intervention and control arm. Discrimination and goodness of fit were assessed using c-statistics and calibration plots for all outcomes. If necessary, the model was recalibrated for differences in baseline risk. C-statistics were compared to those of existing models in SwedeHF.

Sensitivity analysis

Models were derived stratified by sex, and MRA use at baseline (as an MRA was one of the main therapies of interest but was already prescribed in 47% of patients from the derivation cohort at baseline). Stratified models were compared to the core model in the derivation cohort.

Prediction of individual treatment benefit

First, the prognostic model is used to estimate a patient's (lifetime) risk on current treatment. Then, the model is combined with causal hazard ratios from trials (Table S7) for the treatment(s) of interest, to estimate a patient's (lifetime) risk on a new treatment regimen (Methods S7).[10,17–19] Individual absolute risk reduction (ARR) with a new treatment is calculated as the difference between the predicted risk on the current and new treatment regimen. Similarly, individual lifetime benefit is calculated as the difference between the predicted life expectancy on current and new treatment. Use of an ACE inhibitor (or equivalent, i.e. ARB), and a beta-blocker is already assumed by the model due to the background and comparator treatment in the derivation cohort. In line with guideline recommendations, treatment benefits can be estimated for MRAs, ARNI, and SGLT2 inhibitors in all patients, and ivabradine, vericiguat, and digoxin in selected patients.[2,3] Therapies were assumed to have no effect on non-CV mortality, among other assumptions (Table S5).

All statistical analyses were performed using R Statistics, version 4.0.3.

Results

Study populations

Baseline characteristics are presented in Table 1, and Table S8 (PARADIGM-HF and ATMOSPHERE separately). In total, 30,594 composite outcomes (of which 22,141 hospitalizations for HF, and 8,453 CV deaths), 18,283 CV deaths, and 8,746 non-CV deaths were recorded during a median follow-up of 3.1 (interquartile range [IQR] 1.6-5.4) years. Composite outcome rates were higher in SwedeHF and ASIAN-HF compared to the trial cohorts (Table S9 & Figure S1). Non-CV mortality rates were highest in SwedeHF. In SwedeHF (only cohort with follow-up beyond five years), median overall and HF hospitalization-free survival were 6.1 and 2.9 years, and 10-year survival rates were 33% (ranging from 73% in women <60 years to 5% in men ≥80 years) and 21% (ranging from 47% in women <60 years to 3% in men ≥80 years) respectively (Figure S1).

Table 1. Baseline characteristics

	Derivation cohort (n = 15,415)	SwedeHF (n = 42,063)	ASIAN-HF (n = 4,479)	DAPA-HF (n = 4,744)
Demographics				
Age	64 (56-72)	73 (64-81)	61 (52-69)	67 (60-74)
Sex (male)	12,058 (78%)	29,875 (71%)	3,508 (78%)	3,635 (77%)
Race				
White	10,136 (66%)	NA	..	3,333 (70%)
Black	537 (4%)	NA	..	226 (5%)
Asian	3,273 (21%)	NA	4,479 (100%)	1,116 (24%)
Other	1,415 (9%)	NA	..	69 (1%)
Region				
North America	779 (5%)	..	..	677 (14%)
Latin America	2,552 (17%)	..	..	817 (17%)
Western Europe	3,902 (25%)	42,063 (100%)	..	2,154 (45%)[a]
Central/Eastern Europe	4,770 (31%)	..	..	..
Asia-Pacific	3,412 (22%)	..	4,479 (100%)	1,096 (23%)
Clinical features of heart failure				
Ischemic aetiology	8,122 (53%)	9,298 (45%)	2,627 (59%)	2,674 (56%)
Duration of heart failure				
<1 year	4,884 (32%)	27,308 (65%)	2,060 (46%)	1,098 (23%)
1-5 years	5,825 (38%)	6,268 (15%)	1,433 (32%)	1,791 (38%)
>5 years	4,702 (30%)	8,487 (20%)	986 (22%)	1,855 (39%)
NYHA class				
I	389 (3%)	2,875 (9%)	594 (15%)	..
II	10,355 (67%)	14,668 (47%)	2,263 (56%)	3,203 (68%)
III	4,459 (29%)	12,428 (40%)	1,037 (26%)	1,498 (32%)

	Derivation cohort (n = 15,415)	SwedeHF (n = 42,063)	ASIAN-HF (n = 4,479)	DAPA-HF (n = 4,744)
IV	197 (1%)	1,137 (4%)	161 (4%)	43 (1%)
Left ventricular ejection fraction (%)	30 (25-34)	NA	27 (22-33)	32 (26-37)
30-39	..	21,201 (50%)	..	..
<30	..	20,862 (50%)	..	..
Medical history				
Prior hospitalization for heart failure	9,462 (61%)	24,535 (58%)	3,434 (78%)	2,251 (47%)
Diabetes mellitus	4,832 (31%)	11,019 (26%)	1,909 (43%)	2,139 (45%)
Atrial fibrillation	5,481 (36%)	21,350 (51%)	804 (18%)	1,818 (38%)
Extracardiac vascular disease	2,411 (16%)	8,352 (20%)	445 (10%)	739 (16%)
Prior stroke	1,217 (8%)	5,601 (13%)	321 (7%)	466 (10%)
Peripheral artery disease	1,418 (9%)	3,477 (8%)	147 (3%)	324 (7%)
Left bundle branch block	3,970 (26%)	8,544 (24%)	575 (13%)	NA
Physical signs				
Systolic blood pressure (mmHg)	127 (115-140)	120 (110-140)	116 (104-130)	121 (110-132)
Heart rate (bpm)	72 (64-80)	72 (64-84)	78 (69-88)	70 (63-78)
Body-mass index (kg/m^2)	27.1 (24.0-30.8)	26.0 (23.0-29.6)	24.3 (21.7-27.5)	27.0 (24.0-31.0)
Laboratory tests				
NT-proBNP (pg/mL)	1418 (770-2774)	2885 (1268-6396)	3015 (1425-6908)[b]	1437 (857-2649)
Sinus rhythm	1244 (694-2521)	2556 (1114-5781)	2831 (1333-6698)[b]	1242 (742-2325)
Atrial fibrillation	1702 (998-3102)	3116 (1370-6603)	3542 (1712-7527)[b]	1795 (1106-3041)
Estimated GFR (mL/min/1.73 m^2)	70 (57-83)	64 (47-82)	63 (44-82)	64 (51-80)
Potassium (mmol/L)	4.5 (4.2-4.7)	4.2 (3.9-4.5)	4.2 (3.9-4.6)	4.5 (4.2-4.8)
Sodium (mmol/L)	141 (139-143)	140 (138-142)	138 (136-141)	140 (138-142)
Haemoglobin (g/dL)	14.0 (12.9-15.0)	13.5 (12.3-14.7)	13.0 (11.6-14.5)	13.6 (12.5-14.6)
Total bilirubin (µmol/L)	11 (9-16)	NA	14 (10-21)	10 (7-14)
Uric acid (µmol/L)	419 (345-506)	NA	412 (327-506)	NA
Treatments				
Diuretic	12,336 (80%)	32,046 (77%)	3,727 (84%)	4,433 (93%)
ACE inhibitor	8,888 (58%)[c]	27,878 (67%)	2,261 (51%)	2,661 (56%)
ARB	..	10,173 (25%)	1,402 (32%)	1,307 (28%)
ARNI	4,187 (27%)[c]	732 (2%)	..	508 (11%)
Aliskiren	4,680 (30%)[c]	..	..	..
Beta-blocker	14,243 (92%)	38,357 (92%)	3,551 (80%)	4,558 (96%)

	Derivation cohort (n = 15,415)	SwedeHF (n = 42,063)	ASIAN-HF (n = 4,479)	DAPA-HF (n = 4,744)
Digoxin	4,781 (31%)	6,105 (15%)	1,190 (27%)	887 (19%)
MRA	7,273 (47%)	15,432 (37%)	2,619 (59%)	3,370 (71%)
SGLT2 inhibitor	..	184 (0.4%)	..	2,373 (50%)[c]
Implantable cardioverter-defibrillator	1,819 (12%)	2,614 (6%)	526 (12%)	1,242 (26%)
Cardiac resynchronization therapy	967 (6%)	1,906 (5%)	351 (8%)	354 (8%)

Baseline characteristics are based on non-imputed data. Continuous variables are presented as median (IQR). Categorical variables are presented as n (%), with percentages referring to complete cases.

Abbreviations: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor-neprilysin inhibitor, GFR = glomerular filtration rate, IQR = interquartile range, MRA = mineralocorticoid receptor antagonist, NA = not available, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association, SD = standard deviation, SGLT2 = sodium/glucose cotransporter 2.

[a] In DAPA-HF a distinction between Western and Central/Eastern Europe was not made. The number of patients in the region 'Europe' is presented.
[b] In ASIAN-HF, NT-proBNP was available for only 23.2% of patients and was likely selectively measured in decompensated individuals. Actual values might be considerably lower.
[c] Therapies used as part of a trial intervention, or active control.

Predictor selection

Ordered from highest to lowest predictive value, the ten strongest predictors initially selected in the core model were: N-terminal pro-B-type natriuretic peptide (NT-proBNP), diabetes mellitus, New York Heart Association (NYHA) class III/IV, prior hospitalization for HF, extracardiac vascular disease (i.e. prior stroke or peripheral artery disease), systolic blood pressure (SBP), uric acid, total bilirubin, LVEF, and sex (Table S10). Additionally, the following seven predictors were selected in the extended model: body-mass index (BMI), estimated glomerular filtration rate (eGFR), sodium, potassium, left bundle branch block (LBBB), heart rate, and haemoglobin. Based on the expert panel's feedback, uric acid and total bilirubin were removed from the final core model, and eGFR was added.

Model development

Hazard ratios in the functions for CV death, first hospitalization for HF or CV death, and non-CV mortality are shown in Table 2 (core model), and Table S11 (model with ten strongest predictors and extended model). Age-specific baseline survivals are presented in Table S12, and Figure S2 shows how these were derived. Geographical differences in baseline risk were small for hospitalization for HF or CV death (ratios for expected divided by observed risk [E/O ratios] 0.93-1.12), but more substantial for CV death alone (E/O ratios ranging from 0.80 in Latin America to 1.42 in Western Europe; Table S13).

The complete risk algorithms are provided in Table S14. The core model was developed into an interactive calculator to allow calculation of a patient's risk in clinical practice (Supplementary Material; Calculator).

Table 2. Hazard ratios in the core LIFE-HF model

	CV death, HR (95% CI)	First hospitalization for HF or CV death, HR (95% CI)	Non-CV mortality, HR (95% CI)
Sex (male)	1.37 (1.24-1.51)	1.31 (1.21-1.41)	1.55 (1.23-1.94)
NYHA class (III/IV)	1.41 (1.31-1.52)	1.35 (1.27-1.44)	1.02 (0.85-1.21)
Prior hospitalization for HF	1.13 (1.05-1.22)	1.33 (1.24-1.41)	1.15 (0.96-1.36)
Diabetes mellitus	1.26 (1.16-1.37)	1.46 (1.37-1.56)	1.29 (1.08-1.55)
Extracardiac vascular disease[a]	1.29 (1.17-1.41)	1.30 (1.21-1.41)	1.30 (1.06-1.59)
Systolic blood pressure[b]	0.81 (0.76-0.86)	0.84 (0.80-0.88)	1.00 (0.88-1.14)
Left ventricular ejection fraction[b]	0.89 (0.84-0.94)	0.86 (0.81-0.91)[c]	0.97 (0.85-1.10)
NT-proBNP[b]	1.87 (1.78-1.98)[d]	1.79 (1.71-1.87)[d]	1.42 (1.26-1.60)[c]
Estimated GFR[b]	0.94 (0.89-1.00)[c]	0.91 (0.87-0.96)[c]	1.11 (0.98-1.26)

Hazard ratios in the Cox proportional hazards functions constituting the core LIFE-HF model. As all outcomes in this study could be predicted by combining these three functions in life-tables, separate functions for first hospitalization for HF, and all-cause mortality were not derived, and hazard ratios are not shown for these outcomes.

Abbreviations: CI = confidence interval, GFR = glomerular filtration rate, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association.

[a] Prior stroke or history of peripheral artery disease.
[b] For all continuous variables, HRs are shown for the 75th vs. 25th percentile (systolic blood pressure 140 vs. 115 mmHg; left ventricular ejection fraction 34 vs. 25%; NT-proBNP 2774 vs. 770 pg/mL; estimated GFR 83 vs. 57 mL/min/1.73 m^2).
[c] Quadratically transformed variable.
[d] Logarithmically transformed variable.

Internal validation in PARADIGM-HF and ATMOSPHERE

For the core model, c-statistics were 0.68 (95% confidence interval [CI] 0.67-0.69) for overall survival , and 0.67 (95% CI 0.66-0.68) for HF hospitalization-free survival (Table 3). Calibration plots of predicted vs. observed 2-year risk of CV death, first hospitalization for HF or CV death, non-CV mortality, and the combined outcomes (i.e. all-cause mortality, and first hospitalization for HF or all-cause mortality) are provided in Figure S3. For the combined outcomes, calibration plots are also shown per geographic region in Figure S4. Validation in subgroups showed that calibration was adequate for both men and women (E/O ratios 0.99-1.03), MRA users and non-users (E/O ratios 0.99-1.02), digoxin users and non-users (E/O ratios 0.90-1.07), patients with and without device therapies (E/O ratios

0.95-1.12), patients with an LVEF of 36-40% (E/O ratios 1.07-1.08), and white and Asian participants (E/O ratios 0.99-1.02; Table S13 & Figure S5). Risks were underestimated in the small group (n = 537) of black participants (E/O ratios 0.70-0.75). Performance of the core model was similar to the model with uric acid and bilirubin, and the extended model (Table S15 & Figure S3).

Table 3. Discrimination of the core LIFE-HF model

	Individual outcomes, c-statistic (95% CI)			Combined outcomes, c-statistic (95% CI)	
	CV death	First hospitalization for HF or CV death	Non-CV mortality[a]	Overall survival	HF hospitalization-free survival
Internal validation	0.69 (0.68-0.70)	0.68 (0.67-0.68)	0.67 (0.65-0.70)	0.68 (0.67-0.69)	0.67 (0.66-0.68)
SwedeHF	0.74 (0.73-0.74)	0.66 (0.66-0.67)	0.65 (0.64-0.65)	0.73 (0.72-0.73)	0.66 (0.66-0.67)
ASIAN-HF	0.65 (0.63-0.67)	0.67 (0.65-0.68)	0.66 (0.62-0.70)	0.65 (0.63-0.66)	0.67 (0.65-0.68)
DAPA-HF	0.71 (0.69-0.74)	0.71 (0.69-0.72)	0.66 (0.60-0.71)	0.70 (0.68-0.72)	0.70 (0.68-0.71)

Harrell's c-statistics for discrimination of the core LIFE-HF model in the derivation and validation cohorts.

Abbreviations: CI = confidence interval.

[a] Discrimination of risk of non-CV mortality can slightly differ depending on which function the function for non-CV mortality is combined with in the life-tables. The results shown in the table are based on analyses in which the function for non-CV mortality was combined with the function for CV death.

Sensitivity analysis

Hazard ratios in the core model all fell within the 95% confidence interval of the hazard ratios derived in strata of sex and MRA use (Table S16). Performance of the stratified models was similar to the core model in all strata (Figure S6). Changes in individual predicted risks were small (Table S17).

External validation in SwedeHF, ASIAN-HF, and DAPA-HF

For the core model, c-statistics for overall and HF hospitalization-free survival were 0.73 (95% CI 0.72-0.73) and 0.66 (95% CI 0.66-0.67) in SwedeHF, 0.65 (95% CI 0.63-0.66) and 0.67 (95% CI 0.65-0.68) in ASIAN-HF, and 0.70 (95% CI 0.68-0.72) and 0.70 (95% CI 0.68-0.71) in DAPA-HF (Table 3). Calibration plots are shown for the combined outcomes in Figure 1, and for the individual outcomes in Figure S7. In ASIAN-HF and DAPA-HF, recalibration of baseline risks was not needed (E/O ratios 0.83-1.17; Table S18). The model calibrated reasonably well in the intervention arm of DAPA-HF (Figure S8), although there was a slight overestimation of risk in this group (E/O ratios 1.11-1.19). In SwedeHF, the

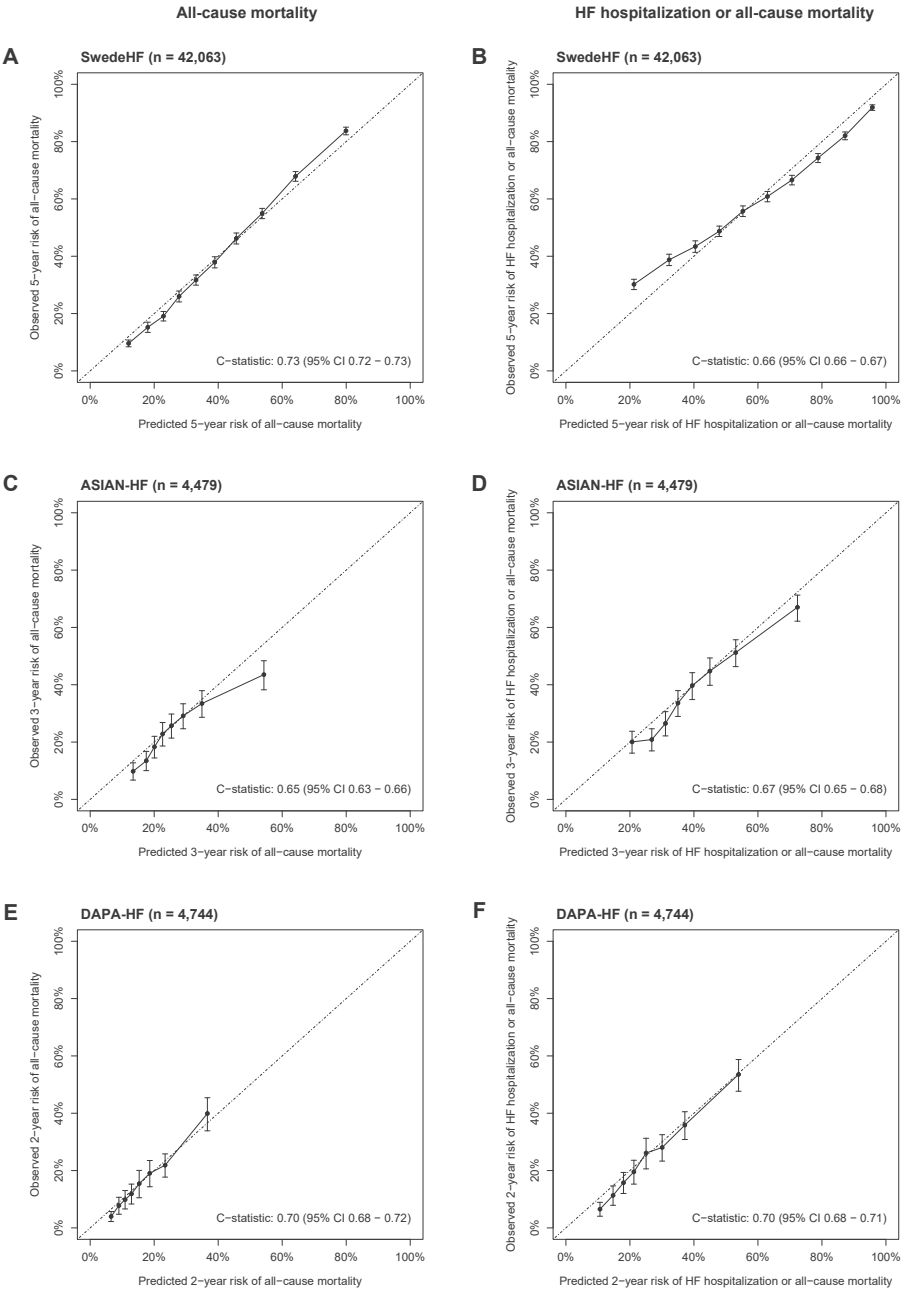
model was recalibrated for differences in baseline risk of CV death (E/O ratio 1.28), and non-CV mortality (E/O ratios 0.56-0.71). After recalibration, calibration was adequate for patients included at the outpatient clinic (i.e. out-patients) and at the end of a hospitalization (i.e. in-patients), MRA users and non-users, patients with and without device therapies, and patients included after January 2010 (E/O ratios 0.90-1.12; Figure S9). For all-cause mortality, the model also showed adequate calibration over a 10-year period, in the total SwedeHF population (E/O ratios 0.97-1.01; Figure 2), and in out-/in-patients and individuals with a life expectancy >5 years (E/O ratios 0.95-1.05; Figure S10). Performance of the core model was similar to the model with uric acid and bilirubin, and the extended model in all validation cohorts (Table S15 & Figure S11). C-statistics were similar to or higher than those of existing models (Figure S12).

Estimation of individual treatment benefit

The LIFE-HF calculator (Supplementary Material; Calculator) also allows for the estimation of individual treatment benefit. Figure 3 (overall survival) and Figure S13 (HF hospitalization-free survival) illustrate how the model is used to estimate treatment benefit for individual patients.

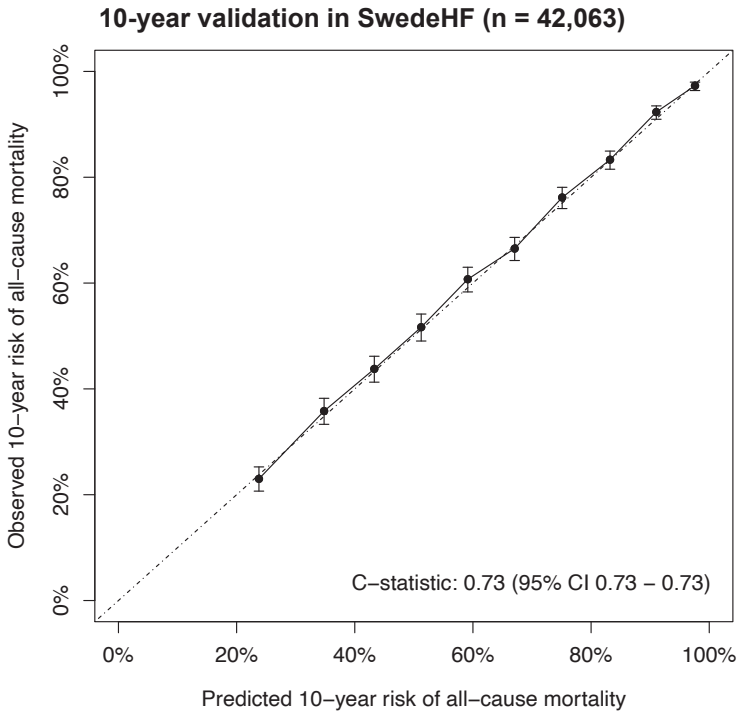
Applying the model to all individuals from the combined PARADIGM-HF and ATMOSPHERE population, the median individual 5-year ARR achieved through treatment optimization (i.e. adding an MRA if not already used, switching from ACE inhibitor to ARNI, and adding an SGLT2 inhibitor) was 7.6% (IQR 5.3-10.8%) for all-cause mortality, and 17.1% (IQR 13.5-22.3%) for hospitalization for HF or all-cause mortality. The same therapy was estimated to afford a median of 2.5 (IQR 1.7-3.7) additional overall, and 3.7 (IQR 2.4-5.5) additional HF hospitalization-free life-years. Five-year ARRs increased with increasing baseline risk (Figure 4). Gains in overall survival decreased with increasing age, and were largest for patients with a moderate 5-year risk of all-cause mortality. Gains in HF hospitalization-free survival decreased with increasing age and baseline risk (Figure S14).

Figure 1. External validation of the core LIFE-HF model



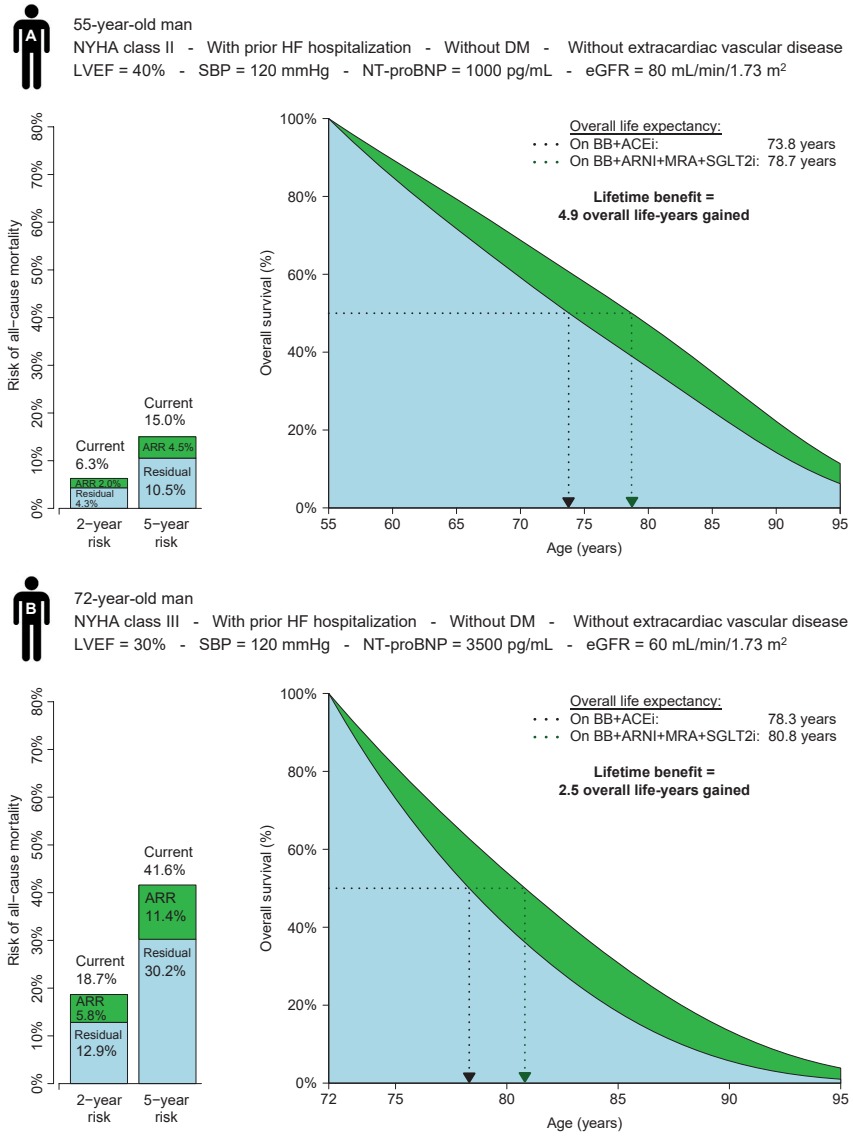
Calibration plots are shown for the predicted risk (as calculated by the core LIFE-HF model) vs. observed risk of all-cause mortality (i.e. 1 minus overall survival) and first hospitalization for HF or all-cause mortality (i.e. 1 minus HF hospitalization-free survival) in SwedeHF (A & B), ASIAN-HF (C & D), and DAPA-HF (E & F). Error bars represent 95% confidence intervals.

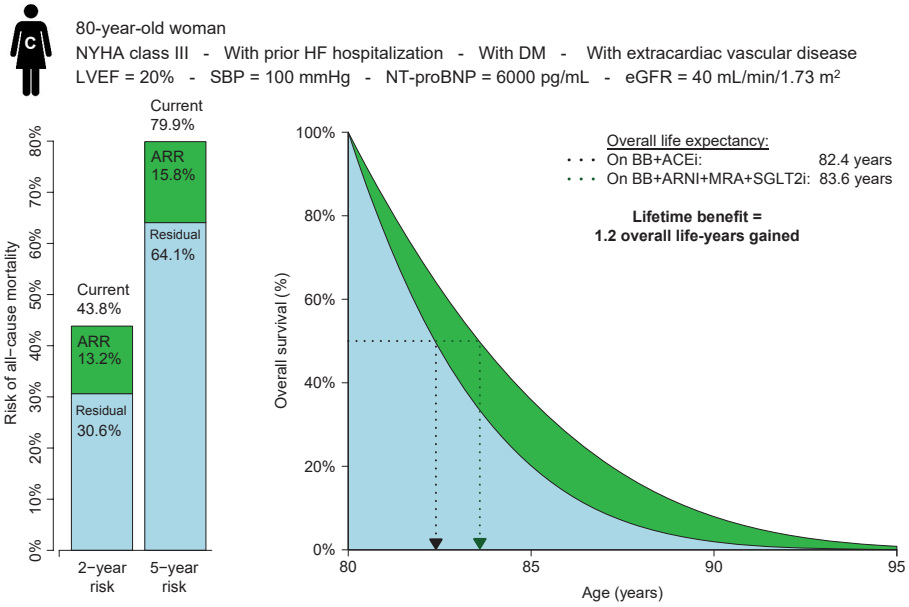
Figure 2. 10-year external validation in SwedeHF



The calibration plot shows the predicted 10-year risk (as calculated by the core LIFE-HF model) vs. observed 10-year risk of all-cause mortality in SwedeHF. Error bars represent 95% confidence intervals.

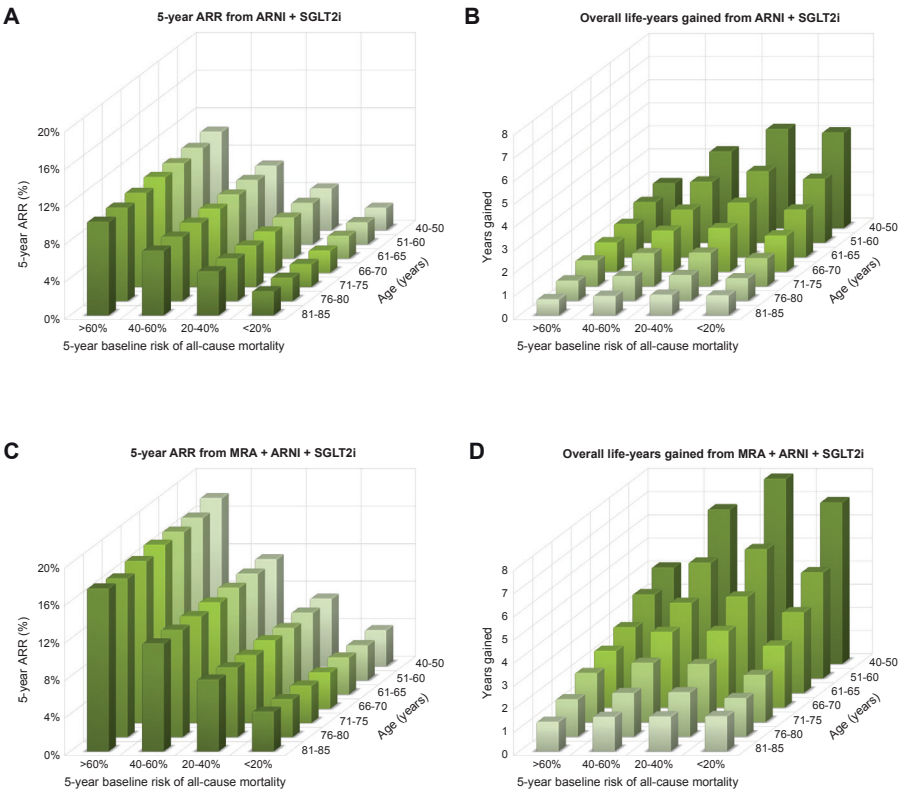
Figure 3. Estimation of individual treatment benefit in exemplar patients





Benefit from switching from ACEi to ARNI, and adding an MRA and an SGLT2i for three exemplar patients currently treated with an ACEi and a beta-blocker. The benefit was estimated using the core LIFE-HF model combined with hazard ratios from the PARADIGM-HF trial, a pooled estimate of the RALES and EMPHASIS-HF trials, and a meta-analysis of the DAPA-HF and EMPEROR-Reduced trials (Table S7), and is presented as absolute reductions in the risk of all-cause mortality, and gain in overall survival. All exemplar patients were from Western Europe.

Figure 4. Treatment benefit stratified by baseline risk and age



Mean 5-year ARR for all-cause mortality (A), and additional years gained in overall survival (B) from switching from ACEi to ARNI and adding an SGLT2i for the 15,415 individuals in PARADIGM-HF and ATMOSPHERE, stratified by baseline 5-year risk and age. Benefit from adding an MRA, switching to ARNI, and adding an SGLT2i is displayed for the 8,142 individuals without an MRA at baseline in PARADIGM-HF and ATMOSPHERE (C & D).

Discussion

Using data of 66,701 individuals, we developed and validated the LIFE-HF model for personalized lifetime prediction of survival and treatment benefit in patients with HFrEF (Graphical Abstract). Unlike previous models, the LIFE-HF model allows estimation of both short-/mid-term risk of HF hospitalization and mortality, and overall and HF hospitalization-free life expectancies for individual patients. Extensive validation demonstrated the predictive reliability of the model in both trial and real-world populations. The model can be combined with the best available evidence from clinical trials to predict individual benefit from guideline-recommended therapies expressed as overall and HF hospitalization-free life-years gained. An interactive calculator has been developed for use in daily clinical practice.

With the LIFE-HF model we expand on previous risk models and a landmark study estimating the lifetime benefits of optimal guideline-recommended therapy for HFrEF on a group level.[8,11–15] The LIFE-HF model can still be used to predict short-/mid-term risk, but in addition enables the prediction of lifetime risk, and allows for the estimation of treatment benefits on an individual level. Lifetime estimates are informative as HFrEF is a chronic disease, and therapies are usually continued lifelong. Some patients may already use one or more of the treatments included in the regimen evaluated by the aforementioned study, or they might have contra-indications for or might not tolerate one of these therapies. The LIFE-HF model predicts individual treatment benefits from switching from any current treatment regimen to any future regimen of guideline-recommended therapies. Individualized treatment benefits are relevant as the absolute effectiveness of therapy varies greatly between individuals, based on baseline risk and remaining life expectancy.[9,10] For younger patients with mild symptoms, short-term risk is generally low, and as a result short-term ARRs achieved with treatment will be small. However, as they will age and their disease may progress, they may have a substantial lifetime risk. As they have a high remaining life expectancy and can therefore be treated over a long period of time, their lifetime treatment benefits may be considerable (at the expense of longer treatment duration and higher costs). On the other hand, older patients with more advanced disease will generally have a high short-term risk and large short-term ARRs, but this does not always translate to considerable lifetime benefit due to their limited life expectancy. This is illustrated by the estimates of the LIFE-HF model for the 15,415 individuals in the derivation cohort, showing that short-term treatment effects in terms of ARRs are indeed larger in patients with a higher 5-year risk, but lifetime treatment effects are generally larger in younger patients with a moderate or low short-term risk.

The LIFE-HF model may help to improve the management of HFrEF patients in multiple ways. First, by calling attention to the consistently high risk of hospitalization and mortality in this population. Second, by emphasizing the absolute benefits of guideline-recommended therapies for patients with HFrEF, including younger patients and patients with mild symptoms. Third, in situations where limited resources affect treatment use, it could help identify patients with both the greatest need for treatment (greatest modifiable risk), and the greatest benefit from treatment (greatest ARR or lifetime gain). Fourth, it could help physicians to communicate risks and treatment benefits to patients. Patients may be reluctant to add another drug to several they might already be taking. Showing them personalized estimates of risk and treatment benefits may increase their willingness to take on and adhere to new treatments. Fifth, it could facilitate shared decision-making by allowing patients to weigh their anticipated benefits against the burden of taking another pill, potential side effects, and costs.

Some methodological aspects should be discussed. The discriminative ability of the LIFE-HF model is moderate, as is the case with other risk scores in HF.[11–15] The maximum c-statistic that can be reached with a prognostic model depends on the distribution of risk in the population.[26] Given the selective nature of the HFrEF population with high risks of hospitalization and mortality in all patients, reaching c-statistics >0.70/>0.75 might not be possible in most cohorts. A head-to-head comparison in SwedeHF showed that the c-statistics of the LIFE-HF model are similar to or higher than those of well-known other models (Figure S12). As discussions on a patient's prognosis, as well as treatment decisions, are usually based on predicted risk, the goodness of fit of these risk estimates (i.e. calibration) is especially important in this setting, and moderate c-statistics are generally accepted.[26–28] Calibration of the LIFE-HF model was adequate in trial and real-world populations, and various subgroups.

Because of the great variety in predictors included in existing models and contrasting results regarding their prognostic value, we avoided an arbitrary selection of predictors by using statistical methods instead.[11,12] To ensure the model would be feasible for use in everyday clinical practice, the selection of predictors was presented to an expert panel. This panel unanimously decided that uric acid and bilirubin should be removed from the model, as these are not routinely measured in clinical practice. They also strongly supported the addition of eGFR to the model. Replacing uric acid and bilirubin by eGFR did not affect model performance, as the final core model was shown to perform similarly to the initial model with uric acid and bilirubin, and the extended model including all seventeen independent predictors.

The model was developed in two clinical trials. Trial participants may not always be fully representative of patients in real-world clinical practice. Especially, they may have a lower absolute risk of events, as they are often younger, healthier, and more closely monitored than real-world patients. Therefore, it was vital the model was also validated in two registries. Prediction models can be updated to tailor predictions to new populations through a recalibration of baseline risks.[29] In PARADIGM-HF and ATMOSPHERE, the true incidence of non-CV mortality in HFrEF patients was likely underestimated due to the exclusion of patients with non-CV life-limiting diseases. As SwedeHF does not have such exclusion criteria (Table S2), we argued that SwedeHF provided more representative estimates of the real-world incidence of CV and non-CV mortality. Therefore, baseline risks for these outcomes were recalibrated in SwedeHF. The recalibrated model was used for the development of the LIFE-HF calculator, made available for use in clinical practice. This means the estimates provided by the LIFE-HF calculator are applicable to real-world patients, i.e. are no longer affected by healthy participant bias in the trials. Geographical differences in baseline risk were accounted for in the model based on data of regional subgroups in the derivation cohort, but these might not be representative of an entire region. If country-specific event rates and mean predictor levels become available in the future, the model should ideally be recalibrated to individual countries (Methods S8).[30] Even though the model was derived in patients with chronic HFrEF, the validation in 19,332 in-patients from SwedeHF showed that the model (without additional recalibration) also accurately predicted 5-year and 10-year risk at discharge after an HF hospitalization. This suggests that, in addition to the out-patient setting, the model may also be reliably used at the end or shortly after an HF hospitalization. Risks were underestimated in the small group of black patients available for analysis. If more data of black HF patients become available in the future, the model should be recalibrated to this population.

The model was developed and validated in study populations with moderate uptake of contemporary guideline-recommended therapies, and most data were from before the introduction of SGLT2 inhibitors. Nevertheless, for the following reasons the model is still applicable to current clinical practice. First, the use of guideline-recommended therapies in the studies was comparable to the uptake of these medications in clinical practice.[4–7] Second, the model, without any adjustment or recalibration, performed equally well in patients with and without an MRA at baseline. Third, the model performed adequately in (the intervention arm) of DAPA-HF, a population with very high uptake of guideline-recommended therapies including an SGLT2 inhibitor. If in the future the uptake of guideline-recommended therapies significantly improves, recalibration of the model may be required, and should be considered as soon as data with long-term follow-up of patients on contemporary treatment including an SGLT2 inhibitor become available.

Study limitations need to be considered. Registries such as SwedeHF can be selective as well, and have imperfect coverage. In 2019, approximately 30% of the prevalent HF population in Sweden was registered in SwedeHF.[31] The model predicts lifetime risk but the validation periods were limited by the follow-up duration in the study populations. However, as the median HF hospitalization-free and overall survival in patients with HFrEF is limited, e.g. 2.9 and 6.1 years respectively in SwedeHF, the 5- and 10-year validations performed for these outcomes are already equivalent to a lifetime validation for the majority of patients. Although for some younger lower-risk patients survival may exceed five or ten years, we did not observe any substantial disagreements between predicted and observed risk in these patients at two, three, five, and ten years follow-up. The fact that the model accurately predicted both the 5- and 10-year risk of all-cause mortality (without additional recalibration), suggests that short-/mid-term estimates can be reliably extrapolated into the future. Additional long-term validations in other populations would still be desirable when appropriate data become available. Extending finite follow-up data to lifetime predictions of risk and treatment benefit is an established methodology that has been applied in many different settings.[8,10,17–19,32] Lifetime estimates have previously been validated for up to 17 years in apparently healthy people, and 12 years in patients with HFrEF.[10,32] Nevertheless, we acknowledge that lifetime estimates remain a projection of the actual lifetime risk and treatment benefit, and are based on several assumptions (Table S5). First, the model assumes that predictors follow a natural course over time. If an unexpected permanent change occurs in one or more predictors, predictions should be repeated. Second, baseline risks are assumed to be stationary. If advances in health care lead to a reduced baseline risk in the future, the model should be recalibrated. When estimating treatment benefits, it is assumed that hazard ratios are equal for all patients, and benefits of multiple therapies are additive. This is supported by subgroup analyses from trials, showing that relative treatment effects are consistent across subgroups, including subgroups of background medication.[20,24] Also, treatment effects are assumed to be constant, and patients are assumed to remain adherent over lifetime treatment. In practice, greater non-adherence might be expected. The estimates of a prediction model are never completely individualized, as not all of a patient's characteristics can be taken into account. Instead, the estimates reflect the average risk and average treatment benefit for a group of patients with identical characteristics with respect to the predictors in the model. In addition to pharmacological therapy, devices have an important role in the management of patients with HFrEF. The effects of devices were not included in the model, but could be added in the future.

In conclusion, the LIFE-HF model predicts both short-/mid-term and lifetime risk of HF hospitalization and mortality, as well as absolute treatment benefits expressed as overall and HF hospitalization-free life-years gained, for individual patients with HFrEF. The model could serve as a tool to improve the management of patients with HFrEF by facilitating personalized medicine and shared decision-making.

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Supplementary material

Supplementary material is available with the online publication, at:

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Or directly via:

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fejhf.3028&file=ejhf3028-sup-0001-Supinfo1.docx (Supplemental Methods, Tables, and Figures)

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fejhf.3028&file=ejhf3028-sup-0002-Supinfo2.zip (LIFE-HF Calculator)

Chapter 6.

Individual lifetime benefit from low-dose colchicine in patients with chronic coronary artery disease

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Abstract

Background and aims

Low-dose colchicine reduces cardiovascular risk in patients with coronary artery disease (CAD), but absolute benefits may vary between individuals. This study aimed to assess the range of absolute benefit from low-dose colchicine according to individual patient risk profile.

Methods

The ESC guideline-recommended SMART-REACH model was combined with the relative treatment effect of low-dose colchicine, and applied to CAD patients from the LoDoCo2 trial and UCC-SMART cohort (n = 10,830). Individual treatment benefit was expressed as 10-year absolute risk reductions (ARRs) for myocardial infarction, stroke, or cardiovascular death (MACE), and MACE-free life-years gained. Predictions were also performed for MACE plus coronary revascularization (MACE+), using a new lifetime model derived in the REACH registry. Colchicine was compared to other ESC guideline-recommended intensified (step 2) prevention strategies, i.e. low density lipoprotein-cholesterol (LDL-C) reduction to 1.4 mmol/L, and systolic blood pressure (SBP) reduction to 130 mmHg. Generalizability to other populations was assessed in CAD patients from REACH North America and Western Europe (n = 25,812).

Results

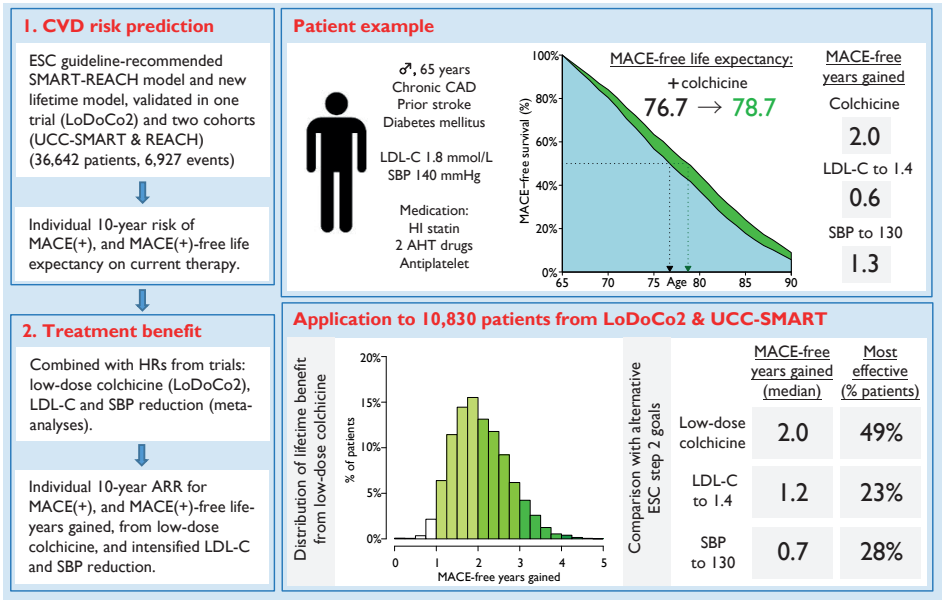
Median 10-year ARR from low-dose colchicine was 4.6% (interquartile range [IQR] 3.6–6.0%) for MACE, and 8.6% (IQR 7.6–9.8%) for MACE+. Lifetime benefit was 2.0 (IQR 1.6–2.5) MACE-free years, and 3.4 (IQR 2.6–4.2) MACE+-free life-years gained. For LDL-C and SBP reduction respectively, median 10-year ARR for MACE was 3.0% (IQR 1.5-5.1%) and 1.7% (IQR 0.0-5.7%), and lifetime benefit was 1.2 (IQR 0.6-2.1) and 0.7 (IQR 0.0-2.3) MACE-free life-years gained. Similar results were obtained for MACE+, and in American and European patients from REACH.

Conclusions

The absolute benefits of low-dose colchicine vary between individual patients with chronic CAD. They may be expected to be of at least similar magnitude to those of intensified LDL-C and SBP reduction in a majority of patients already on conventional lipid-lowering and blood pressure-lowering therapy.

Graphical abstract

Individual lifetime benefit from low-dose colchicine in chronic CAD



Introduction

Patients with coronary artery disease (CAD) remain at high risk of cardiovascular events, despite the routine use of lipid-lowering, blood pressure-lowering, and antithrombotic therapies.[1,2] In recent years, anti-inflammatory therapy has emerged as another effective prevention strategy for patients with CAD.[3–5] In the 2021 European Society of Cardiology (ESC) Cardiovascular Disease (CVD) Prevention Guidelines, the anti-inflammatory drug colchicine (in a low dose; 0.5 mg once daily) has a class IIb recommendation (level A evidence).[1] Together with intensified lipid-lowering (i.e. low density lipoprotein-cholesterol [LDL-C] <1.4 mmol/L) and blood pressure-lowering (i.e. systolic blood pressure [SBP] <130 mmHg) therapy, dual antiplatelet therapy, low-dose rivaroxaban, and eicosapentaenoic acid (EPA), low-dose colchicine is among the intensified (step 2) prevention strategies that may be considered in patients with established CVD in addition to conventional (step 1) preventive therapy (i.e. smoking cessation, LDL-C <1.8 mmol/L, SBP <140 mmHg, and antithrombotic therapy).

The absolute benefits of preventive therapies are expected to vary between patients, depending on baseline CVD risk, remaining life expectancy, and current levels of treatment targets.[6] Patients with a high CVD risk and long potential treatment duration will likely gain the most from intensified treatment, whereas patients with a very low risk or limited life expectancy will receive a smaller benefit that may not outweigh the costs and risk of side effects. Moreover, patients with high levels of LDL-C and SBP may benefit most from intensified lipid-lowering and blood pressure-lowering therapy, whereas patients already on these therapies and with LDL-C and SBP levels close to treatment targets may benefit more from other therapies to further reduce their residual risk of CVD. Therefore, the ESC Guidelines recommend that decisions on intensification of preventive therapy are based on a patient's 10-year CVD risk, lifetime risk, and individual treatment benefit, as estimated by the SMART-REACH model.[1,7] Applying this model to a group of patients with chronic CAD and otherwise varying characteristics could provide insight into the distribution of the individual absolute benefit from low-dose colchicine, and how this relates to other prevention strategies in this population.

The primary objective of this study was to assess the range of individual absolute benefit from low-dose colchicine in patients with chronic CAD according to patient risk profile. The secondary objective was to compare low-dose colchicine to other ESC guideline-recommended step 2 prevention strategies, i.e. LDL-C reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg, in addition to conventional therapy.

Methods

Study populations

Data were used from all participants enrolled in the LoDoCo2 trial (n = 5,522), a randomized, placebo-controlled clinical trial comparing low-dose colchicine (0.5 mg once daily) to placebo for the prevention of major cardiovascular events in patients with chronic CAD from the Netherlands and Australia.[5] In addition, data from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) study were used, an ongoing prospective cohort study of patients with established CVD at the University Medical Centre Utrecht, the Netherlands.[8] Patients with chronic CAD (defined as a history of myocardial infarction [MI], percutaneous coronary intervention [PCI], or coronary artery bypass grafting [CABG]) included between September 1996 and January 2019 were selected (n = 5,308). Finally, we used data from the REACH registry, a prospective cohort study of patients with established CVD recruited from general practitioners and medical specialist outpatient clinics worldwide.[9] Western European patients with established CVD, i.e. CAD, cerebrovascular disease, or peripheral artery disease (n = 14,522), and North American patients with chronic CAD (n = 15,764) were selected. Detailed descriptions of the original studies have been published elsewhere.[5,8,9] All studies were approved by an institutional review board, and written informed consent was obtained from all participants. Eligibility criteria are described in Table S1. Missing data (Table S2) were handled by multiple imputation (Methods S1).

Outcomes

Outcomes of interest were (i) MI, ischemic stroke, or cardiovascular death (MACE), and (ii) coronary revascularization (i.e. PCI or CABG), MI, ischemic stroke, or cardiovascular death (MACE+). The competing outcome was non-cardiovascular mortality. Detailed endpoint definitions are provided in Table S3.

External validation of the SMART-REACH model

The SMART-REACH model is the ESC guideline-recommended tool for prediction of 10-year risk of MACE, and MACE-free life expectancy in patients with established CVD.[1,7] In this study, the model was externally validated in LoDoCo2, and temporal validation was performed in UCC-SMART (validation had previously been performed on a smaller dataset).[7] If necessary, the model was recalibrated for differences in baseline risk. Model performance was assessed using measures of discrimination and calibration, i.e. plots of predicted vs. observed risk.

Development and validation of a lifetime prediction model for MACE+

As the primary endpoint of the LoDoCo2 trial included coronary revascularizations, we developed a new model (i.e. the SMART-REACH+ model) based on the same methodology used for the original SMART-REACH model.[7,10] Cox proportional hazards functions were derived in REACH Western Europe (n = 14,522) for: (i) MACE+, and (ii) non-cardiovascular mortality. Predictors, pre-specified based on the original SMART-REACH model, were: sex, current smoking, diabetes mellitus, SBP, total cholesterol, creatinine, CAD, cerebrovascular disease, peripheral artery disease, atrial fibrillation, and heart failure. Age was used as the time scale of the model (i.e. left truncation), so that participants contributed data to the model from their age at study entry to their age at time of an event or censoring. This allows for the estimation of age-specific baseline survivals, used to make predictions beyond the follow-up duration of the original cohort (Methods S2 & Figure S1). Model assumptions are described in Table S4.

Consistent with the original SMART-REACH model, the SMART-REACH+ model was externally validated in LoDoCo2 and UCC-SMART.

Estimating CVD risk and CVD-free life expectancy for individual patients

For all patients in LoDoCo2 and UCC-SMART (n = 10,830), survival free of MACE, and MACE+ (i.e. the CVD events of interest) were estimated using the SMART-REACH and SMART-REACH+ models, by making use of life-tables.[10] Starting from the age of each patient at baseline, the risk of the CVD event of interest (a_t) and the risk of non-cardiovascular mortality (b_t) were estimated for each consecutive life-year, up to the maximum age of 100 years. A CVD-free survival probability (p_t) was obtained for each life-year, by subtracting CVD risk and non-cardiovascular mortality risk from 1 ($p_t = 1 - a_t - b_t$). The probability of being alive and free of the CVD event of interest at the start of each life-year (e_t), was calculated by multiplying the CVD-free survival probabilities of all the previous life-years (e.g. for a 60-year old: $e_{t=63} = p_{t=60} * p_{t=61} * p_{t=62}$). Altogether, these predictions form an individual life-table for each patient. Predictions of 10-year risk of MACE and MACE+ were derived from the life-tables by calculating the cumulative cause-specific event risk truncated at 10 years after the starting age. MACE-free and MACE+-free life expectancy were defined as the age where the cumulative MACE-free and MACE+-free survival probabilities (e_t) in the life-table equalled 0.50 (= 50%).

Prediction of individual benefit from low-dose colchicine

The prognostic models were combined with hazard ratios (HRs) from the LoDoCo2 trial, in line with previously described methods.[7,10] HRs were 0.72 for MACE, and 0.69 for MACE+.[5] Subsequently, ten-year risks of MACE and MACE+, and MACE-free and MACE+-free life expectancies on low-dose colchicine were estimated for each patient in LoDoCo2 and UCC-SMART. Individual 10-year absolute risk reduction (ARR) was defined as the difference between the predicted 10-year risk with and without low-dose colchicine. Likewise, lifetime benefit was defined as the difference between on- and off-colchicine life expectancies, expressed as MACE-free and MACE+-free life-years gained. Low-dose colchicine was assumed to have no effect on non-cardiovascular mortality, among other assumptions (Table S4). Additionally, analyses were performed stratified by smoking status, baseline risk and age, cohort, and country.

Comparison with other step 2 prevention strategies

Low-dose colchicine was compared to the following ESC guideline-recommended intensified (step 2) prevention goals: LDL-C reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg.[1] Benefits from achieving these targets were estimated for all patients with available baseline measurements of LDL-C and SBP by combining the models with an HR of 0.78 for every 1 mmol/L reduction from baseline to target LDL-C (i.e. $HR_{\text{LDL-C reduction}} = 0.78^{\wedge(\text{baseline LDL-C} - 1.4)}$), and a hazard ratio of 0.80 for every 10 mmHg reduction from baseline to target SBP (i.e. $HR_{\text{SBP reduction}} = 0.80^{\wedge(\text{baseline SBP} - 130)/10}$), in line with large-scale meta-analyses.[11,12] Estimates should be interpreted as the predicted benefits of achieving these targets, regardless of the lipid-lowering and blood pressure-lowering therapies currently used by a patient and the therapies prescribed to reach the targets. As some patients meeting treatment targets reflects clinical practice, patients with baseline LDL-C ≤1.4 mmol/L or SBP ≤130 mmHg were not excluded from the analyses, but were considered to have no benefit from reaching targets they already met at baseline. A sensitivity analysis was performed in patients not meeting treatment targets at baseline.

Generalizability to other populations

As LoDoCo2 and UCC-SMART only include patients from the Netherlands and Australia, a sensitivity analysis was performed in which the models were applied to patients with chronic CAD from REACH North America (n = 15,764) and REACH Western Europe (n = 10,048).

All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

To facilitate use of the models in clinical practice, low-dose colchicine was added to the existing online SMART-REACH calculator (available at www.U-Prevent.com), and a new calculator was developed for the SMART-REACH+ model (Supplemental Material; Calculator).

Results

Patient characteristics

Patients from UCC-SMART and REACH Western Europe more often had extracardiac vascular disease, and had higher cholesterol and creatinine levels than patients from LoDoCo2 (Table 1). Despite differences in cardiovascular risk profiles, the distribution in medical treatment strategies was similar between LoDoCo2 and UCC-SMART. In the combined LoDoCo2 and UCC-SMART study population, mean baseline LDL-C was 2.4±0.9 mmol/L (n = 8,595) and SBP was 137±19 mmHg (n = 8,801). Respectively, 26.6% and 10.0% of patients met the LDL-C step 1 (≤1.8 mmol/L) and step 2 (≤1.4 mmol/L) targets, and 63.5% and 41.7% met the SBP step 1 (≤140 mmHg) and step 2 (≤130 mmHg) targets at baseline (Figure S2).

Table 1. Baseline characteristics

Characteristic	LoDoCo2 (n = 5,522)	UCC-SMART (n = 5,308)	REACH Western Europe (n = 14,522)
Age	65.8±8.6	60.9±9.6	68.4±9.6
Female sex	846 (15%)	1,007 (19%)	4,073 (28%)
Current smoker	651 (12%)	1,272 (24%)	2,300 (16%)
Systolic blood pressure (mmHg)	137±19	137±20	140±19
≤140 mmHg	2,299 (64%)	3,287 (62%)	8,827 (61%)
≤130 mmHg	1,516 (42%)	2,151 (41%)	5,459 (38%)
Total cholesterol (mmol/L)	4.1±1.0	4.6±1.1	5.1±1.2
LDL-cholesterol (mmol/L)	2.1±0.8	2.6±0.9	3.2±1.0[c]
≤1.8 mmol/L	1,360 (40%)	924 (17%)	669 (7%)
≤1.4 mmol/L	518 (15%)	338 (6%)	234 (2%)
Creatinine (µmol/L)	84±14	93±31	96±25
Medical History			
Prior acute coronary syndrome	4,658 (84%)	2,919 (55%)	6,680 (46%)
Prior coronary revascularization[a]	4,621 (84%)	3,875 (73%)	6,390 (44%)
Coronary artery disease	5,522 (100%)	5,308 (100%)	10,048 (69%)
Cerebrovascular disease	398 (11%)	495 (9%)	4,551 (31%)
Peripheral artery disease	72 (2%)	414 (8%)	3,426 (24%)
Diabetes mellitus	1,007 (18%)	1,008 (19%)	4,893 (34%)
Atrial fibrillation	649 (12%)	275 (5%)[b]	1,670 (12%)

Characteristic	LoDoCo2 (n = 5,522)	UCC-SMART (n = 5,308)	REACH Western Europe (n = 14,522)
Heart failure	NA	NA	2,275 (16%)
Left ventricular ejection fraction <50%	1,805 (33%)	NA	NA
Medication			
Antiplatelet therapy	5,031 (91%)	4,610 (87%)	9,674 (67%)
Anticoagulant	672 (12%)	665 (13%)	1,904 (13%)
Statin	5,188 (94%)	4,297 (81%)	10,340 (71%)
Antihypertensive medication	4,980 (90%)	4,782 (90%)	13,138 (90%)

Baseline characteristics are based on non-imputed data. Continuous variables are presented as mean±SD, categorical variables as N (%). Percentages refer to complete cases.

Abbreviations: LDL = low density lipoprotein, NA = not available.

[a] Prior percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG).
[b] Only atrial fibrillation at baseline (based on an electrocardiogram). History of atrial fibrillation was not available.
[c] Calculated using a modified Friedewald formula including total cholesterol and triglycerides, as LDL-cholesterol (and HDL-cholesterol) measurements were not available in REACH.[38]

Outcomes

In LoDoCo2, 272 MACE, 451 MACE+, and 88 non-cardiovascular deaths occurred during a median follow-up of 2.5 years (interquartile range [IQR] 1.8-4.0). In UCC-SMART, 1,026 MACE, 1,885 MACE+, and 616 non-cardiovascular deaths occurred during a median follow-up of 9.0 years (IQR 4.7-13.0). Kaplan-Meier curves are presented in Figure S3.

Development of the SMART-REACH+ model

Multivariable hazard ratios are presented in Table S5. Age-specific baseline survivals and the completed risk algorithms are provided in Table S6 & S7. The interactive calculator is provided in the Supplemental Material.

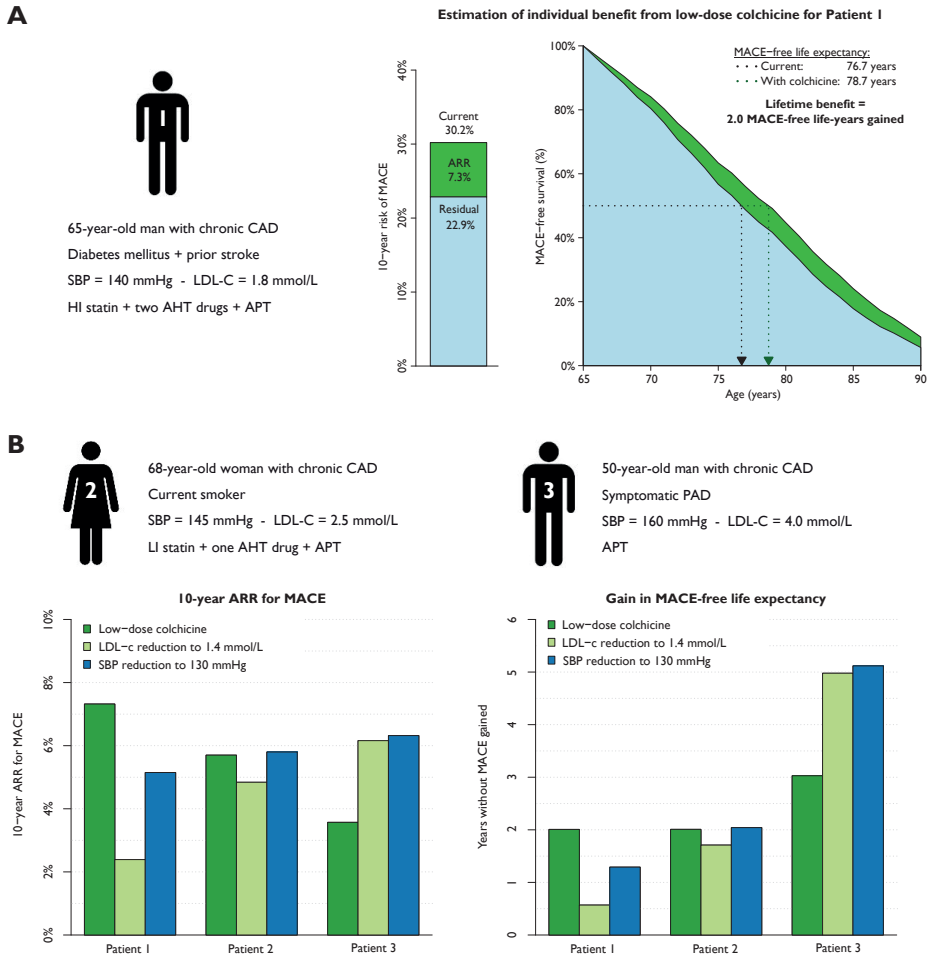
External validation in LoDoCo2 and UCC-SMART

External validation of the SMART-REACH and SMART-REACH+ models showed good agreement between the predicted and observed 3-year (LoDoCo2) and 10-year (UCC-SMART) risk of MACE and MACE+ (Figure S4).

Absolute benefit from low-dose colchicine

The estimation of (lifetime) benefit from low-dose colchicine for an individual patient is illustrated in Figure 1A (outcome is MACE), and Figure S5A (outcome is MACE+).

Figure 1. Estimation of individual benefit from low-dose colchicine in exemplar patients

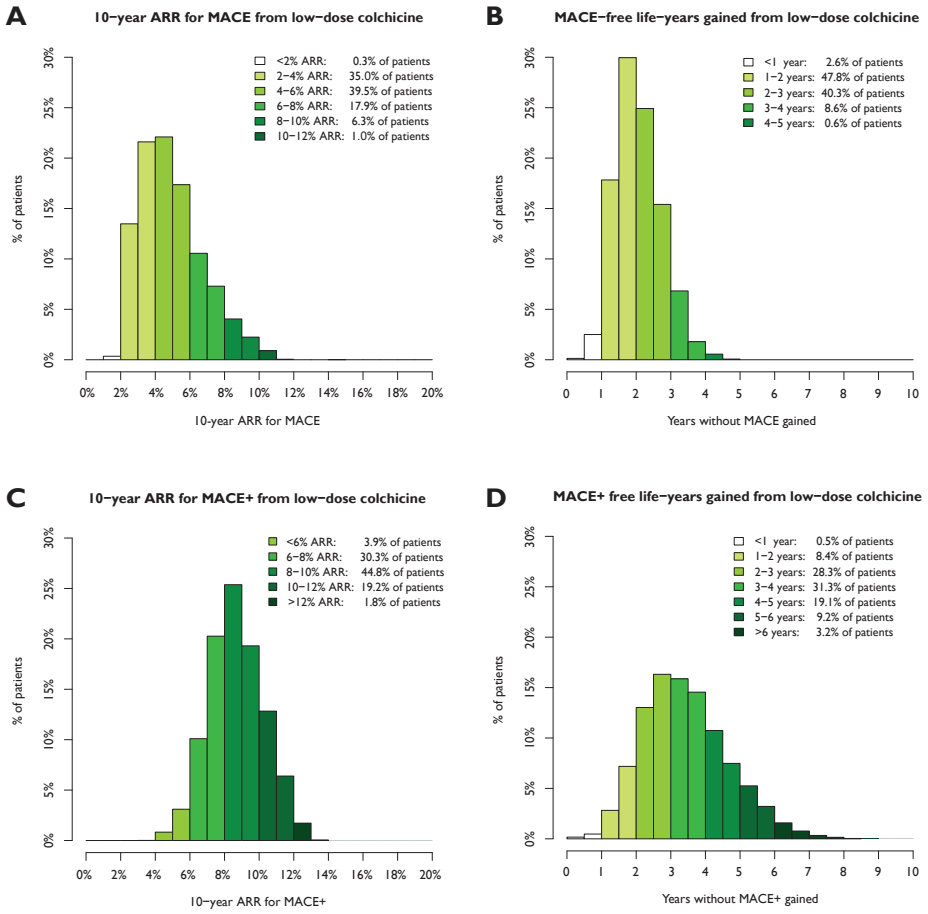


Estimation of 10-year ARR for MACE and MACE-free life-years gained from low-dose colchicine in an individual patient (A), and a comparison of low-dose colchicine with LDL-C reduction to 1.4 mmol/L and SBP reduction to 130 mmHg in three individual patients (B). For viewing purposes, not all predictors were presented in the figure. These were as follows: total cholesterol = 4.0 (1), 4.5 (2), and 6.0 (3) mmol/L; creatinine = 100 (1), 90 (2), and 80 (3) μmol/L; AF = No for all; HF = No for all. If a condition is not mentioned in the description of the patient, it means the condition was absent (e.g. for patients 2 and 3 diabetes mellitus is not mentioned in the description, which means these patients did not have diabetes mellitus). All patients were real-world patients (recalibration factors from UCC-SMART were applied).

In the combined LoDoCo2 and UCC-SMART study population, median 10-year baseline risk (without low-dose colchicine) of MACE was 17.8% (IQR 13.4-23.9%), MACE+ was 32.0% (IQR 27.6-37.7%), and non-cardiovascular mortality was 6.3% (IQR 3.2-11.1%) (distributions in Figure S6 & S7). Median predicted baseline survival free of MACE was 18.0 years (IQR 13.7-23.0), and free of MACE+ was 13.6 years (IQR 10.9-16.8). The distribution

of the estimated 10-year and lifetime benefit from low-dose colchicine is shown in Figure 2. The median 10-year benefit from low-dose colchicine, in terms of the estimated absolute reduction in the 10-year risk of MACE, was 4.6% (IQR 3.6–6.0%) (Table 2). This translates to an individual number needed to treat (iNNT) of 21.6 (IQR 16.7–28.2) to avoid one MACE event over 10 years of treatment (Figure S8). The median estimated lifetime benefit, in terms of years gained in life expectancy free of MACE, was 2.0 years (IQR 1.6–2.5 years). Median predicted 10-year ARR for MACE+ was 8.6% (IQR 7.6–9.8%), 10-year iNNT was 11.6 (IQR 10.2–13.2), and gain in MACE+-free life expectancy was 3.4 years (IQR 2.6–4.2 years) (Table 2).

Figure 2. Distribution of the individual benefit from low-dose colchicine



Distribution of the individual absolute benefit from low-dose colchicine in the combined LoDoCo2 and UCC-SMART study population (n = 10,830), expressed as 10-year ARR for MACE (A), MACE-free life-years gained (B), 10-year ARR for MACE+ (C), and MACE+-free life-years gained (D).

Table 2. Median benefit from low-dose colchicine and intensive LDL-C and SBP reduction

		MACE		MACE+	
	n	**10-year ARR, median (IQR)**	**Life-years gained, median (IQR)**	**10-year ARR, median (IQR)**	**Life-years gained, median (IQR)**
Total population					
Low-dose colchicine	10,830	4.6% (3.6–6.0%)	2.0 (1.6–2.5)	8.6% (7.6–9.8%)	3.4 (2.6–4.2)
LDL-C reduction to 1.4 mmol/L	8,595[a]	3.0% (1.5–5.1%)	1.2 (0.6–2.1)	5.2% (2.5–8.7%)	1.8 (0.8–3.3)
SBP reduction to 130 mmHg	8,801[b]	1.7% (0.0–5.7%)	0.7 (0.0–2.3)	2.9% (0.0–9.5%)	0.9 (0.0–3.4)
All three strategies combined	8,576[c]	8.7% (6.2–12.5%)	4.0 (2.9–5.5)	15.9% (12.2–21.1%)	6.6 (4.6–9.5)
Patients not on targets					
LDL-C reduction to 1.4 mmol/L	7,729[d]	3.3% (1.9–5.4%)	1.4 (0.8–2.3)	5.8% (3.3–9.1%)	2.0 (1.1–3.6)
SBP reduction to 130 mmHg	5,055[e]	4.7% (2.4–8.4%)	2.0 (1.0–3.4)	8.2% (4.3–13.6%)	2.9 (1.4–5.1)

Median estimated benefit from low-dose colchicine, LDL-C reduction to 1.4 mmol/L, SBP reduction to 130 mmHg, and combined therapy with all three strategies, in the combined LoDoCo2 and UCC-SMART study population (n = 10,830). Additionally, median benefit from LDL-C and SBP reduction are presented for patients not yet meeting LDL-C and SBP targets at baseline.

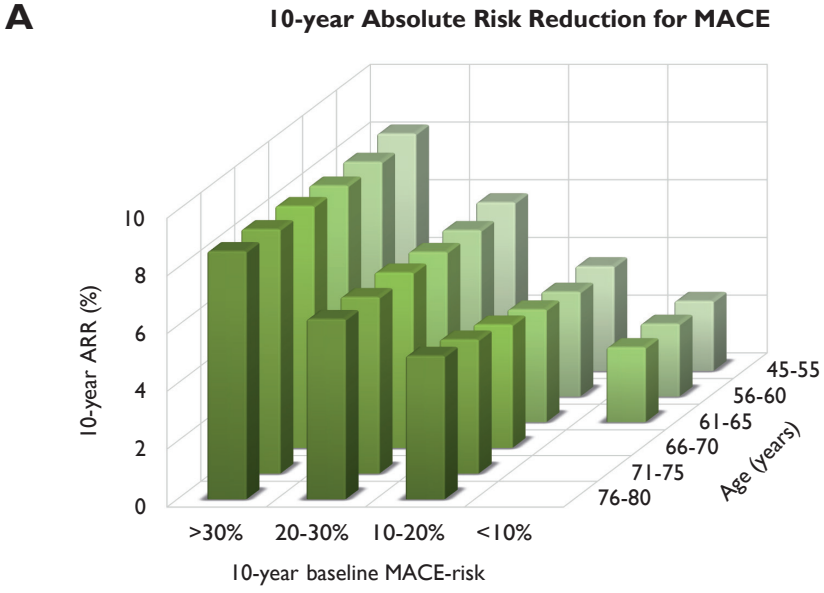
Abbreviations: ARR = absolute risk reduction, IQR = interquartile range, LDL-C = low density lipoprotein cholesterol, MACE(+) = major adverse cardiovascular event (+ coronary revascularization), SBP = systolic blood pressure.

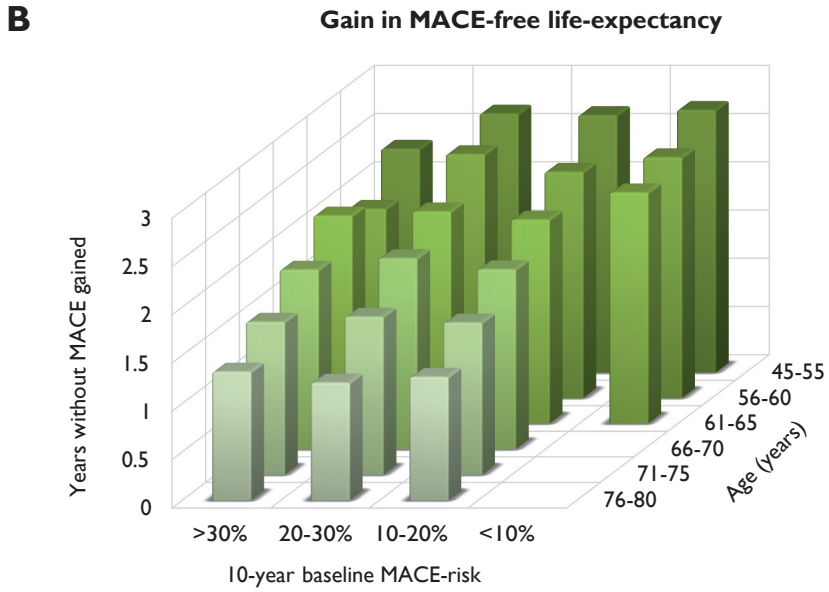
[a] Patients with available baseline LDL-C.
[b] Patients with available baseline SBP.
[c] Patients with available baseline LDL-C and SBP.
[d] Patients with baseline LDL-C >1.4 mmol/L.
[e] Patients with baseline SBP >130 mmHg.

Stratified analyses

Estimated CVD risk reductions from low-dose colchicine were larger for current smokers compared to non-smokers (median 10-year ARR: 5.2% vs. 4.5% for MACE, and 8.9% vs. 8.5% for MACE+), but as smoking increases the risk of non-cardiovascular mortality, gains in CVD-free life expectancy were similar or smaller (median 2.1 vs. 2.0 MACE-free years gained, and 3.1 vs. 3.4 MACE+-free years gained; Figure S9). Estimated 10-year CVD risk reductions increased with increasing baseline risk, while gains in CVD-free life expectancy decreased with increasing age and remained relatively stable over risk strata (Figure 3 & Figure S10). Due to the increased (i.e. real-world) incidence of non-cardiovascular mortality in UCC-SMART, the estimated gain in MACE-free (median 1.7 vs. 2.3 years) and MACE+-free life expectancy (median 3.1 vs. 3.6 years) was lower in this cohort compared to the LoDoCo2 trial population, while 10-year risk reductions were similar (Figure S11). Likewise, within LoDoCo2, the slightly higher risk of non-cardiovascular mortality in participants from Australia led to slightly smaller estimated gains in MACE-free (median 2.2 vs. 2.5 years) and MACE+-free life expectancy (median 3.5 vs. 3.8 years) as compared to participants from the Netherlands (Figure S12).

Figure 3. Absolute benefit from low-dose colchicine stratified by baseline risk and age





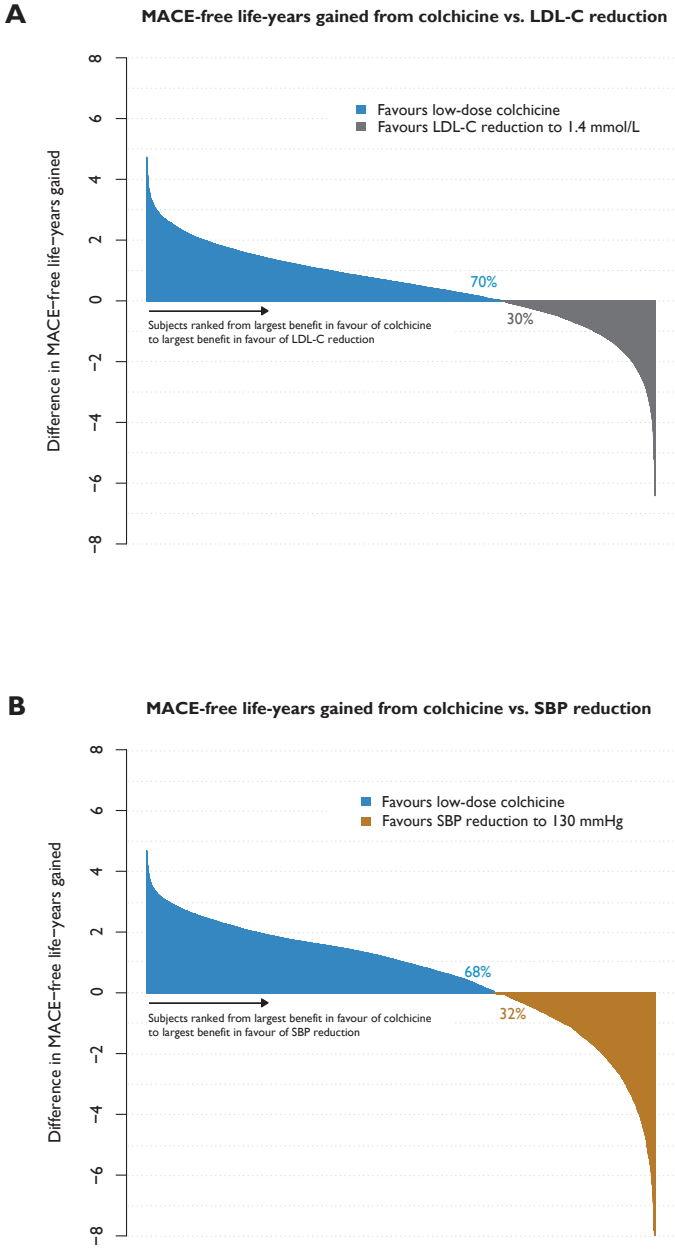
Mean 10-year ARR for MACE (A), and years gained in MACE-free life expectancy (B) from low-dose colchicine, stratified by baseline 10-year risk and age. As there were no patients aged 66 years or older with a baseline risk <10%, these cells were left blank.

Comparison with intensified LDL-C and SBP reduction

Comparison of low-dose colchicine with intensified LDL-C and SBP reduction is demonstrated for three individual patients in Figure 1B and Figure S5B.

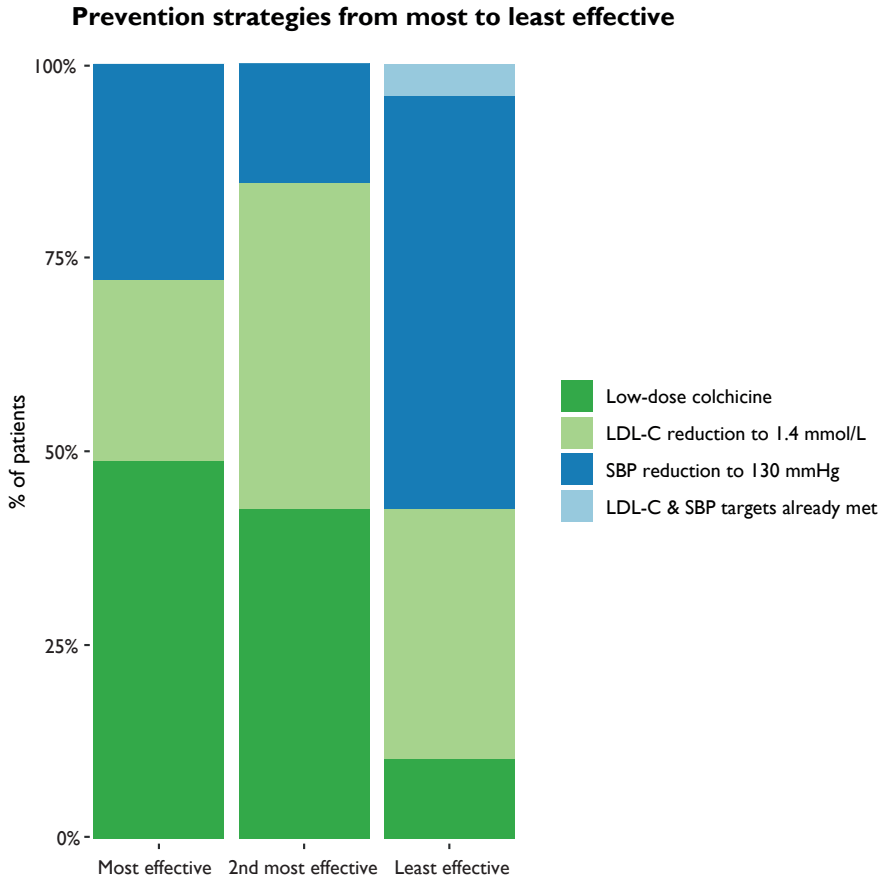
The median estimated 10-year CVD risk reductions and gains in CVD-free life expectancy were smaller with intensified LDL-C and SBP reduction than with low-dose colchicine (Table 2 & Figure S13). For each individual patient, differences in the estimated lifetime benefits of low-dose colchicine as compared to intensified LDL-C and SBP reduction are shown in Figure 4 (MACE) and Figure S14 (MACE+). These differences are also presented in histograms in Figure S15. Based on the estimated gain in MACE-free life expectancy, low-dose colchicine was expected to be the most, second most, and least effective strategy in 48.7%, 40.9%, and 10.4% of patients respectively (Figure 5).

Figure 4. Individual lifetime benefit from low-dose colchicine compared to intensified LDL-C and SBP reduction



Difference in MACE-free life-years gained from low-dose colchicine, as compared to intensified LDL-C (A) and SBP (B) reduction for all individuals with available baseline LDL-C (n = 8,595) and SBP (n = 8,801). Differences are calculated as individual MACE-free life-years gained from low-dose colchicine minus individual MACE-free life-years gained from LDL-C reduction to 1.4 mmol/L, or SBP reduction to 130 mmHg. From left to right, individuals are ranked from largest benefit in favour of colchicine to largest benefit in favour of LDL-C or SBP reduction.

Figure 5. Prevention strategies ranked from most to least effective



Low-dose colchicine, LDL-C reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg ranked from most to least effective based on the number of MACE-free life-years gained in patients with available baseline LDL-c and SBP (n = 8,576). If patients already met both LDL-C and SBP targets, this was reported under 'Least effective', and low-dose colchicine was considered the most effective strategy. If one of LDL-C or SBP targets was already met, this was considered the least effective strategy, and the two remaining strategies were divided into most and second most effective.

In patients not meeting the LDL-C target at baseline (n = 7,729), median estimated CVD risk reductions and gains in CVD-free life expectancy were still smaller with intensified LDL-C reduction than with low-dose colchicine (Table 2). In patients not meeting the SBP target at baseline (n = 5,055), the median estimated benefits of intensified SBP reduction and low-dose colchicine were similar. For all patients individually, comparisons are presented in Figure S16. Low-dose colchicine was expected to be the most, second most, and least effective strategy in respectively 31.0%, 49.7%, and 19.3% of patients not meeting any of the two targets at baseline (n = 4,567; Figure S16E).

Benefits of combined therapy

Median estimated 10-year ARRs from combined therapy with low-dose colchicine, LDL-C reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg, were 8.7% (IQR 6.2–12.5%) for MACE, and 15.9% (IQR 12.2–21.1%) for MACE+ (Table 2; distributions in Figure S17). Median estimated gains in MACE- and MACE+-free life expectancy were 4.0 years (IQR 2.9–5.5 years), and 6.6 years (IQR 4.6–9.5 years) respectively.

Generalizability to North America and Western Europe

CAD patients from REACH North America and Western Europe were older and more often had extracardiac vascular disease and diabetes mellitus than patients from LoDoCo2 and UCC-SMART (Table S8). Patients from REACH Western Europe also had higher cholesterol levels. Performance of the models was adequate in these populations as well (Figure S18). Baseline CVD risk was higher in REACH North America (e.g. median predicted 10-year risk of MACE; 29.1%) and Western Europe (29.8%), than in LoDoCo2 and UCC-SMART (17.8%). As a result, estimated 10-year CVD risk reductions from low-dose colchicine and other therapies were larger (Table S9 & Figure S19). But due to the older age and increased risk of non-cardiovascular mortality (median 10-year risk; 9.8% and 8.4% vs. 6.3%), estimated gains in CVD-free life expectancy were similar. In REACH North America, like in LoDoCo2 and UCC-SMART, the estimated benefits of low-dose colchicine exceeded those of intensified LDL-C and SBP reduction in the majority of patients (Figure S20). In REACH Western Europe, the estimated benefits of low-dose colchicine exceeded those of intensified SBP reduction, but due to the higher baseline cholesterol levels, were smaller than those of intensified LDL-C reduction in the majority of patients.

Discussion

Using data of 36,642 patients with chronic CAD from various populations, we demonstrated the range of individual absolute 10-year and lifetime benefit from anti-inflammatory treatment with low-dose colchicine. When added to conventional lipid-lowering and blood pressure-lowering therapy, the estimated absolute benefits of low-dose colchicine regularly exceeded those of intensified LDL-C and SBP reduction. The SMART-REACH and SMART-REACH+ models enable identification of patients with a relevant benefit from low-dose colchicine in clinical practice.

An important challenge for physicians in everyday clinical practice is translating trial results and guideline recommendations to individual patients. The lifetime models presented in this study provide personalized estimates of the absolute 10-year and lifetime benefit from

low-dose colchicine, and other preventive therapies, expressed as absolute risk reductions and CVD-free life-years gained. A physician could use these estimates to discuss with a patient whether the estimated benefit from low-dose colchicine is worthwhile by comparing colchicine to other preventive therapies, and by weighing benefit against the potential burden of taking an extra pill, costs, and risk of side effects. This could support clinical and shared decision-making with respect to the initiation of ESC guideline-recommended step 2 prevention strategies in clinical practice.

The 2021 ESC CVD Prevention Guidelines recommend that low-dose colchicine may be considered as a step 2 secondary prevention strategy, particularly in high-risk patients with other insufficiently controlled risk factors or recurrent CVD events under optimal therapy.[1] This study showed that 10-year absolute risk reductions from low-dose colchicine are largest for patients with a high baseline risk of CVD. However, as with other preventive therapies, lifetime benefit in terms of CVD-free life-years gained was shown to be largest for younger individuals, irrespective of baseline CVD risk. So, the benefits of low-dose colchicine exist for low-risk individuals as well, and as also shown in this study, may be expected to be of at least similar magnitude to those of intensified LDL-C and SBP reduction. This is a supported by a recent analysis of three contemporary cardiovascular trials, showing that among patients receiving contemporary statins, inflammation (assessed by C-reactive protein [CRP]) is a stronger predictor of cardiovascular events and death than LDL-C.[2] This suggests that lowering inflammation may be a more effective approach to reducing the residual risk of CVD than intensification of lipid-lowering therapy. These findings may support a broader use of low-dose colchicine in the secondary prevention of CVD.

In this study of patients with chronic CAD, the majority of whom were already using lipid-lowering (88%) and blood pressure-lowering (90%) medication, the expected benefits of low-dose colchicine regularly exceeded those of intensified LDL-C reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg. This observation can be partially attributed to the fact that some patients already met the LDL-C and SBP targets at baseline. But a majority of patients using lipid-lowering and blood pressure-lowering medication, and a proportion of patients already (closely) meeting treatment targets reflects clinical practice.[13,14] Also, low-dose colchicine was still estimated to be the most or second most effective preventive therapy in large proportions of patients not meeting LDL-C and SBP targets. Patients with high levels of LDL-C (>3.0 mmol/L) or SBP (>145 mmHg) were generally estimated to have a larger benefit from LDL-C or SBP reduction. But this is assuming that treatment targets are reached, and maintained for the patients' remaining lifetimes. In practice, reaching and maintaining LDL-C and SBP targets is not always possible due to side-effects of, and non-adherence to lipid-lowering and blood pressure-lowering medication.[14,15] Low-dose colchicine is relatively cheap, with low-priced generics available worldwide (though not

in the US), and may therefore be a reasonable alternative to expensive therapies such as proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, especially in low- and middle-income countries.[16] Lastly, colchicine treatment does not preclude intensified lipid-lowering or blood pressure-lowering therapy. In fact, all could be used simultaneously, resulting in the combined benefits also presented in this study.

On the other hand, intensive lipid-lowering (e.g. PCSK9 inhibition) or blood pressure-lowering therapy might lead to LDL-C or SBP reductions beyond treatment targets, associated with greater benefits than presented in this study.[17] Also, the relative treatment effects of LDL-C and SBP reduction are well established, while those of low-dose colchicine were based on the results of a single trial. Ongoing trials should help to further establish the efficacy of low-dose colchicine.[18,19] Side-effects and non-adherence might occur with low-dose colchicine as well. In LoDoCo2, 15.4% of patients who entered the one-month open-label colchicine run-in period did not undergo randomization (9.4% due to perceived side effects, predominantly gastrointestinal upset).[5] Early intolerance due to gastrointestinal effects has been estimated to affect ~10% of patients receiving low-dose colchicine.[20] After randomization, 10.5% of participants in the colchicine arm prematurely discontinued study medication (3.4% due to perceived side effects). The discontinuation rate was exactly the same (10.5%) in the placebo arm, with the same proportion of participants (3.4%) discontinuing study treatment due to perceived side effects. The discontinuation rate of low-dose colchicine in LoDoCo2 was lower than that observed with statins (average 13.9%) and PCSK9 inhibitors (average 13.0%) in previous trials.[21–23] By using hazard ratios from the per-protocol analysis, the estimates presented in this study take into account the discontinuation rate of colchicine observed during the trial. Myalgia was reported by 21.2% in the colchicine group vs 18.5% in the placebo group (cumulative incidence ratio, 1.15; 95% CI 1.01-1.31). But the rates of cancer, hospitalization for infection, pneumonia, or a gastrointestinal reason, and all other adverse events were similar in the colchicine and placebo groups.[5] This is in line with evidence collected over decades of use of low-dose colchicine in a range of diseases (e.g. gout and Familial Mediterranean Fever), and several meta-analyses including one of all trials in CAD (>11,000 patients), which together have indicated that long-term tolerance is excellent, and low-dose colchicine is safe, i.e. does not increase the risk of infection, cancer, cytopenia, or myotoxicity.[20,24–27] As the analyses in the current study rely on effect estimates derived from LoDoCo2 and other previous trials, and these effect estimates were neutral with respect to infections and other adverse events, new analyses of these outcomes using the methodology applied in this study would yield neutral results as well, and would not provide new evidence. Therefore, calculations were not performed for non-cardiovascular outcomes.

An assumption made in this study is that the relative treatment effects of low-dose colchicine, derived from the LoDoCo2 trial conducted in the Netherlands and Australia, are generalizable to other countries. The COLCOT and CANTOS trials demonstrated the efficacy of anti-inflammatory therapy in patients with CAD from various countries and several continents, but region-specific results have not been reported.[3,4] Although it is possible that the relative treatment effects of low-dose colchicine differ between regions, this is not expected based on the results of geographic subgroup analyses of other recent cardiovascular trials.[23,28,29] Assuming consistent relative treatment effects, it was shown in this study that the absolute long-term treatment benefits of low-dose colchicine, and how these relate to benefits of intensified LDL-C and SBP reduction, are largely generalizable to North America and Western Europe. This said, the estimated absolute risk reductions were larger in REACH North America and Western Europe. This was due to the higher baseline CVD risk in these cohorts, which might be explained by older age, increased prevalence of comorbidities, and higher cholesterol levels that might be related to the study period (2003-2009) and the inclusion of patients from primary care. The higher cholesterol levels in REACH Western Europe led to increased predicted benefits for intensified LDL-C reduction, which exceeded the benefits of low-dose colchicine in the majority of patients. When determining whether the results from LoDoCo2/UCC-SMART, REACH North America, or REACH Western Europe are most representative, one should therefore keep the population of interest in mind. The model also assumes that low-dose colchicine has no effect on non-cardiovascular mortality. In LoDoCo2, there were numerically more non-cardiovascular deaths in the colchicine (53 [1.9%]) compared to the placebo group (35 [1.3%]), but this difference was not significant.[5] Colchicine was not associated with any specific cause of death, in particular, deaths due to cancer and infection were equivalent.[30] This is in line with previous trials. In COLCOT (low-dose colchicine after MI), the rates of non-cardiovascular (23 [1.0%] vs 20 [0.8%] deaths) and all-cause mortality (43 [1.8%] vs 44 [1.8%] deaths) were similar between the colchicine and placebo groups.[4] In a meta-analysis of all trials with colchicine in CAD, low-dose colchicine was not associated with an increased risk of non-cardiovascular or all-cause mortality.[24] For all-cause mortality, this is supported by meta-analyses of trials with colchicine for any cardiovascular indication, and across a range of diseases (non-cardiovascular mortality was not reported in these studies).[25,31] So, as there is no evidence that low-dose colchicine affects the risk of non-cardiovascular or all-cause mortality, separate calculations were not performed for these outcomes. But by including functions that predict non-cardiovascular mortality in the models, the calculations for MACE(+) presented in this study were adjusted for the competing risk of non-cardiovascular death.

Strengths of this study are the large sample size, inclusion of both trial and real-world patients from various regions, and the translation of short-term relative treatment effects of colchicine on a group-level to long-term absolute treatment benefits for individual patients. Study limitations should be considered. The models predict lifetime risk but could only be validated for a 3-year period in LoDoCo2 and REACH, due to the limited follow-up time in these studies. The models assume that risk factors follow a natural course over age and that the relative treatment effects of low-dose colchicine remain constant over time, so that the CVD-free survival curve stays on the expected trajectory and the benefits of low-dose colchicine continue to accrue over a patient's remaining lifetime (which mostly goes far beyond three years). This study therefore shows a projection of the lifetime benefits of low-dose colchicine, which might deviate from the actual benefits. However, it is reassuring that the models performed well over a 10-year period in UCC-SMART, one of the cohorts with the longest follow-up of CAD patients worldwide, and that the validation in UCC-SMART was consistent with the shorter-term validations in LoDoCo2 and REACH. In addition, in a previous study, lifetime estimates based on the methodology applied in this study were shown to be reliable for up to at least 17 years.[10] Discriminative ability of the models was moderate, which is in line with other commonly used risk scores in patients with established CVD, e.g. the ESC guideline-recommended SMART and EUROASPIRE models.[1,32,33] As treatment decisions are usually based on predicted risk, the goodness of fit of these risk estimates, i.e. calibration, is especially important in this setting.[34–36] Calibration of the models used in this study was adequate in both trial, and real-world data from various regions. There were missing data for some of the model predictors. However, even the predictor variable with the largest number of missing values, i.e. total cholesterol, was still available for 32,999 (80%) patients across all populations. Multiple imputation was used to minimize the effect of missing data on the study results. If all data had been available, this likely would have yielded slightly different risk estimates for individual patients with missing predictor information. But on a population-level it is unlikely that missing data has substantially affected the results presented in this study, as validation of the models showed that despite of predictor information being partially imputed for some patients, CVD risks were still accurately predicted. As treatment benefits directly depend on the predicted risk, the adequate calibration of the model across all populations indicates that these were reliably predicted as well. Finally, the effects of low-dose colchicine may vary according to baseline levels of, and on-treatment reductions in inflammatory markers. In CANTOS, cardiovascular risk reduction with canakinumab was shown to be greater among patients with a more pronounced on-treatment reduction in CRP, and patients reaching a CRP level <2 mg/L.[37] A similar effect is conceivable for patients on colchicine. As CRP and other inflammatory markers were not routinely measured in LoDoCo2, this could not be evaluated or included in the model.

In conclusion, the absolute benefit from low-dose colchicine varies between individual patients with chronic CAD. This study showed that in an era where lipid-lowering and blood pressure-lowering therapies are already routinely used, the benefits of low-dose colchicine may be expected to be of at least similar magnitude to those of intensified LDL-C and SBP reduction in a majority of patients with chronic CAD. Using the ESC guideline-recommended SMART-REACH model and newly developed SMART-REACH+ model, lifetime benefit from low-dose colchicine (and other therapies) can be estimated for individual patients, supporting decision-making with respect to the initiation of ESC guideline-recommended step 2 prevention strategies in clinical practice.

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Chapter 7.

Effects of icosapent ethyl according to baseline residual risk in patients with atherosclerotic cardiovascular disease: results from REDUCE-IT

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Submitted

Abstract

Background

Icosapent ethyl lowers triglycerides and significantly reduces major adverse cardiovascular events (MACE), though treatment effects may vary between individuals. This study aimed to determine the relative and absolute effects of icosapent ethyl on MACE according to baseline CVD risk in patients with atherosclerotic cardiovascular disease (ASCVD).

Methods

Participants from REDUCE-IT with ASCVD were included (n = 5,785). The primary outcome was 3-point MACE, i.e. non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Baseline 5-year risk of MACE was estimated using the SMART2 risk score. Modification of the relative treatment effects of icosapent ethyl by baseline risk was assessed using Cox proportional hazards models including a treatment-by-risk interaction. Next, treatment effects were assessed stratified by quartiles of baseline risk.

Results

During a median follow-up of 4.8 years (interquartile range 3.2-5.3), MACE occurred in 361 vs 489 patients in the icosapent ethyl vs placebo group (95% confidence interval [CI]); hazard ratio (HR) 0.72 (0.63-0.82), absolute risk reduction (ARR) 4.4% (2.6-6.2%), number needed to treat (NNT) 23 (16-38), 5-year Kaplan-Meier estimated cumulative incidence reduction (CIR) 5.7% (3.5-7.9%). Icosapent ethyl significantly reduced MACE in all risk quartiles, with an HR (95% CI) of 0.62 (0.43-0.88), 0.66 (0.48-0.92), 0.69 (0.53-0.90), and 0.78 (0.63-0.96) respectively (p for treatment-by-risk interaction = 0.106). The ARR (95% CI) increased across risk quartiles, i.e. was 3.9% (1.0-6.8%), 4.3% (1.2-7.3%), 5.1% (1.4-8.7%), and 5.6% (1.3-10.0%) respectively. This translates to NNTs (95% CI) of 26 (15-98), 24 (14-84), 20 (11-70), and 18 (10-77). The 5-year CIR (95% CI) was 4.8% (1.3-8.2%), 5.0% (1.3-8.7%), 6.1% (1.7-10.5%), and 7.7% (2.3-13.2%) respectively. Consistent results were obtained for 5-point MACE, additionally including coronary revascularization and unstable angina.

Conclusion

Among patients with ASCVD and elevated triglyceride levels, icosapent ethyl significantly reduces the risk of MACE irrespective of baseline CVD risk, though absolute benefits are largest for patients at the highest risk.

Graphical abstract

Study population

REDUCE-IT participants with ASCVD (n = 5,785):

Icosapent ethyl 2 g b.i.d. (n = 2,892)

vs

Placebo (n = 2,893)

CVD risk prediction

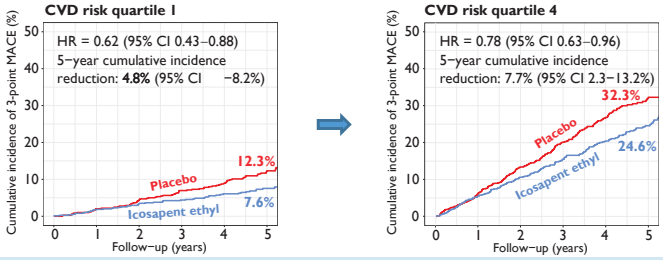
1. Predict individual baseline 5-year risk of 3-point MACE (MI, stroke, or CV death) with SMART2 risk score.
2. Divide study population in CVD risk quartiles.

Effects of icosapent ethyl

1. Test treatment-by-risk interaction.
2. Assess treatment effects stratified by CVD risk quartiles.

5,785 patients with ASCVD – **4.8** years median follow-up – **850** 3-point MACE events

Cumulative incidence of MACE in the lowest vs highest CVD risk quartile



Effects of icosapent ethyl on 3-point MACE according to CVD risk quartile

	All ASCVD patients	CVD risk quartile 1	CVD risk quartile 2	CVD risk quartile 3	CVD risk quartile 4
5-year risk	3.6-83.0%	<11.5%	11.5-16.0%	16.1-23.3%	>23.3%
HR* (95% CI)	0.72 (0.63-0.82)	0.62 (0.43-0.88)	0.66 (0.48-0.92)	0.69 (0.53-0.90)	0.78 (0.63-0.96)
ARR (95% CI)	4.4% (2.6-6.2%)	3.9% (1.0-6.8%)	4.3% (1.2-7.3%)	5.1% (1.4-8.7%)	5.6% (1.3-10.0%)
NNT (95% CI)	23 (16-38)	26 (15-98)	24 (14-84)	20 (11-70)	18 (10-77)

* Treatment-by-risk interaction: p = 0.106

Introduction

Patients with atherosclerotic cardiovascular disease (ASCVD) remain at high risk of recurrent cardiovascular events, despite the routine use of lipid-lowering, blood pressure-lowering, and antithrombotic therapies.[1,2] This residual risk can be partially attributed to elevated triglyceride levels.[3,4] In the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) icosapent ethyl, a highly purified eicosapentaenoic acid (EPA) ethyl ester that lowers triglycerides, reduced the risk of major adverse cardiovascular events (MACE) by ~25%.[5] Clinical guidelines state that icosapent ethyl may be considered to reduce residual CVD risk in high-risk patients with ASCVD and triglycerides >1.5/>1.7 mmol/L (>135/>150 mg/dL) despite optimal statin treatment.[6–10]

In clinical trials such as REDUCE-IT, the treatment effect is usually reported on a group level in terms of an average hazard ratio (HR). However, considerable differences in treatment efficacy may exist between individuals.[11,12] For example, treatment effects may differ between patients with and without a history of ASCVD. The absolute effects of icosapent ethyl in patients with established ASCVD specifically, have not been assessed yet. Also, within patients with ASCVD there may be heterogeneity of treatment effects. First, the relative treatment effect (i.e. the HR) may be modified by a patient's characteristics, or baseline risk of CVD. Second, even in case of an equal relative treatment effect, the absolute treatment effect (i.e. absolute risk reduction [ARR] or gain in CVD-free survival) may still vary substantially between patients based on differences in baseline CVD risk, and remaining life expectancy. Previous reports have proposed that this heterogeneity of treatment effects should be assessed systematically in all trials by evaluating the interaction between treatment effects and individual baseline risk as predicted by a multivariable risk model.[11,13,14] The SMART2 and SMART-REACH risk models are the ESC guideline-recommended tools for prediction of 10-year and lifetime CVD risk in patients with ASCVD.[6,15,16] Applying these models to REDUCE-IT participants and evaluating the impact of baseline CVD risk on the efficacy of icosapent ethyl, could help identify the optimal target population for icosapent ethyl therapy, which could support individualized clinical decision making, and future guideline recommendations.

This study aimed to assess the relative and absolute treatment effects of icosapent ethyl on MACE according to individual baseline CVD risk in patients with ASCVD.

Methods

Study population

REDUCE-IT was a randomized, double-blind, placebo-controlled trial (registration number: NCT01492361) in which participants were randomly assigned to receive 2 g of icosapent ethyl twice daily or placebo.[5] Patients were eligible if they had established ASCVD or diabetes mellitus with at least one additional risk factor, had a fasting triglyceride level of 150 to 499 mg/dL (1.69 to 5.63 mmol/L) and a low-density lipoprotein cholesterol (LDL-c) level of 41 to 100 mg/dL (1.06 to 2.59 mmol/L), and had been receiving a stable dose of a statin for at least four weeks (complete eligibility criteria in Table S1). Detailed descriptions of the trial have been published elsewhere.[5,17] The trial was approved by the local health authorities, institutional review boards, and ethics committees, and written informed consent was obtained from all participants. For the current study, all participants with established ASCVD (n = 5,785) were selected.

SMART2 and SMART-REACH risk models

The SMART2 and SMART-REACH risk models are the ESC guideline-recommended tools for prediction of 10-year (SMART2) and lifetime (SMART-REACH) risk of CVD (i.e. non-fatal myocardial infarction [MI], non-fatal stroke, or cardiovascular death) in patients with ASCVD.[6,15,16] For the current study, SMART2 was used to predict 5-year CVD risk, using the 5-year baseline survival provided in the original report, to be able to directly validate the predicted risks to the observed risks in REDUCE-IT (median follow-up ~5 years).[15] Predictions are based on a selection of established CVD risk factors (Table S2). Descriptions of the development and validation of the models have been published previously.[15,16] Online calculators are freely available on www.U-Prevent.com.

Outcomes

The primary outcome was 3-point MACE, i.e. a composite of non-fatal MI, non-fatal stroke, or cardiovascular death (the outcome predicted by the models). The secondary outcome was 5-point MACE, i.e. a composite of non-fatal MI, non-fatal stroke, cardiovascular death, coronary revascularization, or unstable angina (the primary endpoint of REDUCE-IT). Detailed outcome definitions are provided in Table S3.

Statistical analysis

Efficacy of icosapent ethyl in patients with ASCVD

Hazard ratios for the relative treatment effect of icosapent ethyl on 3-point MACE, 5-point MACE, and their components, were established using Cox proportional hazards models. The ARR was calculated as the proportion of patients with an event in the placebo group minus the proportion of patients with an event in the icosapent ethyl group at the end of follow-up. The number needed to treat (NNT) was calculated as 1/ARR. In addition, reductions in the cumulative incidence of MACE were calculated as the difference between the Kaplan-Meier estimated cumulative incidence of MACE in the placebo vs icosapent ethyl group at 5 years follow-up, i.e. the 5-year cumulative incidence reduction (CIR). Advantages of this method over the conventional ARR calculation are that it takes the time to event and censoring into account, and has a clear timespan (5 years in this case). The conventional ARR was still reported as well to allow a comparison between this study and the main trial report or previous REDUCE-IT subgroup analyses.[5,18–24]

Validation of the SMART2 and SMART-REACH risk models in REDUCE-IT

The SMART2 and SMART-REACH risk models were externally validated in REDUCE-IT. The models were recalibrated to match the underlying event rates in the study population (Methods S1). Model performance was assessed using c-statistics for discrimination, and plots of the predicted vs. observed 5-year risk for calibration. The SMART2 risk score was then used to estimate the baseline 5-year risk of 3-point MACE for all individuals in the study population. Based on these estimates the population was divided into risk quartiles. Baseline characteristics were presented stratified by these quartiles.

Interaction between baseline 5-year CVD risk and the treatment effects of icosapent ethyl

To assess whether the relative treatment effect of icosapent ethyl was modified by baseline CVD risk, a Cox proportional hazards model was derived for 3-point MACE, with allocation to icosapent ethyl, predicted baseline 5-year risk, and an interaction between these two as predictors, in line with previously proposed methods.[11,13,14] The treatment-by-risk interaction was tested for statistical significance using a likelihood ratio test comparing a model with to a model without the interaction term. Next, the relative treatment effect of icosapent ethyl was determined within each risk quartile by deriving quartile-specific models. Heterogeneity of absolute treatment effects was assessed by calculating the ARR, NNT, and 5-year CIR in each quartile separately, using the same methods applied in the overall study population.

Lifetime CVD risk and treatment benefits of icosapent ethyl

The SMART-REACH model was used to estimate the baseline lifetime risk of 3-point MACE, and MACE-free survival for all individuals in the study population. The lifetime

benefits of icosapent ethyl were estimated by combining the model with the average relative treatment effect for patients with ASCVD presented in the original trial report, i.e. an HR of 0.72, according to previously described methods (explained in Methods S2).[12,16] MACE-free survival with and without icosapent ethyl was presented for each risk quartile in survival curves based on the average predicted survival in each quartile at 1-year time intervals. Lifetime benefit was expressed in terms of MACE-free life-years gained, defined as the difference between the median MACE-free survival (where the curve crosses 50%) with and without icosapent ethyl (Methods S2).

Continuous relation between baseline CVD risk and the treatment effects of icosapent ethyl

In addition to the analyses in risk quartiles, the relation between baseline 5-year risk and the treatment effects of icosapent ethyl was also assessed continuously. For the relative treatment effect this was done by deriving a Cox model including a restricted cubic splines function for the treatment-by-risk interaction. As the ARR and 5-year CIR cannot be directly derived from a statistical model, these were determined in increasingly small risk groups, after which their continuous relation with baseline risk was estimated using a restricted cubic splines function weighted for the accuracy of the estimate in each group. Corresponding 95% confidence intervals (CIs) were derived from 10,000 bootstrap samples. A detailed description of the methodology is provided in Methods S3.

The same analyses were performed for 5-point MACE. To be able to predict the risk of 5-point MACE, even though the models were originally developed for 3-point MACE, the models' baseline risks were recalibrated to the event rate of this new outcome while using the original model coefficients (Methods S1). As this only changes the absolute risk value, rather than the ranking of participants, the distribution of participants over the risk quartiles was the same for 3-point and 5-point MACE.

Missing data (≤0.3% for all predictor variables except years since first CVD event [9.9%]; Table S4) were imputed by single imputation using predictive mean matching. All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

Results

Baseline characteristics

Baseline characteristics are presented for the total ASCVD population, and stratified for CVD risk quartiles in Table 1. Predicted baseline 5-year risk of 3-point MACE across risk quartiles was (mean [range]): 9.0% (3.6-11.4%), 13.7% (11.5-16.0%), 19.3% (16.1-23.3%), and 33.7% (23.4-83.0%), and risk of 5-point MACE was: 14.3% (5.8-18.0%), 21.5% (18.1-

24.9%), 29.7% (25.0-35.3%), and 48.4% (35.4-94.6%). Levels of non-lipid CVD risk factors increased across risk quartiles, while lipid concentrations and the use of lipid-lowering therapy remained relatively stable (Table 1).

Table 1. Baseline characteristics

	Total ASCVD population (n = 5,785)	**Risk quartile 1 (n = 1,452)**	**Risk quartile 2 (n = 1,442)**	**Risk quartile 3 (n = 1,445)**	**Risk quartile 4 (n = 1,446)**
SMART2 predicted 5-year risk[a]					
3-point MACE (%), mean (range)	18.9 (3.6-83.0)	9.0 (3.6-11.4)	13.7 (11.5-16.0)	19.3 (16.1-23.3)	33.7 (23.4-83.0)
5-point MACE (%), mean (range)	28.4 (5.8-94.6)	14.3 (5.8-18.0)	21.5 (18.1-24.9)	29.7 (25.0-35.3)	48.4 (35.4-94.6)
Demographic					
Age	63.2±8.7	56.1±6.5	60.9±6.9	65.2±6.7	70.8±7.0
Sex (male)	4,536 (78%)	1,109 (76%)	1,128 (78%)	1,120 (78%)	1,179 (82%)
Geographic region					
United States and Canada	2,010 (35%)	380 (26%)	443 (31%)	514 (36%)	673 (47%)
The Netherlands	1,499 (26%)	338 (23%)	378 (26%)	397 (28%)	386 (27%)
Eastern Europe	1,667 (29%)	553 (38%)	455 (32%)	390 (27%)	269 (19%)
Australia and New Zealand	234 (4%)	71 (5%)	65 (5%)	52 (4%)	46 (3%)
Other[b]	375 (6%)	110 (8%)	101 (7%)	92 (6%)	72 (5%)
Current smoking	956 (17%)	101 (7%)	239 (17%)	281 (19%)	335 (23%)
History of ASCVD					
Coronary artery disease	4,532 (78%)	1,057 (73%)	1,128 (78%)	1,160 (80%)	1,187 (82%)
Cerebrovascular disease	1,147 (20%)	98 (7%)	180 (13%)	309 (21%)	560 (39%)
Peripheral artery disease	688 (12%)	56 (4%)	109 (8%)	179 (12%)	344 (24%)
Abdominal aortic aneurysm	75 (1%)	0 (0%)	3 (0%)	13 (1%)	59 (4%)
Years since first manifestation of ASCVD, median (IQR)	5 (2-11)	2 (1-5)	4 (1-9)	7 (3-12)	10 (5-16)
Comorbidities					
Diabetes mellitus	2,404 (42%)	236 (16%)	517 (36%)	704 (49%)	947 (66%)
Atrial fibrillation	550 (10%)	66 (5%)	110 (8%)	140 (10%)	234 (16%)
Heart failure	1,216 (21%)	305 (21%)	278 (19%)	291 (20%)	342 (24%)
Physical examination					
Body-mass index (kg/m^2)	30.9±5.0	30.6±4.7	30.9±4.9	31.2±4.9	31.0±4.9
Systolic blood pressure (mmHg)	133±16	129±13	132±15	134±15	136±17
Laboratory measurements					
Non-HDL-cholesterol (mmol/L)	3.1±0.5	3.0±0.5	3.1±0.5	3.1±0.5	3.2±0.5
LDL-cholesterol (mmol/L)	2.0±0.5	1.9±0.5	2.0±0.5	2.0±0.5	2.0±0.5

	Total ASCVD population (n = 5,785)	Risk quartile 1 (n = 1,452)	Risk quartile 2 (n = 1,442)	Risk quartile 3 (n = 1,445)	Risk quartile 4 (n = 1,446)
HDL-cholesterol (mmol/L)	1.0±0.2	1.1±0.2	1.1±0.2	1.0±0.2	1.0±0.2
Triglycerides (mmol/L)	2.7±0.9	2.5±0.8	2.6±0.9	2.7±0.9	2.7±0.9
Estimated GFR (mL/min/1.73 m^2)	74±18	84±13	79±15	72±16	61±17
C-reactive protein (mg/L), median (IQR)	2.0 (1.0-4.2)	1.3 (0.7-2.4)	2.1 (1.0-3.7)	2.4 (1.2-4.6)	3.1 (1.5-6.2)
Eicosapentaenoic acid (µg/mL), median (IQR)	27.1 (17.2-41.8)	27.6 (17.2-42.6)	27.3 (17.2-41.3)	27.4 (17.6-43.7)	26.1 (16.9-40.0)
Medication use					
Allocation to icosapent ethyl	2,892 (50%)	757 (52%)	699 (48%)	694 (48%)	742 (51%)
Statin intensity					
Low	223 (4%)	32 (2%)	49 (3%)	60 (4%)	82 (6%)
Moderate	3,520 (61%)	869 (60%)	861 (60%)	886 (61%)	904 (63%)
High	2,026 (35%)	549 (38%)	528 (37%)	495 (34%)	454 (31%)
Ezetimibe	431 (8%)	98 (7%)	106 (7%)	115 (8%)	112 (8%)
Antihypertensive agents					
None	212 (4%)	68 (5%)	52 (4%)	57 (4%)	35 (2%)
One	1,065 (18%)	355 (24%)	286 (20%)	240 (17%)	184 (13%)
Two	2,176 (38%)	649 (45%)	583 (40%)	522 (36%)	442 (29%)
Three or more	2,332 (40%)	380 (26%)	521 (36%)	626 (43%)	805 (56%)
Antithrombotic therapy					
None	296 (5%)	42 (3%)	62 (4%)	90 (6%)	102 (7%)
Antiplatelet monotherapy	3,566 (62%)	873 (60%)	934 (65%)	906 (63%)	853 (59%)
Dual antiplatelet therapy	1,574 (27%)	508 (35%)	384 (27%)	344 (24%)	338 (23%)
Vitamin K antagonist	505 (9%)	49 (3%)	88 (6%)	138 (10%)	230 (16%)

All data in n (%) or mean±SD, unless otherwise specified.

[a] Baseline 5-year risk of MACE as predicted by the SMART2 risk score. For both 3-point and 5-point MACE the risks have been recalibrated to match the event rates for these outcomes in the study population.
[b] This includes India and South Africa.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, GFR = glomerular filtration rate, HDL = high-density lipoprotein, IQR = interquartile range, LDL = low-density lipoprotein, MACE = major adverse cardiovascular events, SD = standard deviation.

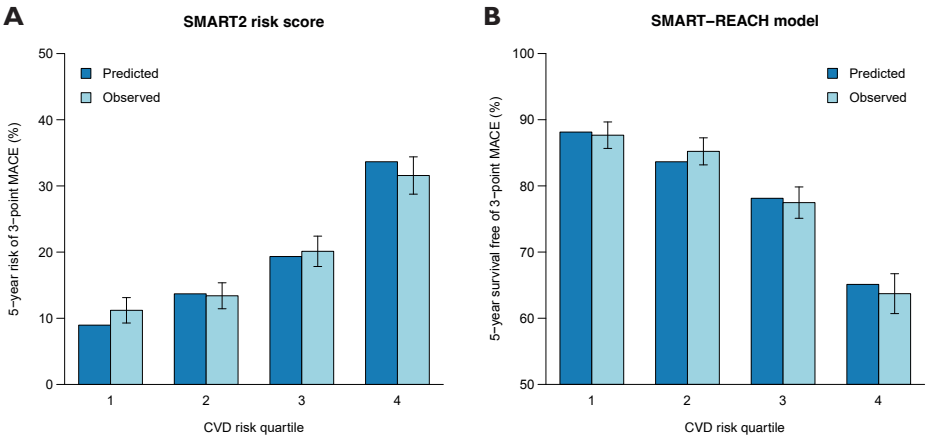
Efficacy of icosapent ethyl in patients with ASCVD

Three-point MACE occurred in 361 (12.5%) vs 489 (16.9%) patients (HR 0.72; 95% CI 0.63-0.82), and 5-point MACE in 559 (19.3%) vs 738 (25.5%) patients (HR 0.73; 95% CI 0.65-0.81) in the icosapent ethyl and placebo group respectively. Over a median follow-up of 4.8 years (interquartile range [IQR] 3.2-5.3), the ARR and NNT (95% CI) were 4.4% (2.6-6.2%) and 23 (16-38) for 3-point MACE, and 6.2% (4.0-8.3%) and 16 (12-25) for 5-point MACE. The reduction in the Kaplan-Meier estimated cumulative incidence at 5 years, i.e. 5-year CIR (95% CI), was 5.7% (3.5-7.9%) for 3-point MACE, and 7.5% (5.0-10.0%) for 5-point MACE (Figure S1). Icosapent ethyl significantly reduced the risk of all other outcomes, except for fatal or non-fatal stroke (HR 0.78; 95% CI 0.58-1.05), and death from any cause (HR 0.86; 95% CI 0.72-1.04) (Figure S1).

Performance of the SMART2 and SMART-REACH risk models in REDUCE-IT

The predicted 5-year risk of MACE and survival free of MACE showed good agreement with the observed risk and survival in the CVD risk quartiles (3-point MACE in Figure 1; 5-point MACE in Figure S2). Consistent results were obtained when the models were validated in octiles of risk (Figure S3).

Figure 1. Calibration of the SMART2 and SMART-REACH risk models in REDUCE-IT

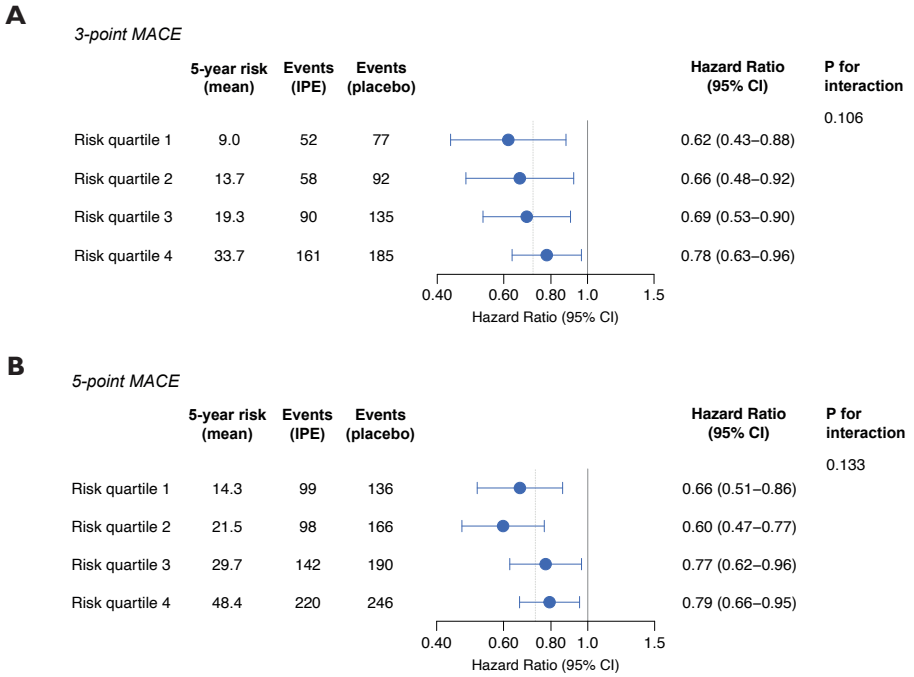


Calibration of the SMART2 and SMART-REACH risk models across CVD risk quartiles in the REDUCE-IT study population. The bars show the mean predicted 5-year risk (by the SMART2 risk score) vs observed 5-year risk of 3-point MACE (A), and mean predicted 5-year survival (by the SMART-REACH model) vs observed 5-year survival free of 3-point MACE (B) across the CVD risk quartiles. Error bars represent 95% confidence intervals.

Interaction between baseline CVD risk and the effects of icosapent ethyl

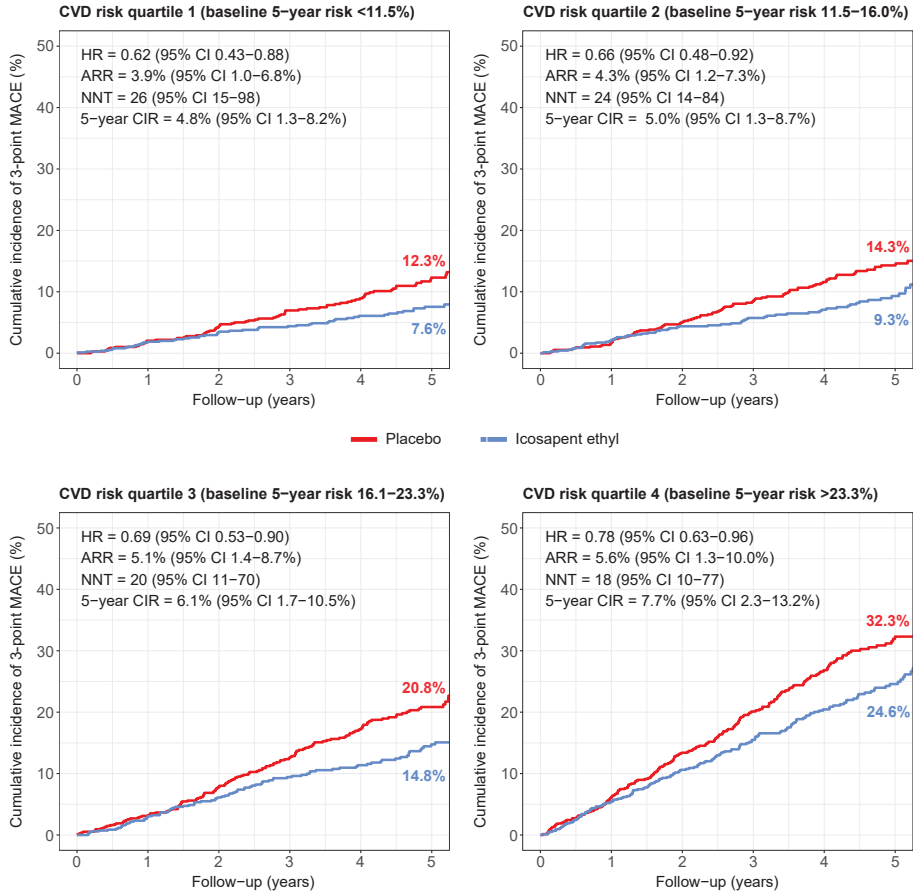
There was no significant interaction between baseline risk and the relative treatment effects of icosapent ethyl (p = 0.106 for 3-point MACE; p = 0.133 for 5-point MACE), although there was a non-significant trend towards an attenuation of the relative effect with increasing baseline risk (Figure 2). The HR (95% CI) ranged from 0.62 (0.43-0.88) in the lowest to 0.78 (0.63-0.96) in the highest risk quartile for 3-point MACE, and from 0.66 (0.51-0.86) to 0.79 (0.66-0.95) for 5-point MACE. Despite the slight attenuation of the relative treatment effect, for 3-point MACE, the absolute treatment effects of icosapent ethyl increased with increasing baseline risk (Figure 3). The ARR and NNT (95% CI) ranged from 3.9% (1.0-6.8%) and 26 (15-98) in the lowest to 5.6% (1.3-10.0%) and 18 (10-77) in the highest risk quartile, and the 5-year CIR ranged from 4.8% (1.3-8.2%) to 7.7% (2.3-13.2%). For 5-point MACE, the favorable relative treatment effects in the lowest risk quartiles were accompanied by relatively large ARRs (6.3% [2.6-10.0%] in quartile 1; 7.9% [4.0-11.8%] in quartile 2), comparable to that observed in the highest risk quartile (6.5% [1.7-11.3%]) (Figure 4).

Figure 2. Relative treatment effects of icosapent ethyl across CVD risk quartiles



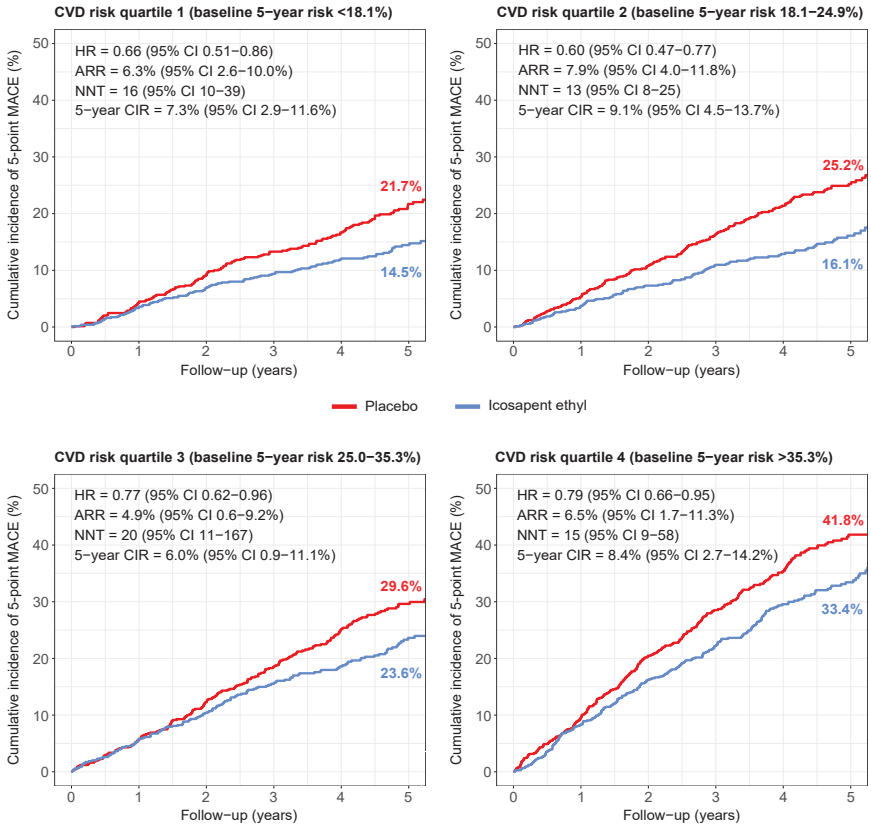
Hazard ratios for the relative treatment effects of icosapent ethyl (IPE) on the risk of 3-point MACE (A) and 5-point MACE (B) in the CVD risk quartiles. The 5-year risk depicts the baseline 5-year risk of 3-point and 5-point MACE as predicted by the SMART2 risk score. The p-value is for the interaction between baseline risk (as a continuous measure) and the relative treatment effect of icosapent ethyl. The grey dotted line denotes the overall trial hazard ratio.

Figure 3. Absolute effects of icosapent ethyl on 3-point MACE across CVD risk quartiles



Kaplan-Meier curves of the cumulative incidence of 3-point MACE in participants randomized to icosapent ethyl and placebo within each CVD risk quartile. The ARR was calculated as the proportion of patients with an event in the placebo group minus the proportion of patients with an event in the icosapent ethyl group at the end of follow-up. The red and blue numbers indicate the cumulative incidence of 3-point MACE at 5 years follow-up in the placebo and icosapent ethyl group respectively. The 5-year cumulative incidence reduction (CIR) was calculated as the difference between these two numbers (±0.1% due to rounding).

Figure 4. Absolute effects of icosapent ethyl on 5-point MACE across CVD risk quartiles

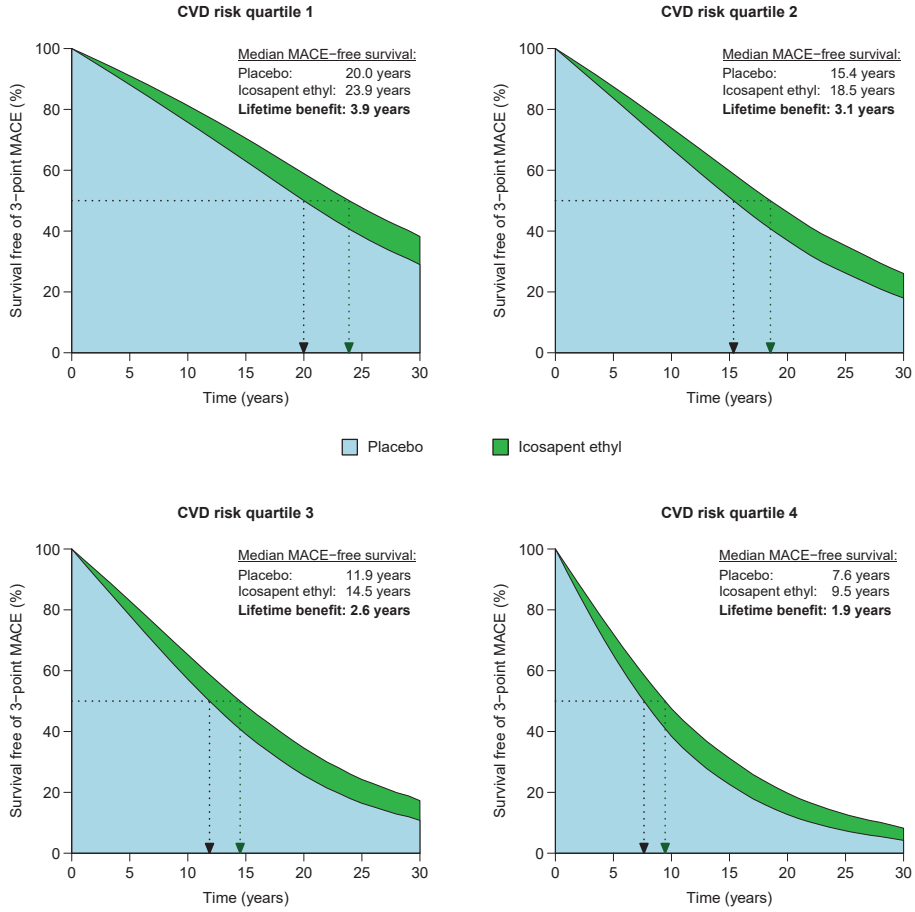


Kaplan-Meier curves of the cumulative incidence of 5-point MACE in participants randomized to icosapent ethyl and placebo within each CVD risk quartile. The ARR was calculated as the proportion of patients with an event in the placebo group minus the proportion of patients with an event in the icosapent ethyl group at the end of follow-up. The red and blue numbers indicate the cumulative incidence of 5-point MACE at 5 years follow-up in the placebo and icosapent ethyl group respectively. The 5-year cumulative incidence reduction (CIR) was calculated as the difference between these two numbers (±0.1% due to rounding).

Lifetime benefit from icosapent ethyl

Predicted baseline survival free of 3-point MACE across risk quartiles was (median [IQR]): 20.0 (10.3-32.6), 15.4 (7.6-25.7), 11.9 (5.7-20.3), and 7.6 (3.5-14.1) years, and survival free of 5-point MACE was: 14.7 (6.9-24.4), 11.0 (5.1-19.0), 8.4 (3.9-14.9), and 5.3 (2.3-9.8) years. The absolute lifetime benefit from icosapent ethyl, expressed as additional life-years without MACE gained, decreased with increasing baseline risk. Gains in MACE-free survival ranged from 3.9 years (IQR 3.4-4.4) in the lowest to 1.9 years (IQR 1.5-2.2) in the highest risk quartile for 3-point MACE (Figure 5), and from 3.3 years (IQR 2.9-3.8) to 1.4 years (IQR 1.1-1.8) for 5-point MACE (Figure S4).

Figure 5. Lifetime benefit from icosapent ethyl across CVD risk quartiles

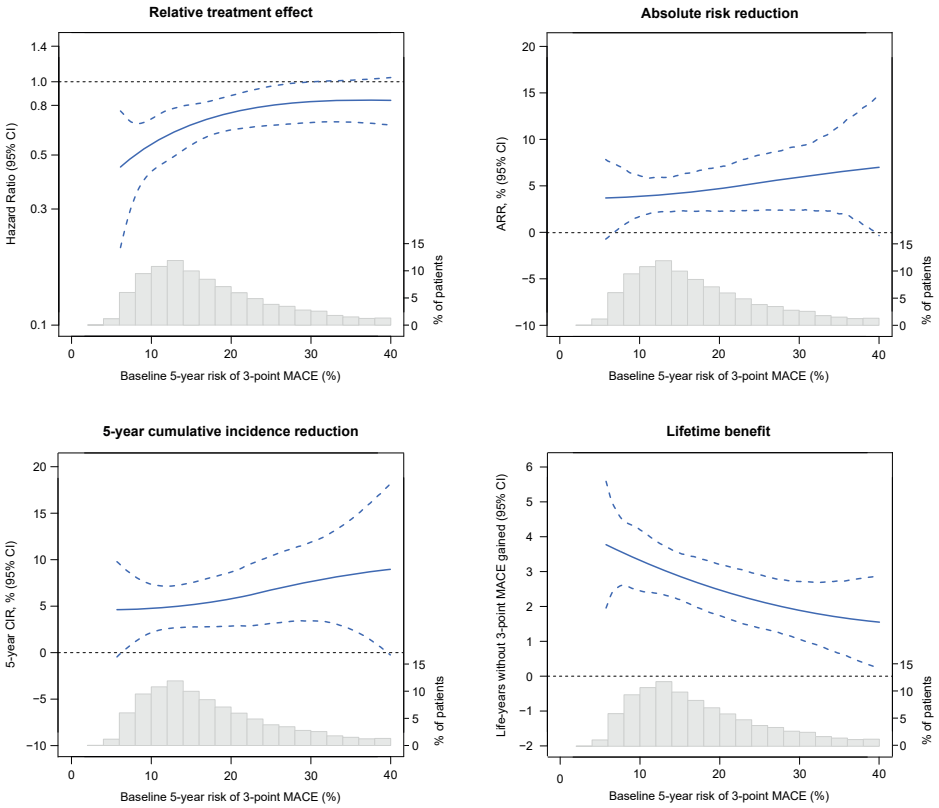


Average predicted survival free of 3-point MACE on placebo and on icosapent ethyl within each CVD risk quartile. Survival on icosapent ethyl was predicted by combining the SMART-REACH model with the overall trial hazard ratio. Median MACE-free survival was defined as the time at which the survival curve crossed 50% (depicted by the dotted lines). Lifetime benefit was expressed in terms of life-years without 3-point MACE gained, and was calculated as the difference between the median MACE-free survival on placebo and icosapent ethyl respectively.

Continuous relation between baseline CVD risk and the effects of icosapent ethyl

For 3-point MACE, the HR (i.e. relative treatment effect) of icosapent ethyl, was most favorable (~0.60) in patients with the lowest baseline risk (5-year risk of 3-point MACE <10%), then gradually increased to ~0.80 at a baseline risk of 20%, and remained largely stable thereafter (Figure 6). Despite the numerical attenuation of the relative treatment effect, the ARR and 5-year CIR gradually increased with increasing baseline risk. Absolute gains in MACE-free survival decreased with increasing baseline risk. Similar trends were observed for 5-point MACE (Figure S5).

Figure 6. Continuous relation between baseline risk and the effects of icosapent ethyl



The continuous relation between baseline 5-year risk of 3-point MACE and the relative and absolute treatment effects of icosapent ethyl on the risk of 3-point MACE, derived from restricted cubic spline functions. The blue dotted lines denote 95% confidence intervals calculated from 10,000 bootstrap samples. The histogram (with corresponding axis at the right side of each plot) shows the distribution of baseline risk in the study population.

Discussion

Using data of 5,785 participants from the REDUCE-IT trial, this study established the efficacy of icosapent ethyl in patients with ASCVD, as well as demonstrated the heterogeneity of its relative and absolute treatment effects according to baseline CVD risk in this population. Icosapent ethyl led to significant relative reductions in the risk of MACE across all CVD risk quartiles. There was no significant interaction between baseline risk and the relative treatment effect of icosapent ethyl, although there was a non-significant trend towards an attenuation of the relative effect with increasing baseline risk. Due to the favorable relative treatment effect at the lower end of the risk spectrum (HR ~0.60), absolute treatment effects were already substantial (ARR ~4%; 5-year CIR ~5%) for patients in the lowest quartile of baseline CVD risk. Despite the slight numerical attenuation of the relative treatment effect towards the upper end of the spectrum (HR ~0.80), absolute treatment effects were still largest (ARR ~6%; 5-year CIR ~8%) for patients in the highest CVD risk quartile.

In trials, relative treatment effect modification is commonly assessed using subgroup analyses. Subgroup analyses in REDUCE-IT have previously shown that the relative treatment effect of icosapent ethyl is consistent across subgroups stratified by renal function, smoking status, and history of coronary revascularization, MI, heart failure, and atrial fibrillation.[18–24] This study, which is the first to assess the efficacy of icosapent ethyl in patients with ASCVD, adds that the relative treatment of icosapent ethyl is also consistent in patients with ASCVD, and that its absolute treatment effects in this group are comparable to those in patients with renal dysfunction (eGFR <60 mL/min/1.73 m^2), prior CABG, and prior MI.[18,20,22] However, conventional subgroup analyses have several limitations.[11,13,14,25,26] First, assessing effect modification in a large number of subgroups leads to a high risk of chance findings.[11,13,14,25,26] If there is no actual interaction effect, the probability of finding a false-positive treatment interaction is still 5% per tested characteristic (if the most common significance level of 0.05 is applied). Also, true interactions may not be discovered (i.e. yielding false-negative findings) as most trials are not adequately powered to detect subgroup differences.[11,13,14,25,26] Furthermore, subgroup analyses induce a reference class problem.[11,13,14] If for example the relative treatment effect varies across both subgroups of age, and subgroups of sex, then it is unclear what the correct effect size is for a young man, or a middle-aged woman. Selecting subgroups based on more than one characteristic would lead to a lower number of participants and endpoints per subgroup, further reducing statistical power. To overcome these limitations, in the present study, relative treatment effect heterogeneity was assessed by evaluating the interaction between the treatment and individual baseline risk as predicted by a multivariable risk model, in accordance with previously proposed methods.[11,13,14] This approach has several advantages over conventional

subgroup analyses. First, as this method does not require stratification into large numbers of subgroups, sufficient power may be maintained to detect heterogeneity of treatment effects, while the risk of chance findings is reduced.[11,13,14] Second, it takes into account multiple characteristics at the same time.[11,13,14] It is likely that a combination of patient characteristics rather than a single characteristic influences the treatment effect. Also, patient characteristics that are not evaluated in subgroup analyses may contribute to treatment effect heterogeneity as well. As many characteristics are included as, or correlated with predictors in the risk model, heterogeneity based on predicted baseline risk accounts for effect modification by all of these factors. By using a publicly available risk model, i.e. the SMART2 and SMART-REACH risk models in this study, the results can be directly applied and used for individualized clinical decision making in clinical practice.

Applying this method to REDUCE-IT revealed no significant interaction between baseline risk and the relative treatment effect of icosapent ethyl. Numerically, the relative treatment effect was larger in patients with a lower baseline risk, but as the treatment-by-risk interaction was non-significant, this finding should be interpreted with caution. If one were to speculate on possible reasons for the more favorable relative treatment effect observed at the lower end of the risk spectrum, one could think of several explanations. First, icosapent ethyl and other interventions targeting CVD risk factors may be more effective in the earlier stages of atherosclerotic disease, as in this stage the development of clinically significant plaques may still be avoided. While in patients with more advanced disease, lowering triglycerides or levels of other risk factors may halt the progression of plaques, but may not cause reversal to a state in which there is no or only minimal atherosclerosis. This is supported by studies of the relation between LDL-c and CVD events, showing that the risk of CVD largely depends on the cumulative exposure to LDL-c at a younger age, and that a genetically determined lower LDL-c (from birth) has a greater influence on CVD risk than the same magnitude of LDL-c reduction with a statin later in life.[27–29] Also, in trials, statins have led to larger relative reductions in the risk of CVD per 1 mmol/L LDL-c reduction in primary as compared to secondary prevention, and younger as compared to older individuals.[30,31] Second, in low-risk patients from REDUCE-IT, their elevated triglyceride level may be (one of) the main driver(s) of their CVD risk, and lowering triglycerides may therefore have a relatively large impact on their risk of future events. Whereas high-risk patients mostly have multiple other and more dominant risk factors (e.g. hypertension, diabetes mellitus, smoking) not modified by icosapent ethyl that, even if triglyceride levels are reduced, may still trigger CVD events. In other words, it may be more difficult to prevent events in high-risk patients with multiple risk factors, potentially explaining the smaller relative risk reduction observed in these patients.

Even if the relative treatment effect of icosapent ethyl is equal for all patients, there are still substantial differences in the absolute treatment effect due to variation in absolute baseline CVD risk. If the overall trial hazard ratio (0.72 for 3-point MACE) would apply to all patients, the expected 5-year absolute reduction in 3-point MACE would range from 2.4% in the lowest risk quartile (baseline 5-year risk 9.0%) to 8.1% in the highest risk quartile (baseline 5-year risk 33.7%). The fact that, in case of an equal relative treatment effect, ARRs are greater and so NNTs are smaller in higher-risk patients means that interventions are usually more (cost-)effective in this group. This is one of the main reasons why in guidelines treatments such as icosapent ethyl are often recommended specifically for patients with a high residual risk. However, the current study showed that in REDUCE-IT, the absolute treatment effects of icosapent ethyl in lower- vs higher-risk patients are in fact much closer together, with an ARR and 5-year CIR that ranged from 3.9% and 4.8% in the lowest to 5.6% and 7.7% in the highest CVD risk quartile. This indicates that icosapent ethyl also leads to substantial absolute reductions in CVD risk in ASCVD patients with elevated triglycerides and a relatively low residual risk. In addition, as lower-risk patients generally have a longer remaining life expectancy, and can therefore be treated over a longer period of time, their expected lifetime benefits often exceed those of high-risk patients, as was also shown in this study. Had total events (i.e. also including second, third, and fourth or more events) been considered, the benefits of icosapent ethyl may have been even larger for both low- and high-risk patients.[32] These results may support a broader use of icosapent ethyl than currently recommended by the ESC and AHA/ACC guidelines, and expert consensus documents.[6–10]

Study limitations should be considered. The median follow-up duration in the trial was 4.8 years and the analyses of observed treatment effects were therefore limited to 5 years. In practice, icosapent ethyl will mostly be continued lifelong. Predicted lifetime benefits were presented in this study, but could only be validated up to 5 years. Like any trial, REDUCE-IT had eligibility criteria, so the results may not be generalizable to all patients in clinical practice. Also, in routine practice, greater non-adherence may be expected, resulting in smaller treatment effects. Side-effects and potential heterogeneity of these side-effects according to baseline risk were not evaluated. But in REDUCE-IT, the rates of adverse events did not differ significantly between the icosapent ethyl and placebo group, with the exception of atrial fibrillation (5.3% vs 3.9%) and peripheral edema (6.5% vs 5.0%).[5] Treatment effect heterogeneity based on effect modifiers that do not influence CVD risk and are not associated with factors that do, is not detected with the methods applied in this study. In practice, greater heterogeneity may be present. The numbers of patients and events in this study allowed for the assessment of treatment effects in quartiles of baseline risk. In case of a larger sample size, treatment effects could have been assessed in a larger number of risk groups, and the continuous relation between baseline risk and treatment effects could have been more accurately estimated.

In conclusion, among patients with ASCVD and elevated triglyceride levels, icosapent ethyl significantly reduces the risk of MACE across all quartiles of baseline CVD risk. The absolute treatment effects increase with increasing baseline CVD risk, but are already substantial for patients in the lowest risk quartile.

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Supplementary material

Methods S1. Recalibration of the SMART2 and SMART-REACH risk models

First, the SMART2 risk score was applied to all patients in the ASCVD study population, predicting each patient's 5-year risk of 3-point MACE, using the coefficients and 5-year baseline hazard published in the original report.[1] To take into account the effect of icosapent ethyl on the risk of 3-point MACE, allocation to icosapent ethyl was added to the model as a dummy variable using the hazard ratio from the trial (HR = 0.72 for participants in the secondary prevention cohort).[2] Next, the expected vs observed (E/O) ratio was calculated by dividing the mean predicted 5-year risk of 3-point MACE (as predicted by the SMART2 risk score including allocation to icosapent ethyl) by the mean observed 5-year risk of 3-point MACE in the study population. To recalibrate the model to the underlying event rate in the study population, the logarithm of the E/O ratio was subtracted from the linear predictor of the model. In this way, the baseline hazard is recalibrated and tailored to the study population, while keeping the original model coefficients. When the recalibrated model was then used to predict each patient's baseline 5-year risk of 3-point MACE, i.e. a patient's predicted risk without icosapent ethyl, the dummy variable for icosapent ethyl was removed from the model.

This methodology was also used to recalibrate the SMART-REACH model. Besides a function for 3-point MACE, the SMART-REACH model also consists of a separate function for non-cardiovascular mortality. Recalibration was also performed for this outcome, using a separate E/O ratio. Like the E/O ratio for 3-point MACE was subtracted from the linear predictor of the function for 3-point MACE, the E/O ratio for non-cardiovascular mortality was subtracted from the linear predictor of the function for non-cardiovascular mortality.

The same methodology was used to make the models suitable for the prediction of 5-point MACE, instead of 3-point MACE (the outcome for which the models were originally developed). For this, the original model coefficients were used, i.e. the assumption was made that the association between the predictors and 5-point MACE was equal to the association between the predictors and 3-point MACE. For both models, the baseline hazard was recalibrated to match the underlying event rate for 5-point MACE in the study population, by calculating the E/O ratio for this outcome and subtracting the E/O ratio from the linear predictor of the model.

Methods S2. Estimation of the lifetime benefits of icosapent ethyl

Lifetime risk of MACE and the lifetime benefits of icosapent ethyl were predicted with the SMART-REACH model, in accordance with previously developed methods.[3,4] First, the SMART-REACH model (recalibrated to the study population; see Methods S1) was used to predict the MACE-free survival without icosapent ethyl for all individuals in the ASCVD study population. This was done by making use of life-tables. Starting from the age of each patient at baseline, the risk of MACE (a_t) and the risk of non-cardiovascular mortality (b_t) were estimated for each consecutive life-year, up to the maximum age of 90 years. A MACE-free survival probability (p_t) was obtained for each life-year, by subtracting MACE risk and non-cardiovascular mortality risk from 1 ($p_t = 1 - a_t - b_t$). The probability of being alive and free of MACE at the start of each life-year (e_t), was calculated by multiplying the MACE-free survival probabilities of all the previous life-years (e.g. for a 60-year old: $e_{t=90} = p_{t=60} * p_{t=61} * p_{t=62} * \ldots\ldots * p_{t=87} * p_{t=88} * p_{t=89}$). Altogether, these predictions form an individual life-table for each patient. For each risk quartile, the average MACE-free survival curve was drawn by taking the mean of the MACE-free survival probabilities (derived from the individual life-tables) of the patients within the risk quartile, at 1 to 30 years after the starting age. The median MACE-free survival without icosapent ethyl in each risk quartile was calculated as the time where the MACE-free survival curve crossed 50%.

Next, the SMART-REACH model was combined with the relative treatment effect of icosapent ethyl for patients with ASCVD derived from the original trial report (HR = 0.72 for 3-point MACE, and HR = 0.73 for 5-point MACE).[2] The model combined with the relative treatment effect was then used to predict the MACE-free survival with icosapent ethyl for all patients. Again, the mean MACE-free survival probability for all patients within a risk quartile at 1-year time intervals was used to draw the average MACE-free survival curve for each risk quartile, and the median MACE-free survival was calculated as the time where the curve crossed 50%. Within each risk quartile, the lifetime benefit from icosapent ethyl was defined as the difference between the median MACE-free survival with and without icosapent ethyl, and was expressed as life-years without MACE gained.

Methods S3. Continuous analyses of the relation between baseline risk and the treatment effects of icosapent ethyl

The continuous relation between the predicted baseline 5-year risk of MACE and the relative treatment effect of icosapent ethyl was assessed by deriving a Cox proportional hazards model including the following terms: allocation to icosapent ethyl, predicted baseline 5-year risk, and the interaction between icosapent ethyl and baseline risk as a restricted cubic spline (with four knots). This model was used to estimate the course of the relative treatment effect across the spectrum of baseline risk. Corresponding 95% confidence intervals were derived by repeating this process in 10,000 bootstrap samples. The 2.5th and 97.5th percentile of the bootstrap samples were used as the lower and upper limit respectively.

Measures of absolute treatment effects such as the absolute risk reduction (ARR) and 5-year cumulative incidence reduction (CIR) cannot be derived directly from a statistical model. So, instead these were determined in increasingly small risk groups. The ARR was defined as the proportion of patients with an event in the placebo group minus the proportion of patients with an event in the icosapent ethyl group at the end of follow-up. The standard error (SE) of the ARR was calculated using the following formula:

$$\sqrt{(E\%_{Placebo} * (1 - E\%_{Placebo}) / N_{Placebo}) + (E\%_{Icosapent\ ethyl} * (1 - E\%_{Icosapent\ ethyl}) / N_{Icosapent\ ethyl})},$$

with *E%* being the proportion of patients with an event in each group, and *N* being the total number of patients in each group. First, the ARR and corresponding SE were determined in the total population. Then, this was done in two risk groups, divided at the median of the baseline 5-year risk of MACE. Subsequently, ARRs and corresponding SEs were also determined in tertiles, quartiles, and quintiles of baseline risk. For each risk group, the mean baseline 5-year risk of MACE was also calculated. This yielded fifteen ARR estimates, associated with varying SEs (the smaller the risk group in which the ARR was determined, the larger the SE), and varying levels of baseline risk (e.g. the ARR determined in the lowest risk tertile belonged to a lower baseline risk than the ARR determined in the highest risk quartile). The continuous relation between the ARR and baseline risk was assessed using a linear model regressing the ARR on baseline risk, with baseline risk as a restricted cubic spline. The model was weighted for the accuracy of each ARR estimate, i.e. the inverse of its SE (1/SE). This model was used to estimate the course of the ARR across the spectrum of baseline risk. This process was repeated in 10,000 bootstrap samples. The mean of the bootstrap samples was used as the final estimate for the course of the ARR over baseline risk. The 2.5th and 97.5th percentiles were used as the lower and upper limits of the 95% confidence intervals respectively.

The 5-year CIR was calculated as the difference between the Kaplan-Meier estimate of the cumulative incidence of MACE in the placebo as compared to the icosapent ethyl group at 5 years follow-up. The SE of the 5-year CIR was calculated using the SEs of the two individual Kaplan-Meier estimates of the cumulative incidence of MACE at 5 years (one for the placebo group and one for the icosapent ethyl group), based on the following formula:

$$\sqrt{(SE_{\text{Placebo}})^2 + (SE_{\text{Icosapent ethyl}})^2}.$$

The course of the 5-year CIR across the spectrum of baseline risk was determined by calculating the 5-year CIR in increasingly small risk groups and repeating this process in 10,000 bootstrap samples, using the same methods as for the ARR (see above).

For the continuous relation between baseline risk and the lifetime benefit of icosapent ethyl, first, the lifetime benefit in terms of life-years without MACE gained was estimated for each individual in the study population using the SMART-REACH model combined with the overall relative treatment effect of icosapent ethyl (see Methods S2). Then, a linear model was derived regressing lifetime benefit on baseline risk, with baseline risk as a restricted cubic spline. This model was used to estimate the course of the lifetime benefit over baseline risk. Again, 95% confidence intervals were derived from 10,000 bootstrap samples.

Table S1. Eligibility criteria of REDUCE-IT

Inclusion criteria[2,5]

Age ≥45 years (if secondary prevention; see below) or ≥50 years (if primary prevention; see below)
 	
Secondary prevention (one of the following)[a]:
• Documented CAD:
  • Multi-vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries with or without antecedent revascularization), or;
  • Prior MI, or;
  • Hospitalization for NSTE-ACS with ST-segment deviation or biomarker positivity.
• Documented cerebrovascular or carotid disease:
  • Prior ischemic stroke, or;
  • Symptomatic carotid arterial stenosis ≥50%, or;
  • Asymptomatic carotid arterial stenosis ≥70%, or;
  • History of carotid revascularization.
• Documented PAD:
  • ABI <0.9 with intermittent claudication, or;
  • History of aorto-iliac or peripheral arterial intervention.
 	
Primary prevention[a]:
• Diabetes mellitus (type 1 or type 2) requiring treatment with medication, AND;
• ≥1 CVD risk factor(s):
  • Age ≥55 years (men) or ≥65 years (women)
  • Current smoking (or stopped smoking <3 months before first visit)
  • Hypertension (≥140/90 mmHg) or on antihypertensive medication
  • HDL-c ≤40 mg/dL (≤1.03 mmol/L) for men or ≤50 mg/dL (≤1.29 mmol/L) for women
  • Hs-CRP >3.0 mg/L
  • Renal dysfunction (CrCL >30 and <60 mL/min)
  • Retinopathy
  • Micro- or macroalbuminuria
  • ABI <0.9
 	
Fasting triglyceride level ≥135 mg/dL (≥1.52 mmol/L) and <500 mg/dL (<5.65 mmol/L)
 	
LDL-C >40 mg/dL (>1.03 mmol/L) and ≤100 mg/dL (≤2.59 mmol/L)
 	
On stable statin therapy (± ezetimibe) for ≥4 weeks prior to randomization
 	
Agree to follow a physician-recommended diet

Exclusion criteria[2,5]
Severe heart failure (NYHA class IV) Life-threatening disease with life expectancy <2 years Severe liver disease HbA1c >10.0% (>86 mmol/mol) Poorly controlled hypertension (≥200/100 mmHg) Planned coronary intervention or non-cardiac major surgical procedure Familial lipoprotein lipase deficiency, apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia Intolerance or hypersensitivity to statin therapy Hypersensitivity to fish and/or shellfish, or ingredients of the study product or placebo History of acute or chronic pancreatitis Malabsorption syndrome or chronic diarrhea

Use of non-study drug, non-statin lipid-altering medications, supplements, or foods including: • Niacin >200 mg/d • Fibrates • OM-3 fatty acid medications • Supplements containing OM-3 fatty acids • Bile acid sequestrants • PCSK9 inhibitors
Use of one of the following medications: • Tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids, cyclophosphamide, or systemic retinoids
Known AIDS
Requirement for dialysis or CrCl <30 mL/min
CK concentration >5 × ULN or CK elevation due to muscle disease
Pregnant or breastfeeding women, or women of child-bearing potential not using an acceptable form of birth control

[a] For the current study, only participants who met the criteria for the secondary prevention stratum in REDUCE-IT were included.
Abbreviations: ABI = ankle-brachial index, AIDS = acquired immunodeficiency syndrome, CAD = coronary artery disease, CK = creatine kinase, CrCl = creatinine clearance, CVD = cardiovascular disease, HbA1c = hemoglobin A1c, HDL-c = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, NSTE-ACS = non-ST-segment elevation acute coronary syndrome, NYHA = New York Heart Association, OM-3 = omega-3, PAD = peripheral artery disease, PCSK9 = proprotein convertase subtilisin/kexin type 9, ULN = upper limit of normal.

Table S2. Predictors in the SMART2 and SMART-REACH risk models

Model	Predictors
SMART2 risk score[1]	Age
	Sex
	Current smoking
	History of coronary artery disease
	History of cerebrovascular disease
	History of peripheral artery disease
	History of abdominal aortic aneurysm
	Years since first ASCVD diagnosis
	Diabetes mellitus
	Systolic blood pressure
	Non-HDL-cholesterol
	Estimated glomerular filtration rate
	High-sensitivity CRP
SMART-REACH model[4]	Age
	Sex
	Current smoking
	Number of ASCVD locations[a]
	Diabetes mellitus
	History of atrial fibrillation
	History of heart failure
	Systolic blood pressure
	Total cholesterol
	Creatinine

[a] Number of ASCVD locations out of coronary artery disease, cerebrovascular disease, and peripheral artery disease (one, two, or three).
Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CRP = C-reactive protein, HDL = high-density lipoprotein.

Table S3. Outcome definitions

Outcome	Definition[2,6]
Myocardial infarction	Evidence of myocardial necrosis (≥1 cardiac biomarker(s) >URL, or post-mortem pathological evidence of acute MI), combined with a clinical presentation consistent with myocardial ischemia, electrocardiographic changes (ST elevation or depression, T-wave inversion, or pathological Q-waves), or evidence from myocardial or coronary artery imaging (loss of viable myocardium, regional wall motion abnormality, or thrombosis/occlusion of coronary artery), including silent MI (new pathological Q-waves, imaging evidence of loss of viable myocardium, or autopsy evidence of a healed or healing MI, without evidence of acute MI).
Stroke	Acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue, or a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
Cardiovascular death	Death resulting from myocardial infarction, heart failure, or stroke, sudden cardiac death, or death due to other cardiovascular causes (e.g. pulmonary embolism, aortic aneurysm rupture, peripheral artery disease, complications of cardiac surgery or revascularization).
Coronary revascularization	A catheter-based or open surgical procedure designed to improve myocardial blood flow, i.e. PCI or CABG.
Unstable angina	Ischemic discomfort (angina or equivalent symptoms) ≥10 minutes in duration occurring at rest or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity, prompting an unscheduled hospitalization within 24 hours of the most recent symptoms, combined with electrocardiographic changes (ST elevation/depression, or T-wave inversion), a positive exercise stress test, evidence from myocardial or coronary artery imaging (wall motion abnormality, perfusion defect/deficit, or lesion/thrombus in coronary artery), or the need for coronary revascularization, with negative cardiac biomarkers and no evidence of acute MI.

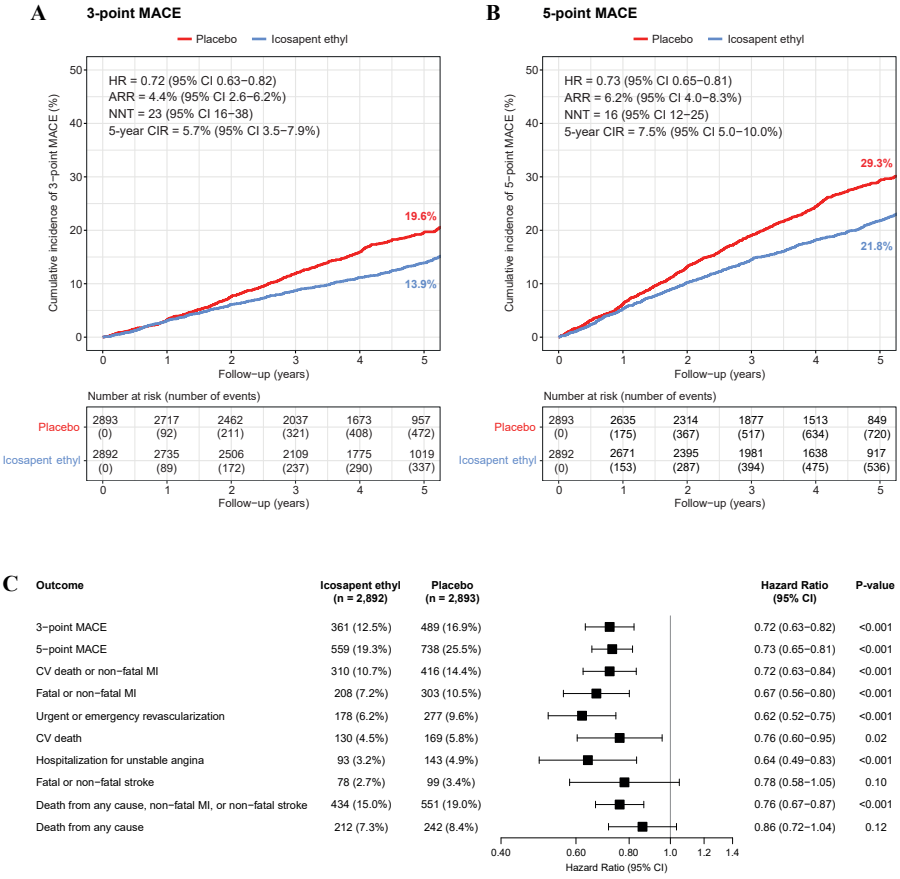
Outcomes were defined in accordance with the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials.[6] All events were adjudicated by an independent clinical endpoint committee blinded for the trial-group assignment.[2]
Abbreviations: CABG = coronary artery bypass graft, MI = myocardial infarction, PCI = percutaneous coronary intervention, URL = upper reference limit.

Table S4. Missing data

Variable	Missing values, n (%)
Age	0 (0.0%)
Sex	0 (0.0%)
Current smoking	2 (0.0%)
Number of ASCVD locations	0 (0.0%)
History of coronary artery disease	0 (0.0%)
History of cerebrovascular disease	0 (0.0%)
History of peripheral artery disease	0 (0.0%)
History of abdominal aortic aneurysm	0 (0.0%)
Years since first ASCVD diagnosis	570 (9.9%)
Diabetes mellitus	3 (0.1%)
History of atrial fibrillation	0 (0.0%)
History of heart failure	3 (0.1%)
Systolic blood pressure	10 (0.2%)
Total cholesterol	5 (0.1%)
Non-HDL-cholesterol	17 (0.3%)
Creatinine	6 (0.1%)
Estimated glomerular filtration rate	6 (0.1%)
High-sensitivity CRP	4 (0.1%)

Overview of the missing data for predictor variables from the SMART2 and SMART-REACH risk models in the study population (n = 5,785).
Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CRP = C-reactive protein, HDL = high-density lipoprotein.

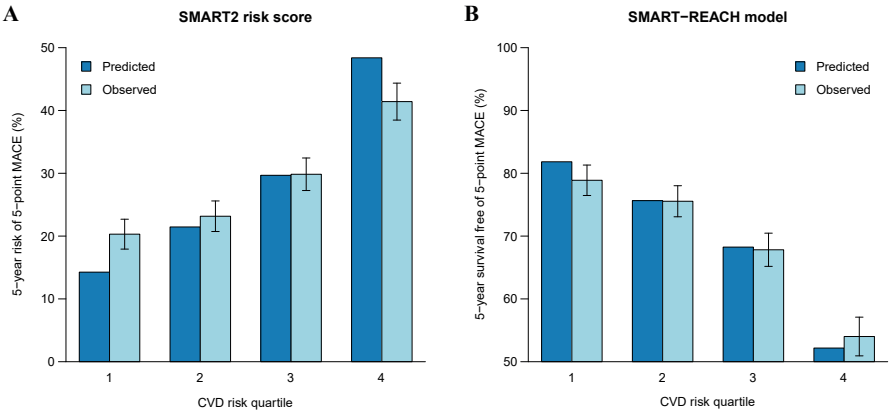
Figure S1. Efficacy of icosapent ethyl in patients with ASCVD



Kaplan-Meier curves of the cumulative incidence of 3-point MACE (A) and 5-point MACE (B), and hazard ratios for all outcomes (C) in REDUCE-IT participants with ASCVD (n = 5,785). ARRs were calculated as the proportion of patients with an event in the placebo group minus the proportion of patients with an event in the icosapent ethyl group at the end of follow-up. The red and blue numbers indicate the cumulative incidence at 5 years follow-up in the placebo and icosapent ethyl group respectively. The 5-year cumulative incidence reductions (CIRs) were calculated as the difference between the red and blue numbers. Three-point MACE is a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Five-point MACE additionally includes coronary revascularization, and unstable angina.

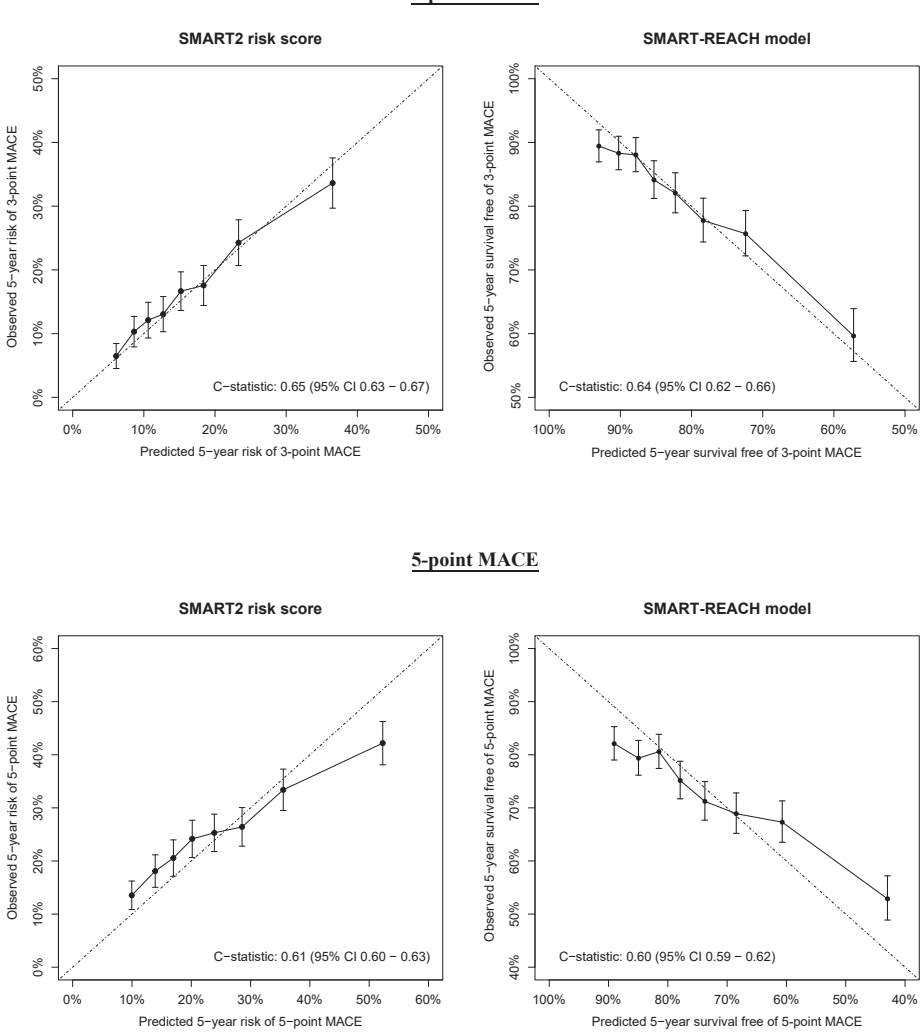
Abbreviations: ARR = absolute risk reduction, CI = confidence interval, CIR = cumulative incidence reduction, CVD = cardiovascular disease, HR = hazard ratio, MACE = major adverse cardiovascular events, NNT = number needed to treat.

Figure S2. Calibration for 5-point MACE across CVD risk quartiles



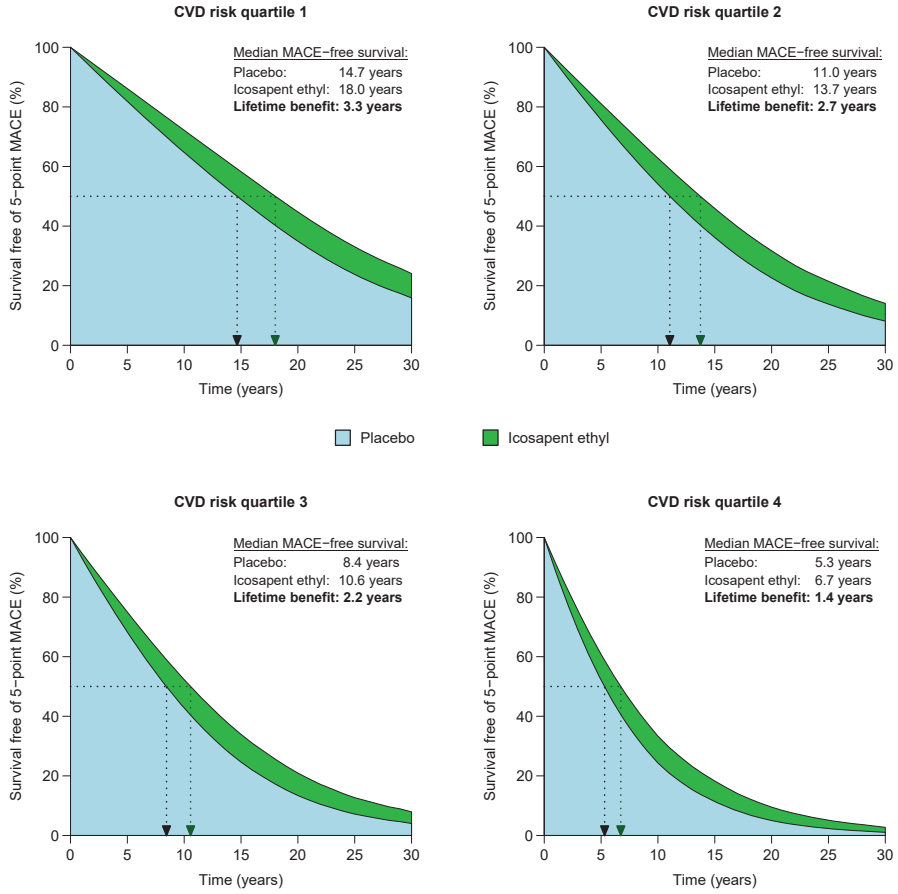
Mean predicted 5-year risk (by the recalibrated SMART2 risk score) vs observed 5-year risk of 5-point MACE (A), and mean predicted 5-year survival (by the recalibrated SMART-REACH model) vs observed 5-year survival free of 5-point MACE (B) across the CVD risk quartiles. Error bars represent 95% confidence intervals. Five-point MACE is a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, coronary revascularization, or unstable angina.
Abbreviations: CVD = cardiovascular disease, MACE = major adverse cardiovascular events.

Figure S3. Validation of the SMART2 and SMART-REACH models in octiles of risk



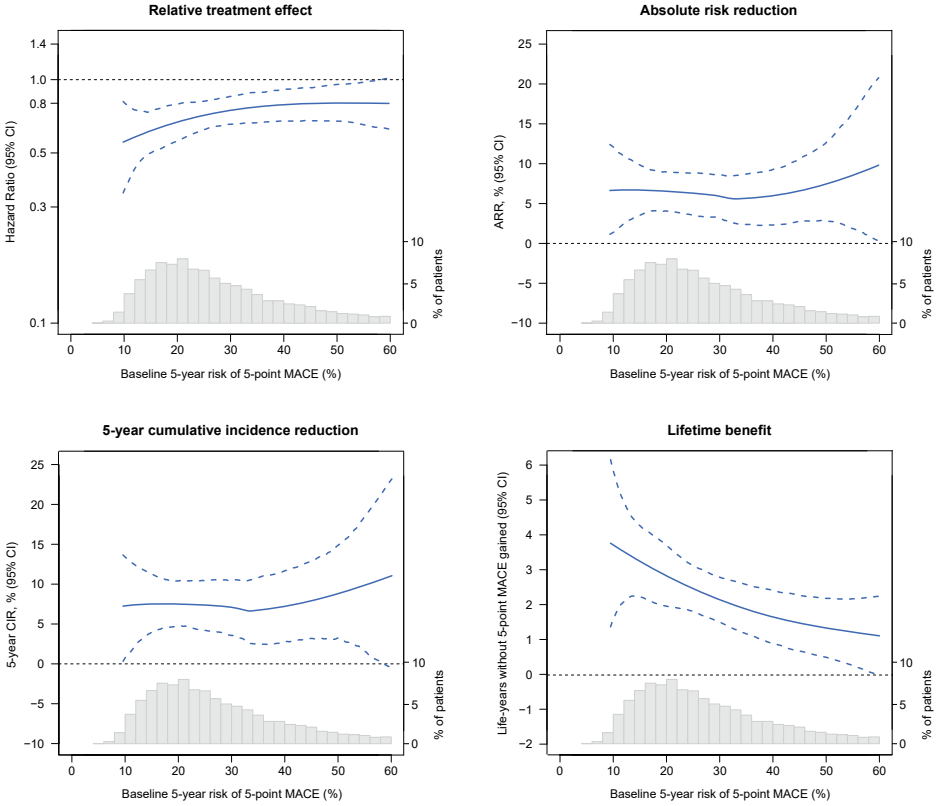
Calibration in octiles of predicted risk and Harrel's c-statistics for the SMART2 and SMART-REACH risk models. Error bars represent 95% confidence intervals. Three-point MACE is a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. Five-point MACE additionally includes coronary revascularization, and unstable angina.
Abbreviations: MACE = major adverse cardiovascular events.

Figure S4. Lifetime benefit for 5-point MACE across CVD risk quartiles



Average predicted survival free of 5-point MACE on placebo and on icosapent ethyl within each CVD risk quartile. Survival on icosapent ethyl was predicted by combining the recalibrated SMART-REACH model with the overall trial hazard ratio. Median MACE-free survival was defined as the time at which the survival curve crossed 50% (depicted by the dotted lines). Lifetime benefit was expressed in terms of life-years without 5-point MACE gained, and was calculated as the difference between the median MACE-free survival on placebo and icosapent ethyl respectively. Five-point MACE is a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, coronary revascularization, or unstable angina.
Abbreviations: CVD = cardiovascular disease, MACE = major adverse cardiovascular events.

Figure S5. Continuous relation between baseline risk and the effects of icosapent ethyl on 5-point MACE



The continuous relation between baseline 5-year risk of 5-point MACE and the relative and absolute treatment effects of icosapent ethyl on the risk of 5-point MACE, derived from restricted cubic spline functions. The blue dotted lines denote 95% confidence intervals calculated from 10,000 bootstrap samples. The histogram (with corresponding axis at the right side of each plot) shows the distribution of baseline risk in the study population. Five-point MACE is a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, coronary revascularization, or unstable angina.

Abbreviations: ARR = absolute risk reduction, CI = confidence interval, CIR = cumulative incidence reduction, MACE = major adverse cardiovascular events.

Supplemental References

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Chapter 8.

Course of the effects of LDL-cholesterol reduction on cardiovascular risk over time: a meta-analysis of 60 randomized controlled trials

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Submitted

Abstract

Background

Individuals with or at high risk of cardiovascular disease (CVD) often receive long-term treatment with low-density lipoprotein cholesterol (LDL-C) lowering therapies, but whether the effects of LDL-C reduction remain stable over time is uncertain. This study aimed to establish the course of the effects of LDL-C reduction on cardiovascular risk over time.

Methods

Randomized controlled trials (RCTs) of LDL-C lowering therapies were identified through a search in MEDLINE and EMBASE (1966-January 2023). The primary analyses were restricted to statins, ezetimibe, and proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, with other therapies included in sensitivity analyses. Random-effects meta-analyses were performed to establish the relative risk (RR) for major vascular events (cardiovascular death, myocardial infarction, unstable angina, coronary revascularization, or stroke) per 1 mmol/L LDL-C reduction. Course of the effects over time was assessed using random-effects meta-regression analyses for the association between follow-up duration, age, and the RR for major vascular events per 1 mmol/L LDL-C reduction. Additionally, treatment-by-time interactions were evaluated in an individual participant data meta-analysis of six atorvastatin trials.

Results

A total of 60 RCTs were identified (408,959 participants, 51,425 major vascular events). The RR for major vascular events per 1 mmol/L LDL-C reduction was 0.78 (95% confidence interval [CI] 0.75-0.81). Follow-up duration was not associated with a change in the RR for major vascular events (RR for change per year 0.994; 95% CI 0.970-1.020; p = 0.66). The RR attenuated with increasing age in primary prevention (RR for change per 5 years 1.097; 95% CI 1.031-1.168; p = 0.003), but not secondary prevention (RR for change per 5 years 0.987; 95% CI 0.936-1.040; p = 0.63). Consistent results were found for statin trials only, and all trials combined. In the individual participant data meta-analysis (31,310 participants, 6,734 major vascular events), the HR for major vascular events did not significantly change over follow-up time (HR for change per year 0.983; 95% CI 0.943-1.025; p = 0.42), or age (HR for change per 5 years 1.022; 95% CI 0.990-1.055; p = 0.18).

Conclusion

Based on available RCT data with limited follow-up duration, the relative treatment effects of LDL-C reduction appear stable over time in secondary prevention, but may attenuate with higher age in primary prevention.

Introduction

Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor of cardiovascular disease (CVD). Numerous randomized controlled trials (RCTs) have demonstrated that lowering LDL-C by treatment with a statin or other lipid-lowering agents significantly reduces the risk of CVD in both primary and secondary prevention populations.[1,2] The reduction in CVD risk observed with lipid-lowering therapy has been shown to be proportional to the absolute reduction in LDL-C.[1,2] All currently available guidelines therefore recommend the use of lipid-lowering therapy to reduce LDL-C to specific treatment goals in people with or at high risk of CVD.[3,4]

In current practice, lipid-lowering therapy is usually initiated following a first CVD event, or when one or more risk factors (e.g. dyslipidaemia, hypertension, diabetes mellitus) are discovered, and is then continued lifelong.[3,4] However, atherosclerosis is a chronic and progressive disease that starts early in life and slowly develops over decades before leading to a major CVD event. Mendelian randomization studies have shown that genetic variants associated with lifelong exposure to lower LDL-C are associated with considerably larger reductions in the risk of CVD than the same magnitude of LDL-C reduction achieved with lipid-lowering therapy in RCTs.[5–8] Following these results, it was hypothesized that lowering LDL-C early in life might be more effective than the current practice of starting lipid-lowering therapy later in life.[5,9,10] On an absolute scale this is likely true, as the effects of a lower exposure to LDL-C have more time to accumulate when therapy is initiated earlier in life. But it also raises the question as to whether the relative treatment effects of LDL-C reduction change over time. Establishing the course of the relative treatment effects of LDL-C reduction over time could help to identify the optimal timing for lipid-lowering therapy, and support the incorporation of the effects of LDL-C reduction in clinical prediction models.

In this meta-regression and individual participant data meta-analysis of RCTs of lipid-lowering therapies, we aimed to establish the course of the relative treatment effects of LDL-C reduction on cardiovascular risk over time, using two definitions of time: (1) follow-up time, and (2) age.

Methods

Contributing studies and data

For the meta-regression analysis, potential trials were identified by updating a search performed in a previous meta-analysis.[2] In this previous study, MEDLINE and EMBASE were searched for trials of lipid-lowering therapies published between 1966 and July 2016,

using the search terms 'LDL lowering' and 'clinical outcomes', limited to 'randomized controlled trials' and 'human'. Trials were included if they were randomized controlled trials with a duration of at least 6 months, studying a lipid-lowering intervention (either lipid-lowering therapy vs placebo or usual care, or more vs less intensive lipid-lowering therapy), and reporting clinical cardiovascular outcomes (at least 50 events). Trials focused on participants with heart failure or end-stage kidney disease were excluded, as lipid-lowering therapy has been shown to be less effective in these populations due to competing non-atherosclerotic risks.[1] For the current study, the search was updated for the time period between July 2016 and January 2023 (full search strategy in Supplemental Methods). In addition to the aforementioned eligibility criteria, trials in which the intervention showed no effect on LDL-C level were excluded. Two authors (PMB and JH) independently screened all records and, if a trial was eligible, collected the following information from each trial: study population (primary or secondary prevention, or both), intervention and control therapy, sample size, mean baseline age (median if mean was not available), mean follow-up duration (median if mean was not available), number of major vascular events, between-group difference in LDL-C, and the relative risk (RR, i.e. hazard ratio or risk ratio if hazard ratio was not available) for major vascular events with 95% confidence intervals (CIs). If a trial included both primary and secondary prevention, separate information was collected for these two groups based on the results of subgroup analyses. If stratified information was not reported, the trial was labelled according to the group the majority of participants belonged to.

For the individual participant data meta-analysis, data were acquired from six trials: the Collaborative Atorvastatin Diabetes Study (CARDS), the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, the Treating to New Targets (TNT) trial, the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN), and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.[11–16] Individual participant data on age, study medication, LDL-C, and (time to) cardiovascular outcomes were harmonized into a pooled dataset.

Outcome

The outcome was the first occurrence of a major vascular event, i.e. cardiovascular death, myocardial infarction, unstable angina, coronary revascularization, or stroke. If this exact outcome was not available, the outcome from the trial that most closely matched the outcome of interest was selected.

Statistical analysis

Meta-analysis of the overall effects of 1 mmol/L LDL-C reduction

The effects of the intervention in each trial were standardized to reflect the effects of a 1 mmol/L reduction in LDL-C, using the RR for major vascular events and the between-group difference in LDL-C: RR per 1 mmol/L LDL-C reduction = $RR^{(1/\text{between-group difference in LDL-C})}$. Meta-analyses were performed using random-effects models, to estimate the RR for major vascular events per 1 mmol/L LDL-C reduction. The primary analysis included all trials of guideline-recommended drugs for LDL-C lowering (i.e. statins, ezetimibe, and proprotein convertase subtilisin–kexin type 9 [PCSK9] inhibitors). Sensitivity analyses were performed using trials of statins only and trials of all lipid-lowering therapies, and stratified for primary and secondary prevention.

Meta-analysis of the effects of LDL-C reduction over follow-up time

In the meta-regression analysis, for all trials, the RR for major vascular events per 1 mmol/L LDL-C reduction was plotted against the average follow-up duration. To assess the association between follow-up duration and the RR for major vascular events, random-effects meta-regression analyses were performed. As the linearity assumption tested based on restricted cubic splines was not violated (p for non-linearity >0.05), the meta-regression analyses were based on linear regression models. The primary analyses included all trials of guideline-recommended therapies, while sensitivity analyses included trials of statins only, and trials of all therapies. All analyses were also performed stratified for primary and secondary prevention.

In the individual participant data meta-analysis, Cox proportional hazards models for the relation between LDL-C reduction and major vascular events were derived in the pooled dataset of the six atorvastatin trials available for analysis. To maintain the randomization within the trials and analyse the data in accordance with the intention-to-treat principle, for participants in the intervention arm of each trial, LDL-C reduction was defined as the average between-group difference in LDL-C in that trial, while it was set to zero for participants in the control arm. The models were stratified by trial to account for between-trial differences in baseline risk. To assess whether the HR for major vascular events per 1 mmol/L LDL-C reduction significantly changed over follow-up time, the proportional hazards assumption was tested based on scaled Schoenfeld residuals. The average change in the HR per year was assessed by adding an interaction term between LDL-C reduction and follow-up time to the model. The course of the relative treatment effects over follow-up time was visually presented in a plot of the HR against follow-up time. Besides in the pooled dataset, the analyses were also performed in the six trials individually.

Meta-analysis of the effects of LDL-C reduction over age

To assess the course of the effects of LDL-C reduction over age (as a second definition of time), first, all meta-regression analyses were repeated after replacing the average follow-up duration by the average age during each trial (i.e. average baseline age + 0.5*average follow-up duration). For age, an additional sensitivity analysis was performed in which the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, a trial with a substantially higher mean age compared to the other trials (i.e. an outlier), was excluded.[17]

Second, the individual participant data meta-analysis was repeated while using age (instead of follow-up time) as the underlying time scale of the Cox proportional hazards models (i.e. left truncation).[18]

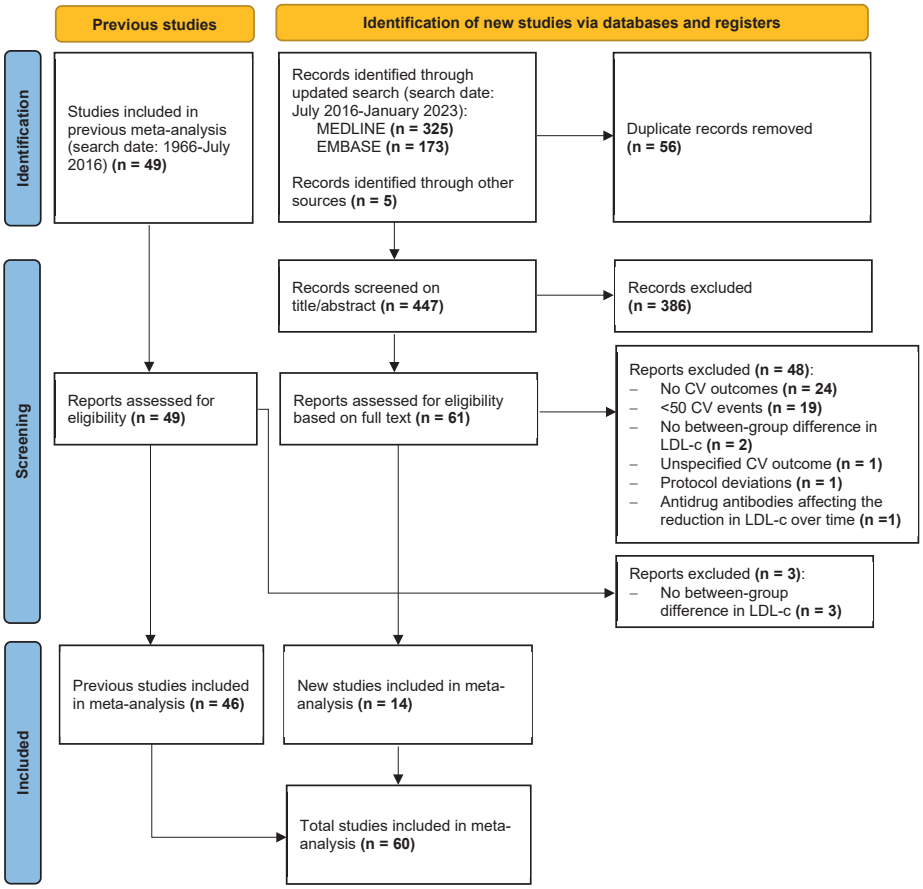
All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

Results

Study selection and characteristics

A total of 496 records (49 studies from previous meta-analysis, 447 new records) were identified and reviewed for eligibility, of which 60 trials were selected (408,959 participants, 51,425 major vascular events) (Figure 1). This included 38 trials of guideline-recommended lipid-lowering therapies: 26 statin trials, 2 trials of ezetimibe, 3 trials of statin/ezetimibe combinations, and 7 trials of PCSK9 inhibitors (275,315 participants, 34,323 major vascular events). In addition, there were 22 trials of other lipid-lowering therapies: 4 diet trials, 2 trials of bile acid sequestrants, 1 trial of ileal bypass surgery, 7 trials of fibrates, 3 trials of niacin (one was a multigroup trial that also studied fibrates), 3 trials of cholesteryl ester transfer protein (CETP) inhibitors, and 3 trials of bempedoic acid (133,644 participants, 17,102 major vascular events). Mean follow-up in the trials was 3.9 years (range 0.9-9.7), and mean age during the trials was 63.9 years (range 48.0-77.0). Trial characteristics are summarized per therapy in Table 1, with characteristics of and references to the individual trials provided in Table S1.

Figure 1. Identification and selection of trials for the meta-regression analysis



PRISMA flowchart showing the identification and selection of trials for the meta-regression analyses.[26] Previous studies indicate trials already identified in a previous meta-analysis.[2]

Table 1. Trial characteristics

	Guideline-recommended lipid-lowering therapies				Other lipid-lowering therapies						
	Statin	**Ezetimibe**	**Statin + ezetimibe**	**PCSK9 inhibitor**	**Diet**	**Bile acid sequestrant**	**Ileal bypass**	**Fibrate[a]**	**Niacin[a]**	**CETP inhibitor**	**Bempedoic acid**
Trials, n	26	2	3	7	4	2	1	7	3	3	3
Participants, n	189,501	19,865	8,513	57,436	1,903	6,084	838	33,471	32,995	44,164	16,978
Primary prevention, n (%)	78,707 (42%)	-	1,873 (22%)	4,465 (8%)	-	6,084 (100%)	-	23,940 (72%)	-	-	4,206 (25%)
Secondary prevention, n (%)	110,794 (58%)	19,865 (100%)	6,640 (78%)	52,971 (92%)	1,903 (100%)	-	838 (100%)	9,531 (28%)	32,995 (100%)	44,164 (100%)	12,772 (75%)
Age during trial, mean (range)	64.1 (57.7-77.0)	64.6 (63.6-65.6)	67.9 (65.5-69.8)	62.3 (58.4-66.9)	NA[b]	54.9	55.9	61.0 (48.0-70.5)	66.0 (65.2-66.9)	66.2 (63.5-69.1)	66.2 (64.8-67.2)
Baseline LDL-C (mmol/L), mean (range)	3.5 (2.3-5.0)	3.0 (2.4-3.5)	3.1 (2.1-3.6)	2.7 (2.4-3.2)	4.8 (4.0-5.6)	5.7 (5.3-6.1)	4.6	3.6 (3.1-4.9)	2.7 (1.6-4.4)	1.9 (1.6-2.1)	3.1 (2.7-3.6)
LDL-C reduction (mmol/L), mean (range)	0.92 (0.35-1.86)	0.42 (0.33-0.50)	0.93 (0.21-1.79)	1.50 (1.24-1.89)	0.71 (0.47-0.88)	0.85 (0.67-1.02)	1.62	0.34 (0.16-0.54)	0.40 (0.16-0.78)	0.75 (0.68-0.83)	0.54 (0.50-0.57)
Follow-up, mean (range)	4.3 (1.9-6.7)	5.0 (3.9-6.0)	3.6 (3.0-4.4)	1.7 (0.9-2.8)	4.1 (3.0-5.0)	4.7 (2.0-7.4)	9.7	4.9 (3.3-6.2)	4.0 (3.0-5.0)	2.6 (1.5-4.1)	1.8 (1.0-3.4)
Major vascular events, n	22,051	5,913	970	5,389	489	470	207	3,799	5,136	5,894	1,946

Characteristics of the trials included in the meta-regression analyses. Means and ranges were calculated from the mean (or median if mean was not available) presented in each trial.

[a] The Coronary Drug Project was a multigroup trial that compared both fibrates and niacin to placebo. This trial was counted, and its participants in the placebo group were included in both columns.

[b] Average age was not available for any of the diet trials.

Abbreviations: CETP = cholesteryl ester transfer protein, LDL-C = low-density lipoprotein cholesterol, NA = not available, PCSK9 = proprotein convertase subtilisin–kexin type 9.

Individual participant data was available for 6 atorvastatin trials (31,310 participants, 6,734 major vascular events). Median follow-up was 4.6 years (interquartile range [IQR] 3.7-5.0), and mean age was 61.6±9.3 years. Patient characteristics are presented in Table 2.

Table 2. Patient characteristics in the trials with available individual participant data

Characteristic	Total (n = 31,310)	CARDS (n = 2,838)	ALLIANCE (n = 2,442)	TNT (n = 10,001)	IDEAL (n = 8,888)	ASPEN (n = 2,410)	SPARCL (n = 4,731)
Age	61.6±9.3	61.7±8.1	61.2±8.8	61.0±8.8	61.7±9.5	61.0±8.2	62.8±11.2
Sex (male)	23,645 (76%)	1,929 (68%)	2,008 (82%)	8,099 (81%)	7,187 (81%)	1,599 (66%)	2,823 (60%)
Current smoker	5,490 (18%)	631 (22%)	475 (19%)	1,341 (13%)	1,835 (21%)	300 (12%)	908 (19%)
CVD prevention population							
Primary prevention	4,480 (14%)	2,838 (100%)	-	-	-	1,642 (68%)	-
Secondary prevention	26,830 (86%)	-	2,442 (100%)	10,001 (100%)	8,888 (100%)	768 (32%)	4,731 (100%)
Diabetes mellitus	9,152 (29%)	2,838 (100%)	540 (22%)	1,501 (15%)	1,069 (12%)	2,410 (100%)	794 (17%)
History of hypertension	14,976 (52%)	2,377 (84%)	NA	5,413 (54%)	2,930 (33%)	1,328 (55%)	2,928 (62%)
Body mass index (kg/m^2)	28.0±4.1	28.8±3.6	NA	28.5±4.6	27.3±3.9	28.9±3.8	27.5±3.9
Systolic blood pressure (mmHg)	135±18	144±16	134±18	131±17	137±20	133±17	139±17
Total cholesterol (mmol/L)	5.0±0.8	5.4±0.8	5.8±0.8	4.5±0.6	5.1±0.7	5.0±0.8	5.5±0.8
LDL-cholesterol (mmol/L)	3.0±0.7	3.0±0.7	3.8±0.7	2.5±0.5	3.1±0.7	2.9±0.7	3.4±0.7
HDL-cholesterol (mmol/L)	1.2±0.3	1.4±0.3	1.0±0.2	1.2±0.3	1.2±0.3	1.2±0.3	1.3±0.3
Triglycerides (mmol/L)	1.8±0.9	1.9±1.1	2.2±1.2	1.7±0.8	1.7±0.9	1.9±1.0	1.6±0.8
Trial intervention							
Atorvastatin 80 mg	7,360 (24%)	-	-	4,995 (50%)	-	-	2,365 (50%)
Atorvastatin 40-80 mg	4,439 (14%)	-	-	-	4,439 (50%)	-	-
Atorvastatin 10-80 mg	1,217 (4%)	-	1,217 (50%)	-	-	-	-
Atorvastatin 10 mg	2,639 (8%)	1,428 (50%)	-	-	-	1,211 (50%)	-
Trial control							
Simvastatin 20-40 mg	4,449 (14%)	-	-	-	4,449 (50%)	-	-
Atorvastatin 10 mg	5,006 (16%)	-	-	5,006 (50%)	-	-	-
Placebo	4,975 (16%)	1,410 (50%)	-	-	-	1,199 (50%)	2,366 (50%)

Characteristic	Total (n = 31,310)	CARDS (n = 2,838)	ALLIANCE (n = 2,442)	TNT (n = 10,001)	IDEAL (n = 8,888)	ASPEN (n = 2,410)	SPARCL (n = 4,731)
Usual care	1,225 (4%)	-	1,225 (50%)	-	-	-	-
Between-group difference in LDL-C (mmol/L)	0.78	1.20	0.39	0.62	0.56	0.88	1.43
Follow-up duration (years), median (IQR)	4.6 (3.7-5.0)	3.9 (3.0-4.7)	4.1 (2.4-5.0)	4.9 (4.3-5.2)	4.7 (4.1-5.0)	4.2 (4.0-4.2)	4.7 (4.2-5.3)
Major vascular events	6,734 (22%)	204 (7%)	667 (27%)	2,566 (26%)	2,186 (25%)	346 (14%)	765 (16%)

All data in n (%) or mean±SD, unless otherwise specified. Proportions refer to complete cases.

Abbreviations: CVD = cardiovascular disease, HDL = high-density lipoprotein, IQR = interquartile range, LDL = low-density lipoprotein, NA = not available, SD = standard deviation.

Overall effects of LDL-C reduction on major vascular events

Based on the 38 trials of guideline-recommended lipid-lowering therapies, the overall RR for major vascular events per 1 mmol/L reduction in LDL-C was 0.78 (95% confidence interval [CI] 0.75-0.81) (Figure 2). Similar results were found for statins only (RR 0.76; 95% CI 0.73-0.79), and for all lipid-lowering therapies combined (RR 0.79; 95% CI 0.76-0.81) (Figure S1). Relative risk reductions were slightly more favourable in primary prevention (for guideline-recommended therapies: RR 0.74; 95% CI 0.68-0.81) as compared to secondary prevention (RR 0.80; 95% CI 0.77-0.83) (Figure S2)

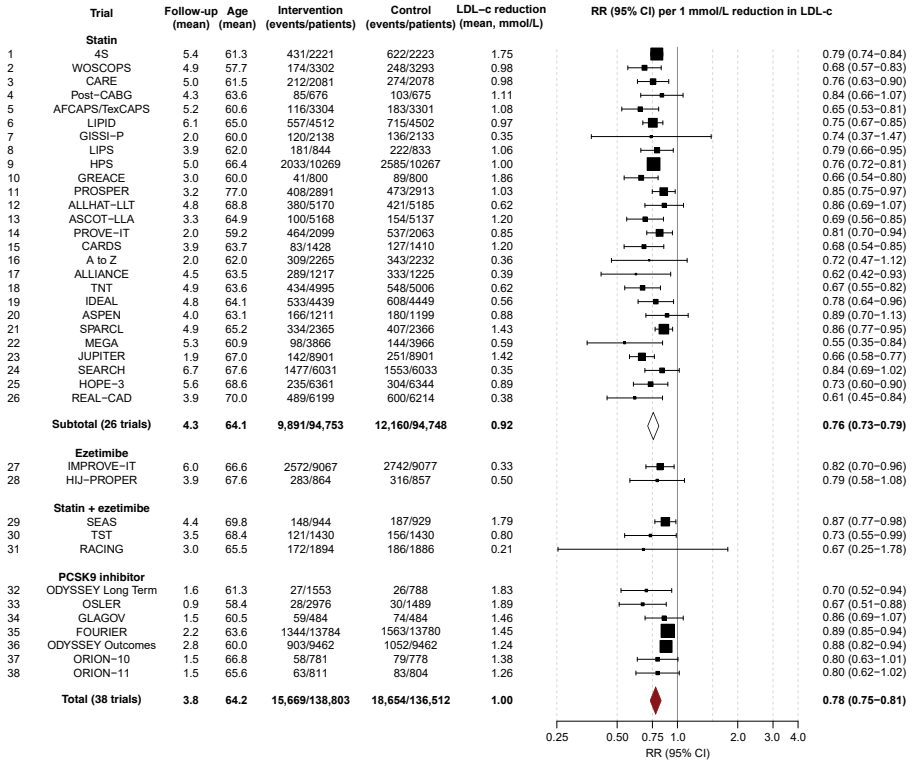
In the individual participant data of the six atorvastatin trials, the overall HR for major vascular events per 1 mmol/L LDL-C reduction was 0.77 (95% CI 0.72-0.82).

Course of the effects of LDL-C reduction over follow-up time

Meta-regression analysis

For guideline-recommended therapies, the average follow-up duration in the trials was not associated with the RR for major vascular events per 1 mmol/L LDL-C reduction (p = 0.66). As indicated by the meta-regression line the pooled RR was stable over follow-up time (RR for change per year 0.994; 95% CI 0.970-1.020) (Figure 3A). Stratification for primary and secondary prevention showed consistent results (Figure 3B). There was also no significant association between follow-up duration and the RR for major vascular events in trials of statins only (Figure S3), and trials of all lipid-lowering therapies (Figure S4).

Figure 2. Meta-analysis of the effects of 1 mmol/L LDL-C reduction on major vascular events

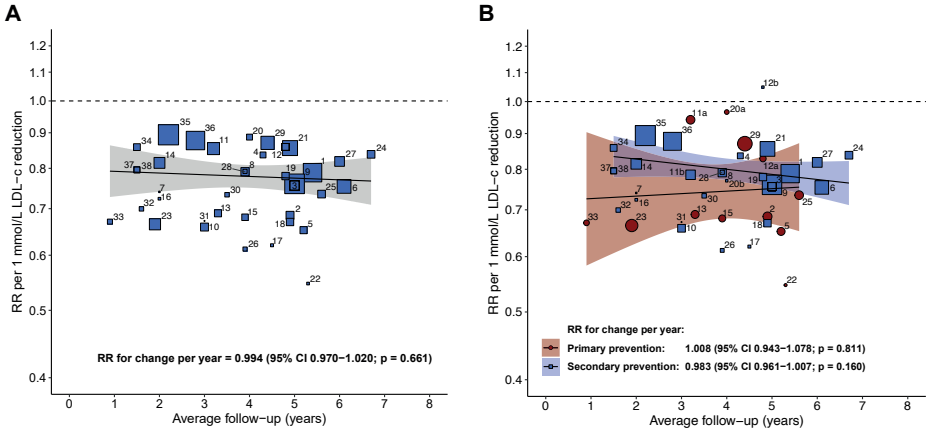


Random-effects meta-analysis of the effects of 1 mmol/L LDL-c reduction on major vascular events, with guideline-recommended lipid-lowering therapies (i.e. statins, ezetimibe, and PCSK9 inhibitors). Follow-up is either mean or median depending on what was presented in each trial. Age indicates the mean age during each trial. The size of the squares is proportional to the weight in the meta-analysis.

Individual participant data meta-analysis

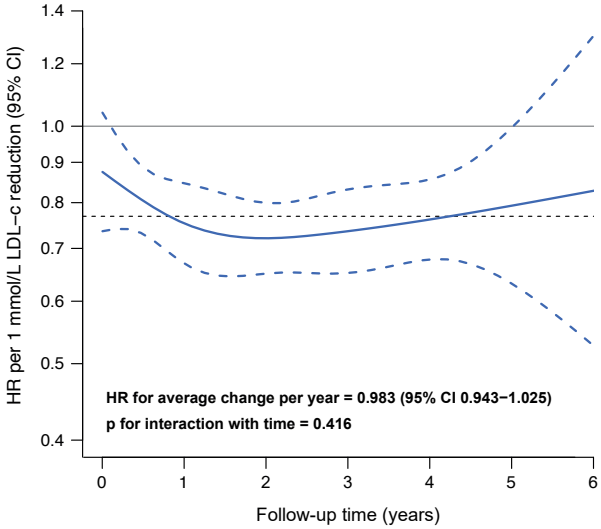
In the pooled data of the six atorvastatin trials, the HR for major vascular events per 1 mmol/L LDL-C reduction did not significantly change over follow-up time (p = 0.42). The HR decreased (i.e. relative risk reduction increased) during the first year of follow-up, but remained largely stable thereafter (HR for average change per year 0.983; 95% CI 0.943-1.025) (Figure 4). There was no significant change in the HR for major vascular events over follow-up time in any of the individual trials (p = 0.13-0.96) (Figure S5).

Figure 3. Meta-regression analysis of the effects of LDL-C reduction over follow-up time



Random-effects meta-regression analysis of the RR for major vascular events per 1 mmol/L LDL-c reduction over follow-up time, using data of the 38 trials of guideline-recommended therapies (i.e. statins, ezetimibe, and PCSK9 inhibitors) combined (A), and stratified for primary and secondary prevention (B). The shaded areas denote 95% confidence intervals. The size of the squares (and circles) is proportional to the weight in the meta-regression analysis. The numbers serve as identifiers for the individual trials and correspond to the number presented for each trial in Figure 2 and Table S1.

Figure 4. Individual participant data meta-analysis of the effects of LDL-C reduction over follow-up time



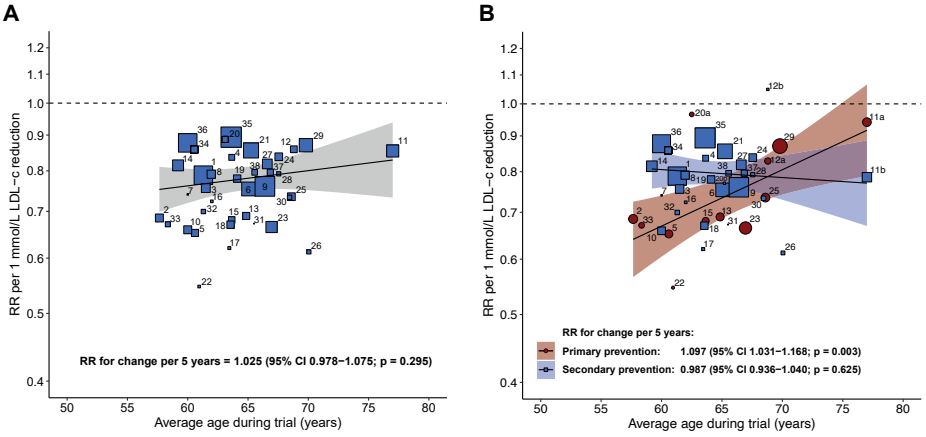
Individual participant data meta-analysis of the HR for major vascular events per 1 mmol/L LDL-c reduction over follow-up time, using data of the six atorvastatin trials for which individual participant data were available. The blue dotted lines denote 95% confidence intervals. The black dotted line denotes the overall HR for major vascular events per 1 mmol/L LDL-c reduction (= 0.77).

Course of the effects of LDL-C reduction over age

Meta-regression analysis

In trials of guideline-recommended therapies, the average age during the trial was not significantly associated with the RR for major vascular events per 1 mmol/L LDL-C reduction (p = 0.30). The meta-regression line showed a non-significant trend towards an attenuation of the RR with increasing age (RR for change per 5 years 1.025; 95% CI 0.978-1.075) (Figure 5A). In primary prevention this trend was significant (RR for change per 5 years 1.097; 95% CI 1.031-1.168; p = 0.003), which translates to an RR of 0.67 (95% CI 0.58-0.77) per 1 mmol/L LDL-C reduction at age 60 years as compared to 0.88 (95% CI 0.75-1.04) at age 75 years (Figure 5B). In secondary prevention the RR did not significantly change with age (RR for change per 5 years 0.987; 95% CI 0.936-1.040; p = 0.63). Similar results were found for trials of statins only (Figure S6), and trials of all lipid-lowering therapies (Figure S7). Excluding the PROSPER trial yielded largely consistent results, although the trend towards an attenuation of the RR with increasing age in primary prevention was no longer statistically significant (RR for change per 5 years 1.086; 95% CI 0.996-1.184; p = 0.06) (Figure S8).

Figure 5. Meta-regression analysis of the effects of LDL-C reduction over age



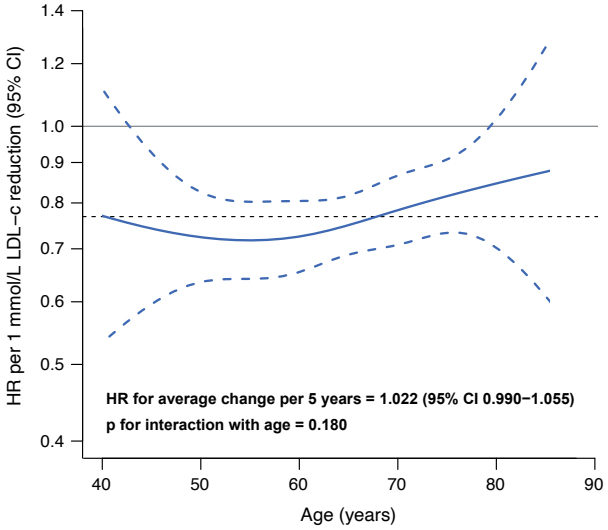
Random-effects meta-regression analysis of the RR for major vascular events per 1 mmol/L LDL-c reduction over age, using data of the 38 trials of guideline-recommended therapies (i.e. statins, ezetimibe, and PCSK9 inhibitors) combined (A), and stratified for primary and secondary prevention (B). The shaded areas denote 95% confidence intervals. The size of the squares (and circles) is proportional to the weight in the meta-regression analysis. The numbers serve as identifiers for the individual trials and correspond to the number presented for each trial in Figure 2 and Table S1.

Individual participant data meta-analysis

In the pooled data of the six atorvastatin trials, the HR for major vascular events per 1 mmol/L LDL-C reduction did not significantly change over age (p = 0.18). Similar to the meta-regression analysis, there was no trend towards an attenuation of the HR with

increasing age in this largely secondary prevention population (Figure 6). The HR for major vascular events did not significantly change over age in any of the individual trials (p = 0.13-0.84) (Figure S9).

Figure 6. Individual participant data meta-analysis of the effects of LDL-C reduction over age



Individual participant data meta-analysis of the HR for major vascular events per 1 mmol/L LDL-c reduction over age, using data of the six atorvastatin trials for which individual participant data were available. The blue dotted lines denote 95% confidence intervals. The black dotted line denotes the overall HR for major vascular events per 1 mmol/L LDL-c reduction (= 0.77).

Discussion

In this meta-analysis of 60 trials of lipid-lowering therapies including 408,959 participants and 51,425 major vascular events (individual participant data of 31,310 participants, and 6,734 major vascular events), every 1 mmol/L reduction in LDL-C was associated with an RR of 0.78 for major vascular events. The RR was slightly more favourable in primary (0.74) as compared to secondary prevention (0.80). Follow-up time was not associated with a change in the relative treatment effects of LDL-C reduction, with the RR for major vascular events remaining stable up to the maximum follow-up duration of 6.7 years (guideline-recommended therapy), or 9.7 years (any therapy). In secondary prevention, the relative treatment effects of LDL-C reduction also remained stable over age, whereas in primary prevention, they significantly attenuated with increasing age.

Previous studies also assessed potential changes in the relative treatment effects of LDL-C reduction over time.[1,19] An individual participant data meta-analysis of 26 statin trials evaluated the efficacy of LDL-C reduction with a statin in subsequent years of follow-up.[1] This showed that the RR for major vascular events per 1 mmol/L LDL-C reduction was approximately the same in each of the five years of follow-up, with exception of the first year in which the effects were smaller. A limitation of this analysis is that by excluding patients with an event in a previous year, in the next year the intervention and control groups are no longer balanced, as the intervention group may then include relatively high-risk patients who would have had an event in a previous year if they had not received a statin. This might have led to an underestimation of the effects of LDL-C reduction in the years after the first year. Yet, the results are in line with the current study (to which this limitation does not apply), with both studies suggesting that the relative treatment effects of LDL-C reduction are stable over follow-up time. In another meta-analysis of largely the same trials, the efficacy of LDL-C reduction with a statin was evaluated in groups of age.[19] This showed a significant trend towards smaller relative risk reductions in major vascular events with older age in primary prevention, while relative risk reductions were similar irrespective of age in secondary prevention. A limitation of this analysis is that age was divided into categories, instead of using it as a continuous measure. Despite differences in the analytical approach, the results of this previous meta-analysis are in line with the current study, with both indicating that the relative treatment effects of LDL-C reduction decrease with age in primary but not secondary prevention.

A potential explanation for the finding that the relative treatment effects of LDL-C reduction attenuate with increasing age in primary prevention, is that LDL-C reduction may be more effective in the earlier stages of atherosclerosis. Lowering LDL-C in younger individuals, in whom atherosclerosis is still absent or in an early stage, may prevent the development of clinically significant atherosclerosis leading up to major vascular events. Whereas in older individuals, in whom atherosclerosis is already advanced, LDL-C reduction may slow its further development but may not cause reversal to a state in which there is no or only minimal atherosclerosis, leaving them at considerable risk of major vascular events. This may also explain the larger relative risk reduction per 1 mmol/L LDL-C reduction observed in primary as compared to secondary prevention, as in secondary prevention patients already have clinically significant atherosclerosis given the fact that they have all had an event. The fact that in secondary prevention there may be less variety in the severity of atherosclerosis, may explain the finding that the RR for major vascular events did not change with age in this population. These findings and explanations are supported by previous studies.[5–8,20] One study showed that the risk of incident CVD depends on cumulative exposure to LDL-C, and that the same amount of accumulated LDL-C at a younger age, compared to older age, resulted in a greater increase in CVD risk.[20] Mendelian randomization studies have shown that a genetically determined lower LDL-C is associated with greater relative reductions in the risk

of major vascular events per 1 mmol/L lower LDL-C than the same magnitude of LDL-C reduction achieved with statins in trials.[5–8] A genetically determined lower LDL-C is present from birth and reduces the cumulative exposure to LDL-C early in life when atherosclerosis is in the early stages, while statins in trials were evaluated in middle-aged individuals with a history of CVD or CVD risk factors and more advanced atherosclerosis. These results support the finding that the relative treatment effects of LDL-C reduction attenuate with increasing age in primary prevention, and that this might be related to the stage of atherosclerosis at the time of treatment. This emphasizes the importance of early identification of individuals at high risk of CVD, followed by early initiation of LDL-C lowering therapy.

Given that participants naturally got older over follow-up time, one would have expected the relative treatment effects of LDL-C reduction in primary prevention to decrease with increasing follow-up duration as well. However, in this study the RR for major vascular events remained stable over follow-up time in both primary and secondary prevention. This may be explained by the fact that the variation of mean age in the trials was much larger than the variation in duration of follow-up. Assuming the relative treatment effects of LDL-C reduction are in fact stable over follow-up time (i.e. treatment duration), an explanation for the seemingly contrasting results may be that the effects of LDL-C reduction are not related to the current age of an individual, but rather to the age at time of initiation of LDL-C lowering therapy. This would indicate that when therapy is initiated at a young age the relative risk reduction per 1 mmol/L LDL-reduction will not only be larger during the first few years, but will remain larger during the entire treatment period regardless of aging.

In a consensus statement from the European Atherosclerosis Society (EAS), a formula is presented that integrates the evidence from Mendelian randomization studies and clinical trials in order to calculate the expected relative risk reduction of major vascular events per 1 mmol/L LDL-C reduction for any given treatment duration.[21] Based on this formula the relative risk reduction per 1 mmol/L LDL-C reduction would be expected to be 22% for a 5-year treatment, as compared to 54% for a 40-year treatment. On an absolute scale, it is true that a longer treatment duration leads to larger risk reductions, as the risk reductions that are achieved during each year of treatment have more time to accumulate if the treatment is continued for a longer period of time. However, on a relative scale this is questionable, as this would require relative risk reductions to increase over time, e.g. the relative risk reduction per 1 mmol/L LDL-C reduction would need to be larger in the thirtieth as compared to the tenth year of treatment. The increase in relative risk reduction over time that is suggested by the formula is not supported by the results of the current and previous studies.[1,19] In fact, in primary prevention, it was shown that the relative treatment effects of LDL-C reduction may decrease as people get older. On the other hand, if a longer treatment duration indicates that the treatment is initiated at a younger age, a larger relative

risk reduction may be expected, but this would be a consequence of the more favourable effects of LDL-C reduction at younger age rather than the treatment duration itself.

Prediction models can be used to estimate the effects of LDL-C reduction on 10-year CVD risk, and CVD-free life expectancy in individual patients in clinical practice. The use of prediction tools such as the SCORE2 (primary prevention) and SMART2 (secondary prevention) risk algorithms, and their lifetime extensions, i.e. the LIFE-CVD and SMART-REACH models, in clinical decision-making is recommended by the European Society of Cardiology (ESC) CVD Prevention Guidelines.[3,22–25] In order to estimate the effects of LDL-C reduction, these tools combine a prognostic risk algorithm with an HR for the relative risk reduction per 1 mmol/L LDL-C lowering. It is assumed that this HR remains constant over time, i.e. treatment duration and age. As shown in the current study, this assumption likely holds in secondary prevention. In primary prevention, the use of an age-dependent HR that increases with increasing age (i.e. relative risk reduction decreases with increasing age) may be considered. To derive the most accurate estimate of the HR at each age, an individual participant data meta-analysis as performed in this study, but with more data from primary prevention trials would be desirable.

Study limitations should be considered. The analyses including follow-up time were limited by the maximum follow-up duration in the trials. Therefore, the effects of LDL-C reduction could not be assessed beyond 9.7 years (6.7 years for guideline-recommended therapies) in the meta-regression analysis, and beyond six years in the individual participant data meta-analysis. So, the results of this study may not be translatable to a longer-term or lifetime treatment period. In the meta-regression analysis, there was a lack of trials with an average age below 55 and above 70 years. The individual participant data meta-analysis improved upon this by including considerable numbers of patients younger than 55 (n = 7,728 [25%]) and older than 70 years (n = 6,078 [19%]). However, individual participant data was available for a limited number of trials, and the number of primary prevention participants in the data was too small for a stratified analysis. If more individual participant data had been available this would have resulted in a more accurate estimation of the course of the effects of LDL-C reduction over age, especially at the lower (<50) and upper end (>75) of the spectrum. Finally, the composite outcome of major vascular events was not identical in each trial, and hazard ratios were not always available (in which case risk ratios were used instead).

In this meta-analysis of 60 RCTs of lipid-lowering therapies, follow-up time was not associated with a change in the RR for major vascular events per 1 mmol/L LDL-C reduction, albeit over a limited follow-up duration that may not reflect long-term treatment. The relative risk reduction per 1 mmol/L LDL-C lowering significantly decreased with increasing age in primary prevention, but remained stable over age in secondary prevention.

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Supplementary material

Methods S1. Search strategy

Pubmed MEDLINE:

(LDL lowering) AND (clinical outcomes) AND ((randomizedcontrolledtrial[Filter]) AND (humans[Filter]) AND (2016/7/1:2023/1/1[pdat]))

EMBASE:

('ldl'/exp OR ldl) AND lowering AND ('clinical'/exp OR clinical) AND ('outcomes'/exp OR outcomes) AND [randomized controlled trial]/lim AND [humans]/lim AND [01-07-2016]/sd NOT [02-01-2023]/sd

Tables S1. Characteristics of the individual trials

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
	Statin											
1	4S[1]	1994	Secondary	Simvastatin 20–40 mg vs placebo	5.4	61.3	CHD death, MI, or resuscitated cardiac arrest	4,444	1,053	1.75	0.66 (0.59-0.74)	0.79 (0.74-0.84)
2	WOSCOPS[2]	1995	Primary	Pravastatin 40 mg vs placebo	4.9	57.7	CHD death or MI	6,595	422	0.98	0.69 (0.57-0.83)	0.68 (0.57-0.83)
3	CARE[3]	1996	Secondary	Pravastatin 40 mg vs placebo	5.0	61.5	CHD death or MI	4,159	486	0.98	0.76 (0.64-0.91)	0.76 (0.63-0.90)
4	Post-CABG[4]	1997	Secondary	Lovastatin 40–80 mg vs lovastatin 2.5-5 mg	4.3	63.7	ACM, MI, stroke, or coronary revascularization	1,351	188	1.11	0.82 (0.63-1.07)	0.84 (0.66-1.07)
5	AFCAPS/ TexCAPS[5]	1998	Primary	Lovastatin 20–40 mg vs placebo	5.2	60.6	CHD death, MI, or unstable angina	6,605	299	1.08	0.63 (0.50-0.79)	0.65 (0.53-0.81)
6	LIPID[6]	1998	Secondary	Pravastatin 40 mg vs placebo	6.1	65.1	CHD death or MI	9,014	1,272	0.97	0.76 (0.68-0.85)	0.75 (0.67-0.85)
7	GISSI-P[7]	2000	Secondary	Pravastatin 20 mg vs usual care	2.0	60.0	ACM, MI, or stroke	4,271	256	0.35	0.90 (0.71-1.15)	0.74 (0.37-1.47)
8	LIPS[8]	2002	Secondary	Fluvastatin 80 mg vs placebo	3.9	62.0	CHD death, MI, or coronary revascularization	1,677	403	1.06	0.78 (0.64-0.95)	0.79 (0.66-0.95)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
9	HPS[9]	2002	Secondary	Simvastatin 40 mg vs placebo	5.0	66.4	CHD death, MI, stroke, or coronary revascularization	20,536	4,618	1.00	0.76 (0.72-0.81)	0.76 (0.72-0.81)
10	GREACE[10]	2002	Secondary	Atorvastatin 10–80 mg vs usual care	3.0	60.0	CHD death or non-fatal MI	1,600	130	1.86	0.46 (0.32-0.66)	0.66 (0.54-0.80)
11	PROSPER[11]	2002	Both	Pravastatin 40 mg vs placebo	3.2	77.0	CHD death, MI, or stroke	5,804	881	1.03	0.85 (0.74-0.97)	0.85 (0.75-0.97)
12	ALLHAT-LLT[12]	2002	Both	Pravastatin 40 mg vs usual care	4.8	68.8	CHD death or MI	10,355	801	0.62	0.91 (0.79-1.04)	0.86 (0.69-1.07)
13	ASCOT-LLA[13]	2003	Primary	Atorvastatin 10 mg vs placebo	3.3	64.9	CHD death or MI	10,305	254	1.20	0.64 (0.50-0.83)	0.69 (0.56-0.85)
14	PROVE-IT[14]	2004	Secondary	Atorvastatin 80 mg vs pravastatin 40 mg	2.0	59.2	ACM, MI, stroke, unstable angina, or coronary revascularization	4,162	1,001	0.85	0.84 (0.74-0.95)	0.81 (0.70-0.94)
15	CARDS[15]	2004	Primary	Atorvastatin 10 mg vs placebo	3.9	63.7	CHD death, MI, stroke, unstable angina, or coronary revascularization	2,838	210	1.20	0.63 (0.48-0.83)	0.68 (0.54-0.85)
16	A to Z[16]	2004	Secondary	Simvastatin 40–80 mg vs placebo/ simvastatin 20 mg	2.0	62.0	CV death, MI, ACS, or stroke	4,497	652	0.36	0.89 (0.76-1.04)	0.72 (0.47-1.12)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
17	ALLIANCE[17]	2004	Secondary	Atorvastatin 10–80 mg vs usual care	4.5	63.5	CHD death, MI, unstable angina, resuscitated cardiac arrest, or coronary revascularization	2,442	622	0.39	0.83 (0.71-0.97)	0.62 (0.42-0.93)
18	TNT[18]	2005	Secondary	Atorvastatin 80 mg vs atorvastatin 10 mg	4.9	63.6	CHD death, MI, stroke, or resuscitated cardiac arrest	10,001	982	0.62	0.78 (0.69-0.89)	0.67 (0.55-0.82)
19	IDEAL[19]	2005	Secondary	Atorvastatin 40-80 mg vs simvastatin 20-40 mg	4.8	64.1	CHD death, MI, stroke, or resuscitated cardiac arrest	8,888	1,141	0.56	0.87 (0.78-0.98)	0.78 (0.64-0.96)
20	ASPEN[20]	2006	Both	Atorvastatin 10 mg vs placebo	4.0	63.1	CV death, MI, stroke, unstable angina, resuscitated cardiac arrest, or coronary revascularization	2,410	346	0.88	0.90 (0.73-1.12)	0.89 (0.70-1.13)
21	SPARCL[21]	2006	Secondary	Atorvastatin 80 mg vs placebo	4.9	65.3	CHD Death, MI, stroke, or cardiac arrest	4,731	741	1.43	0.80 (0.69-0.92)	0.86 (0.77-0.95)
22	MEGA[22]	2006	Primary	Pravastatin 10–20 mg vs usual care	5.3	61.0	CHD death, MI, stroke, unstable angina, or coronary revascularization	7,832	242	0.59	0.70 (0.54-0.90)	0.55 (0.35-0.84)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
23	JUPITER[23]	2008	Primary	Rosuvastatin 20 mg vs placebo	1.9	67.0	CV death, MI, stroke, unstable angina, or coronary revascularization	17,802	393	1.42	0.56 (0.46-0.69)	0.66 (0.58-0.77)
24	SEARCH[24]	2010	Secondary	Simvastatin 80 mg vs simvastatin 20 mg	6.7	67.6	CHD death, MI, stroke, or coronary revascularization	12,064	3,030	0.35	0.94 (0.88-1.01)	0.84 (0.69-1.02)
25	HOPE-3[25]	2016	Primary	Rosuvastatin 10 mg vs placebo	5.6	68.6	CV death, MI, or stroke	12,705	539	0.89	0.76 (0.64-0.91)	0.73 (0.60-0.90)
26	REAL-CAD[26]	2018	Secondary	Pitavastatin 4 mg vs pitavastatin 1 mg	3.9	70.1	CV death, MI, stroke, unstable angina, or coronary revascularization	12,413	1,089	0.38	0.83 (0.73-0.93)	0.61 (0.45-0.84)
	Ezetimibe											
27	IMPROVE-IT[27]	2015	Secondary	Ezetimibe 10 mg + simvastatin 40 mg vs placebo + simvastatin 40 mg	6.0	66.6	CV death, MI, stroke, unstable angina, or coronary revascularization	18,144	5,314	0.33	0.94 (0.89-0.99)	0.82 (0.70-0.96)
28	HIJ-PROPER[28]	2017	Secondary	Ezetimibe 10 mg + pitavastatin 1-4 mg vs pitavastatin 1-4 mg	3.9	67.6	ACM, MI, stroke, unstable angina, or coronary revascularization	1,721	599	0.50	0.89 (0.76-1.04)	0.79 (0.58-1.08)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
	Statin + ezetimibe											
29	SEAS[29]	2008	Primary	Simvastatin 40 mg + ezetimibe 10 mg vs placebo	4.4	69.8	CV death, MI, stroke, unstable angina, or coronary revascularization	1,873	335	1.79	0.78 (0.63-0.97)	0.87 (0.77-0.98)
30	TST[30]	2020	Secondary	LDL-C target <1.8 mmol/L vs 2.3-2.8 mmol/L (achieved with statin ± ezetimibe)	3.5	68.5	CV death, ACS, stroke, coronary revascularization, or carotid revascularization	2,860	277	0.80	0.78 (0.61-0.98)	0.73 (0.55-0.99)
31	RACING[31]	2022	Secondary	Rosuvastatin 10 mg + ezetimibe 10 mg vs rosuvastatin 20 mg	3.0	65.5	CV death, MI, stroke, hospitalization for angina/ HF/PAD, or coronary or peripheral artery revascularization	3,780	358	0.21	0.92 (0.75-1.13)	0.67 (0.25-1.78)
	PCSK9 inhibitor											
32	ODYSSEY Long Term[32]	2015	Secondary	Alirocumab 150 mg every 2 weeks vs placebo	1.6	61.3	CHD death, MI, stroke, or unstable angina	2,341	53	1.83	0.52 (0.31-0.89)	0.70 (0.52-0.94)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
33	OSLER[33]	2015	Primary	Evolocumab 140 mg every 2 weeks or 420 mg every month vs + standard of care vs standard of care	0.9	58.4	ACM, MI, stroke, TIA, unstable angina, or coronary revascularization	4,465	58	1.89	0.47 (0.28-0.78)	0.67 (0.51-0.88)
34	GLACOV[34]	2016	Secondary	Evolocumab 420 mg every month vs placebo	1.5	60.6	ACM, MI, stroke, unstable angina, or coronary revascularization	968	133	1.46	0.80 (0.58-1.10)	0.86 (0.69-1.07)
35	FOURIER[35]	2017	Secondary	Evolocumab 140 mg every 2 weeks or 420 mg every month vs placebo	2.2	63.6	CV death, MI, stroke, unstable angina, or coronary revascularization	27,564	2,907	1.45	0.85 (0.79-0.92)	0.89 (0.85-0.94)
36	ODYSSEY Outcomes[36]	2018	Secondary	Alirocumab 75 mg every 2 weeks vs placebo	2.8	60.0	CHD death, MI, stroke, or unstable angina	18,924	1,955	1.24	0.85 (0.78-0.93)	0.88 (0.82-0.94)
37	ORION-10[37]	2020	Secondary	Inclisiran 284 mg every 3-6 months vs placebo	1.5	66.9	CV death, MI, cardiac arrest, or stroke	1,559	137	1.38	0.73 (0.53-1.01)	0.80 (0.63-1.01)
38	ORION-11[37]	2020	Secondary	Inclisiran 284 mg every 3-6 months vs placebo	1.5	65.6	CV death, MI, cardiac arrest, or stroke	1,615	146	1.26	0.75 (0.55-1.03)	0.80 (0.62-1.02)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
	Diet											
39	Research Committee[38]	1965	Secondary	Low fat diet vs usual diet	3.0	NA	ACM or MI	252	94	0.47	1.00 (0.73-1.38)	1.00 (0.51-1.97)
40	Oslo[39]	1970	Secondary	Low saturated fat and high polyunsaturated fat diet vs usual diet	5.0	NA	CHD death or MI	412	142	0.88	0.75 (0.57-0.99)	0.72 (0.53-0.99)
41	MRC Soya-Bean[40]	1968	Secondary	Low saturated fat diet plus Soya-bean oil vs usual diet	3.4	NA	ACM or MI	393	136	0.85	0.82 (0.62-1.08)	0.79 (0.57-1.09)
42	LA Veteran's Study[41]	1969	Secondary	Low saturated fat and high polyunsaturated fat diet vs usual diet	5.0	NA	CHD death or MI	846	117	0.62	0.80 (0.57-1.12)	0.70 (0.40-1.20)
	Bile acid sequestrant											
43	Upjohn[42]	1978	Primary	Colestipol 15 g vs placebo	2.0	54.9	CHD death, MI, unstable angina, or heart failure	2,278	128	0.67	0.72 (0.51-1.01)	0.61 (0.37-1.02)
44	Lipid Research Clinics[43]	1984	Primary	Cholestyramine resin 24 g vs placebo	7.4	NA	CHD death or MI	3,806	342	1.02	0.81 (0.66-1.00)	0.81 (0.66-1.00)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
	Ileal bypass											
45	POSCH[44]	1990	Secondary	Ileal bypass surgery vs no surgery	9.7	55.9	CHD death or MI	838	207	1.62	0.65 (0.47-0.90)	0.77 (0.63-0.94)
	Fibrate											
46	Coronary Drug Project[45,a]	1975	Secondary	Clofibrate 1.8 g vs placebo	5.0	NA	CHD death or MI	3,892	1,148	0.31	0.93 (0.83-1.04)	0.79 (0.55-1.14)
47	WHO CO-OP[46]	1978	Primary	Clofibrate 1.6 g vs placebo	5.3	48.0	CHD death or MI	10,627	375	0.41	0.80 (0.66-0.98)	0.58 (0.36-0.94)
48	HHS[47]	1987	Primary	Gemfibrozil 1.2 g vs placebo	5.0	NA	CHD death or MI	4,081	140	0.54	0.66 (0.47-0.92)	0.46 (0.25-0.85)
49	BIP[48]	2000	Secondary	Bezafibrate 400 mg vs placebo	6.2	63.2	CHD death or MI	3,090	443	0.16	0.91 (0.76-1.08)	0.54 (0.18-1.59)
50	DAIS[49]	2001	Secondary	Fenofibrate 200 mg vs placebo	3.3	58.5	ACM, MI, unstable angina, or coronary revascularization	418	88	0.27	0.77 (0.53-1.12)	0.38 (0.09-1.54)
51	LEADER[50]	2002	Primary	Bezafibrate 400 mg vs placebo	4.6	70.5	CHD death, MI, or stroke	1,568	310	0.31	0.96 (0.76-1.21)	0.88 (0.41-1.85)
52	FIELD[51]	2005	Both	Fenofibrate 200 mg vs placebo	5.0	64.7	CV death, MI, stroke, or coronary revascularization	9,795	1,295	0.36	0.89 (0.80-0.99)	0.72 (0.54-0.97)

N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
	Niacin											
53	Coronary Drug Project[45,a]	1975	Secondary	Niacin 3 g vs placebo	5.0	NA	CHD death or MI	3,908	1,126	0.78	0.85 (0.76-0.96)	0.81 (0.70-0.94)
54	AIM-HIGH[52]	2011	Secondary	Niacin 1.5-2 g + simvastatin ± ezetimibe vs placebo + simvastatin ± ezetimibe	3.0	65.2	CHD death, MI, stroke, unstable angina, or coronary revascularization	3,414	556	0.16	1.02 (0.87-1.20)	1.13 (0.40-3.17)
55	HPS2-Thrive[53]	2014	Secondary	Niacin 2 g/ laropiprant 40 mg + simvastatin ± ezetimibe vs placebo + simvastatin ± ezetimibe	3.9	66.9	CHD death, MI, stroke, or coronary revascularization	25,673	3,454	0.26	0.96 (0.90-1.03)	0.85 (0.66-1.11)
	CETP inhibitor											
56	DEFINE[54]	2010	Secondary	Anacetrapib 100 mg vs placebo	1.5	63.5	CV death, MI, stroke, or unstable angina	1,623	70	0.83	0.62 (0.38-1.01)	0.56 (0.31-1.01)
57	ACCELER-ATE[55]	2017	Secondary	Evacetrapib 130 mg vs placebo	2.1	66.0	CV death, MI, stroke, unstable angina, or coronary revascularization	12,092	1,542	0.75	1.01 (0.91-1.11)	1.01 (0.88-1.16)

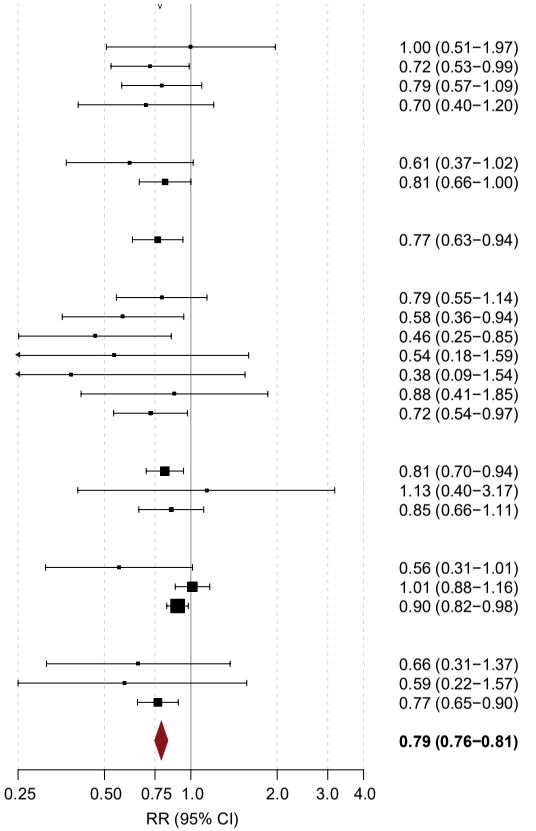
N	Trial	Year published	Prevention population	Intervention	Average follow-up (years)	Average age (years)	Outcome selected	Sample size	Major vascular events	LDL-C difference (mmol/L)	RR (95% CI)	RR per 1 mmol/L LDL-C reduction (95% CI)
58	REVEAL[56]	2017	Secondary	Anacetrapib 100 mg vs placebo	4.1	69.1	CHD death, MI, stroke, or coronary revascularization	30,449	4,282	0.68	0.93 (0.88-0.99)	0.90 (0.82-0.98)
	Bempedoic acid											
59	CLEAR Harmony[57]	2019	Secondary	Bempedoic acid 180 mg vs placebo	1.0	66.6	CV death, MI, stroke, unstable angina, or coronary revascularization	2,229	110	0.50	0.81 (0.56-1.17)	0.66 (0.31-1.37)
60	CLEAR Wisdom[58]	2019	Secondary	Bempedoic acid 180 mg vs placebo	1.0	64.8	CV death, MI, stroke, unstable angina, or coronary revascularization	779	53	0.54	0.75 (0.44-1.27)	0.59 (0.22-1.57)
61	CLEAR Outcomes[59]	2023	Both	Bempedoic acid 180 mg vs placebo	3.4	67.2	CV death, MI, stroke, unstable angina, or coronary revascularization	13,970	1,783	0.57	0.86 (0.78-0.94)	0.77 (0.65-0.90)

[a] The Coronary Drug Project was a multigroup trial that compared both fibrates and niacin to placebo, and is therefore mentioned twice in the table (under both fibrates and niacin).
Abbreviations: ACM = all-cause mortality, ACS = acute coronary syndrome, CETP = cholesteryl ester transfer protein, CHD = coronary heart disease, CI = confidence interval, CV = cardiovascular, HF = heart failure, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, PAD = peripheral artery disease, PCSK9 = proprotein convertase subtilisin–kexin type 9, RR = relative risk, TIA = transient ischaemic attack.

Figure S1. Overall meta-analysis with all lipid-lowering therapies

	Trial	Follow-up (mean)	Age (mean)	Intervention (events/patients)	Control (events/patients)	LDL−c reduction (mean, mmol/L)	RR (95% CI) per 1 mmol/L reduction in LDL-c
	Statin						
1	4S	5.4	61.3	431/2221	622/2223	1.75	0.79 (0.74−0.84)
2	WOSCOPS	4.9	57.7	174/3302	248/3293	0.98	0.68 (0.57−0.83)
3	CARE	5.0	61.5	212/2081	274/2078	0.98	0.76 (0.63−0.90)
4	Post−CABG	4.3	63.6	85/676	103/675	1.11	0.84 (0.66−1.07)
5	AFCAPS/TexCAPS	5.2	60.6	116/3304	183/3301	1.08	0.65 (0.53−0.81)
6	LIPID	6.1	65.0	557/4512	715/4502	0.97	0.75 (0.67−0.85)
7	GISSI−P	2.0	60.0	120/2138	136/2133	0.35	0.74 (0.37−1.47)
8	LIPS	3.9	62.0	181/844	222/833	1.06	0.79 (0.66−0.95)
9	HPS	5.0	66.4	2033/10269	2585/10267	1.00	0.76 (0.72−0.81)
10	GREACE	3.0	60.0	41/800	89/800	1.86	0.66 (0.54−0.80)
11	PROSPER	3.2	77.0	408/2891	473/2913	1.03	0.85 (0.75−0.97)
12	ALLHAT−LLT	4.8	68.8	380/5170	421/5185	0.62	0.86 (0.69−1.07)
13	ASCOT−LLA	3.3	64.9	100/5168	154/5137	1.20	0.69 (0.56−0.85)
14	PROVE−IT	2.0	59.2	464/2099	537/2063	0.85	0.81 (0.70−0.94)
15	CARDS	3.9	63.7	83/1428	127/1410	1.20	0.68 (0.54−0.85)
16	A to Z	2.0	62.0	309/2265	343/2232	0.36	0.72 (0.47−1.12)
17	ALLIANCE	4.5	63.5	289/1217	333/1225	0.39	0.62 (0.42−0.93)
18	TNT	4.9	63.6	434/4995	548/5006	0.62	0.67 (0.55−0.82)
19	IDEAL	4.8	64.1	533/4439	608/4449	0.56	0.78 (0.64−0.96)
20	ASPEN	4.0	63.1	166/1211	180/1199	0.88	0.89 (0.70−1.13)
21	SPARCL	4.9	65.2	334/2365	407/2366	1.43	0.86 (0.77−0.95)
22	MEGA	5.3	60.9	98/3866	144/3966	0.59	0.55 (0.35−0.84)
23	JUPITER	1.9	67.0	142/8901	251/8901	1.42	0.66 (0.58−0.77)
24	SEARCH	6.7	67.6	1477/6031	1553/6033	0.35	0.84 (0.69−1.02)
25	HOPE−3	5.6	68.6	235/6361	304/6344	0.89	0.73 (0.60−0.90)
26	REAL−CAD	3.9	70.0	489/6199	600/6214	0.38	0.61 (0.45−0.84)
	Subtotal (26 trials)	**4.3**	**64.1**	**9,891/94,753**	**12,160/94,748**	**0.92**	**0.76 (0.73−0.79)**
	Ezetimibe						
27	IMPROVE−IT	6.0	66.6	2572/9067	2742/9077	0.33	0.82 (0.70−0.96)
28	HIJ−PROPER	3.9	67.6	283/864	316/857	0.50	0.79 (0.58−1.08)
	Statin + ezetimibe						
29	SEAS	4.4	69.8	148/944	187/929	1.79	0.87 (0.77−0.98)
30	TST	3.5	68.4	121/1430	156/1430	0.80	0.73 (0.55−0.99)
31	RACING	3.0	65.5	172/1894	186/1886	0.21	0.67 (0.25−1.78)
	PCSK9 inhibitor						
32	ODYSSEY Long Term	1.6	61.3	27/1553	26/788	1.83	0.70 (0.52−0.94)
33	OSLER	0.9	58.4	28/2976	30/1489	1.89	0.67 (0.51−0.88)
34	GLAGOV	1.5	60.5	59/484	74/484	1.46	0.86 (0.69−1.07)
35	FOURIER	2.2	63.6	1344/13784	1563/13780	1.45	0.89 (0.85−0.94)
36	ODYSSEY Outcomes	2.8	60.0	903/9462	1052/9462	1.24	0.88 (0.82−0.94)
37	ORION−10	1.5	66.8	58/781	79/778	1.38	0.80 (0.63−1.01)
38	ORION−11	1.5	65.6	63/811	83/804	1.26	0.80 (0.62−1.02)
	Subtotal (38 trials)	**3.8**	**64.2**	**15,669/138,803**	**18,654/136,512**	**1.00**	**0.78 (0.75−0.81)**

	Diet						
39	Research Committee	3.0	NA	46/123	48/129	0.47	1.00 (0.51−1.97)
40	Oslo	5.0	NA	61/206	81/206	0.88	0.72 (0.53−0.99)
41	MRC Soya−Bean	3.4	NA	62/199	74/194	0.85	0.79 (0.57−1.09)
42	LA Veteran's Study	5.0	NA	52/424	65/422	0.62	0.70 (0.40−1.20)
	Bile acid sequestrant						
43	Upjohn	2.0	54.9	54/1149	74/1129	0.67	0.61 (0.37−1.02)
44	Lipid Research Clinics	7.4	NA	155/1906	187/1900	1.02	0.81 (0.66−1.00)
	Ileal bypass						
45	POSCH	9.7	55.9	82/421	125/417	1.62	0.77 (0.63−0.94)
	Fibrate						
46	Coronary Drug Project	5.0	NA	309/1103	839/2789	0.31	0.79 (0.55−1.14)
47	WHO CO−OP	5.3	47.9	167/5331	208/5296	0.41	0.58 (0.36−0.94)
48	HHS	5.0	NA	56/2051	84/2030	0.54	0.46 (0.25−0.85)
49	BIP	6.2	63.2	211/1548	232/1542	0.16	0.54 (0.18−1.59)
50	DAIS	3.3	58.4	38/207	50/211	0.27	0.38 (0.09−1.54)
51	LEADER	4.6	70.5	150/783	160/785	0.31	0.88 (0.41−1.85)
52	FIELD	5.0	64.7	612/4895	683/4900	0.36	0.72 (0.54−0.97)
	Niacin						
53	Coronary Drug Project	5.0	NA	287/1119	839/2789	0.78	0.81 (0.70−0.94)
54	AIM−HIGH	3.0	65.2	282/1718	274/1696	0.16	1.13 (0.40−3.17)
55	HPS2−Thrive	3.9	66.9	1696/12838	1758/12835	0.26	0.85 (0.66−1.11)
	CETP inhibitor						
56	DEFINE	1.5	63.5	27/811	43/812	0.83	0.56 (0.31−1.01)
57	ACCELERATE	2.1	66.0	774/6038	768/6054	0.75	1.01 (0.88−1.16)
58	REVEAL	4.1	69.0	2068/15225	2214/15224	0.68	0.90 (0.82−0.98)
	Bempedoic acid						
59	CLEAR Harmony	1.0	66.6	68/1487	42/742	0.50	0.66 (0.31−1.37)
60	CLEAR Wisdom	1.0	64.8	32/522	21/257	0.54	0.59 (0.22−1.57)
61	CLEAR Outcomes	3.4	67.2	831/6992	952/6978	0.57	0.77 (0.65−0.90)
	Total (60* trials)	**3.9**	**63.9**	**23,789/205,899**	**27,636/203,060**	**0.85**	**0.79 (0.76−0.81)**



Random-effects meta-analysis of the effects of 1 mmol/L LDL-c reduction on major vascular events, with any type of lipid-lowering therapy. Follow-up is either mean or median depending on what was presented in each trial. Age indicates the mean age during each trial. The size of the squares is proportional to the weight in the meta-analysis.

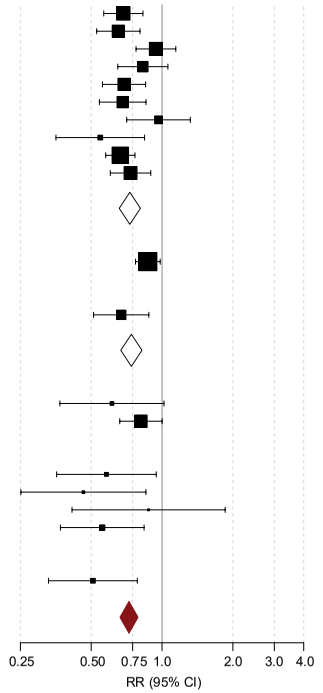
* The Coronary Drug Project was a multigroup trial that compared both fibrates and niacin to placebo, and is counted only once in the total number of trials.

Abbreviations: CETP = cholesteryl ester transfer protein, CI = confidence interval, HR = hazard ratio, LDL-c = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin–kexin type 9.

Figure S2. Overall meta-analysis in primary and secondary prevention

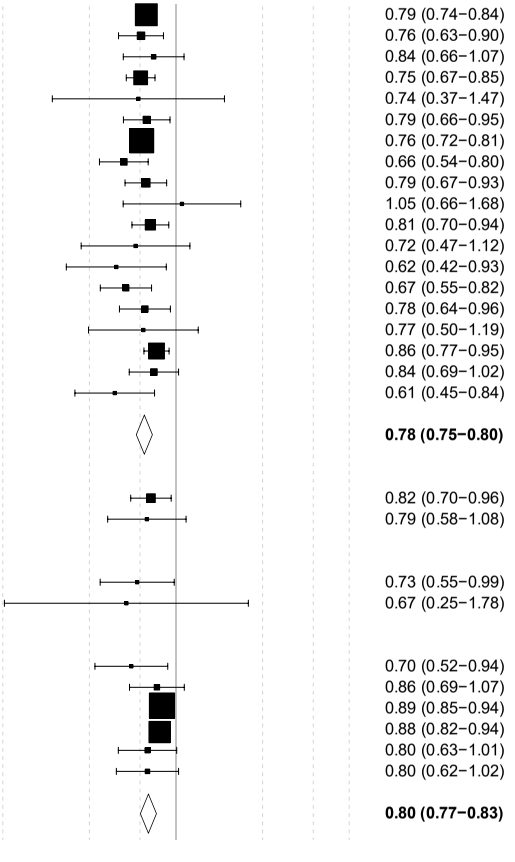
A. Primary prevention

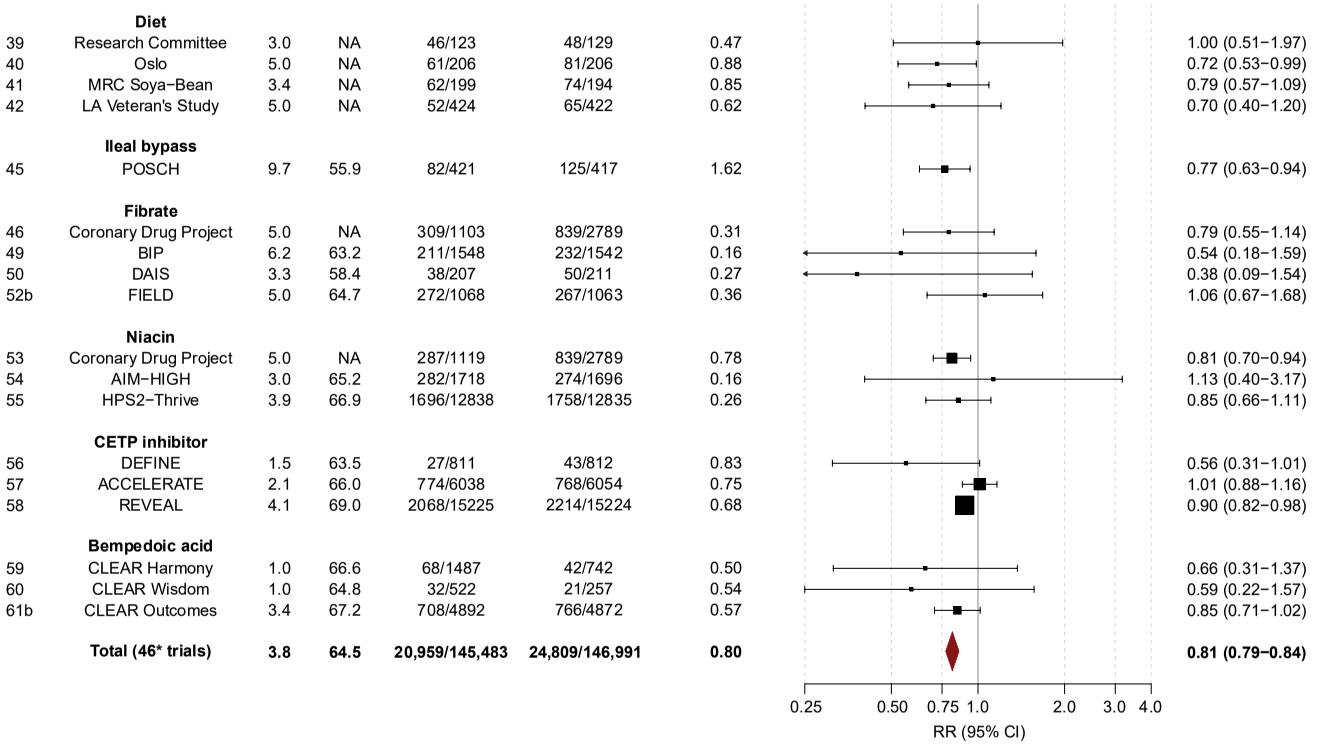
	Trial	Follow-up (mean)	Age (mean)	Intervention (events/patients)	Control (events/patients)	LDL−c reduction (mean, mmol/L)	RR (95% CI) per 1 mmol/L reduction in LDL-c
	Statin						
2	WOSCOPS	4.9	57.7	174/3302	248/3293	0.98	0.68 (0.57−0.83)
5	AFCAPS/TexCAPS	5.2	60.6	116/3304	183/3301	1.08	0.65 (0.53−0.81)
11a	PROSPER	3.2	77.0	181/1585	200/1654	1.03	0.94 (0.78−1.14)
12a	ALLHAT−LLT	4.8	68.8	NA/4475	NA/4405	0.62	0.83 (0.65−1.06)
13	ASCOT−LLA	3.3	64.9	100/5168	154/5137	1.20	0.69 (0.56−0.85)
15	CARDS	3.9	63.7	83/1428	127/1410	1.20	0.68 (0.54−0.85)
20a	ASPEN	4.0	62.5	100/959	102/946	0.88	0.97 (0.71−1.32)
22	MEGA	5.3	60.9	98/3866	144/3966	0.59	0.55 (0.35−0.84)
23	JUPITER	1.9	67.0	142/8901	251/8901	1.42	0.66 (0.58−0.77)
25	HOPE−3	5.6	68.6	235/6361	304/6344	0.89	0.73 (0.60−0.90)
	Subtotal (10 trials)	**4.2**	**65.2**	**1,229/39,349**	**1,713/39,357**	**0.99**	**0.73 (0.67−0.80)**
	Statin + ezetimibe						
29	SEAS	4.4	69.8	148/944	187/929	1.79	0.87 (0.77−0.98)
	PCSK9 inhibitor						
33	OSLER	0.9	58.4	28/2976	30/1489	1.89	0.67 (0.51−0.88)
	Subtotal (11 trials)	**4.0**	**65.0**	**1,405/43,269**	**1,930/41,775**	**1.13**	**0.74 (0.68−0.81)**
	Bile acid sequestrant						
43	Upjohn	2.0	54.9	54/1149	74/1129	0.67	0.61 (0.37−1.02)
44	Lipid Research Clinics	7.4	NA	155/1906	187/1900	1.02	0.81 (0.66−1.00)
	Fibrate						
47	WHO CO−OP	5.3	47.9	167/5331	208/5296	0.41	0.58 (0.36−0.94)
48	HHS	5.0	NA	56/2051	84/2030	0.54	0.46 (0.25−0.85)
51	LEADER	4.6	70.5	150/783	160/785	0.31	0.88 (0.41−1.85)
52a	FIELD	5.0	64.7	341/3827	415/3837	0.36	0.56 (0.37−0.84)
	Bempedoic acid						
61a	CLEAR Outcomes	3.4	67.2	111/2100	161/2106	0.57	0.51 (0.33−0.79)
	Total (19 trials)	**4.2**	**63.8**	**2,439/60,416**	**3,219/58,858**	**0.92**	**0.72 (0.67−0.78)**



B. Secondary prevention

	Trial	Follow-up (mean)	Age (mean)	Intervention (events/patients)	Control (events/patients)	LDL−c reduction (mean, mmol/L)	RR (95% CI) per 1 mmol/L reduction in LDL-c
	Statin						
1	4S	5.4	61.3	431/2221	622/2223	1.75	0.79 (0.74−0.84)
3	CARE	5.0	61.5	212/2081	274/2078	0.98	0.76 (0.63−0.90)
4	Post−CABG	4.3	63.6	85/676	103/675	1.11	0.84 (0.66−1.07)
6	LIPID	6.1	65.0	557/4512	715/4502	0.97	0.75 (0.67−0.85)
7	GISSI−P	2.0	60.0	120/2138	136/2133	0.35	0.74 (0.37−1.47)
8	LIPS	3.9	62.0	181/844	222/833	1.06	0.79 (0.66−0.95)
9	HPS	5.0	66.4	2033/10269	2585/10267	1.00	0.76 (0.72−0.81)
10	GREACE	3.0	60.0	41/800	89/800	1.86	0.66 (0.54−0.80)
11b	PROSPER	3.2	77.0	227/1306	273/1259	1.03	0.79 (0.67−0.93)
12b	ALLHAT−LLT	4.8	68.8	NA/695	NA/780	0.62	1.05 (0.66−1.68)
14	PROVE−IT	2.0	59.2	464/2099	537/2063	0.85	0.81 (0.70−0.94)
16	A to Z	2.0	62.0	309/2265	343/2232	0.36	0.72 (0.47−1.12)
17	ALLIANCE	4.5	63.5	289/1217	333/1225	0.39	0.62 (0.42−0.93)
18	TNT	4.9	63.6	434/4995	548/5006	0.62	0.67 (0.55−0.82)
19	IDEAL	4.8	64.1	533/4439	608/4449	0.56	0.78 (0.64−0.96)
20b	ASPEN	4.0	65.2	66/252	78/253	0.76	0.77 (0.50−1.19)
21	SPARCL	4.9	65.2	334/2365	407/2366	1.43	0.86 (0.77−0.95)
24	SEARCH	6.7	67.6	1477/6031	1553/6033	0.35	0.84 (0.69−1.02)
26	REAL−CAD	3.9	70.0	489/6199	600/6214	0.38	0.61 (0.45−0.84)
	Subtotal (19 trials)	**4.2**	**64.5**	**8,282/55,404**	**10,026/55,391**	**0.86**	**0.78 (0.75−0.80)**
	Ezetimibe						
27	IMPROVE−IT	6.0	66.6	2572/9067	2742/9077	0.33	0.82 (0.70−0.96)
28	HIJ−PROPER	3.9	67.6	283/864	316/857	0.50	0.79 (0.58−1.08)
	Statin + ezetimibe						
30	TST	3.5	68.4	121/1430	156/1430	0.80	0.73 (0.55−0.99)
31	RACING	3.0	65.5	172/1894	186/1886	0.21	0.67 (0.25−1.78)
	PCSK9 inhibitor						
32	ODYSSEY Long Term	1.6	61.3	27/1553	26/788	1.83	0.70 (0.52−0.94)
34	GLAGOV	1.5	60.5	59/484	74/484	1.46	0.86 (0.69−1.07)
35	FOURIER	2.2	63.6	1344/13784	1563/13780	1.45	0.89 (0.85−0.94)
36	ODYSSEY Outcomes	2.8	60.0	903/9462	1052/9462	1.24	0.88 (0.82−0.94)
37	ORION−10	1.5	66.8	58/781	79/778	1.38	0.80 (0.63−1.01)
38	ORION−11	1.5	65.6	63/811	83/804	1.26	0.80 (0.62−1.02)
	Subtotal (29 trials)	**3.7**	**64.5**	**13,884/95,534**	**16,303/94,737**	**0.93**	**0.80 (0.77−0.83)**



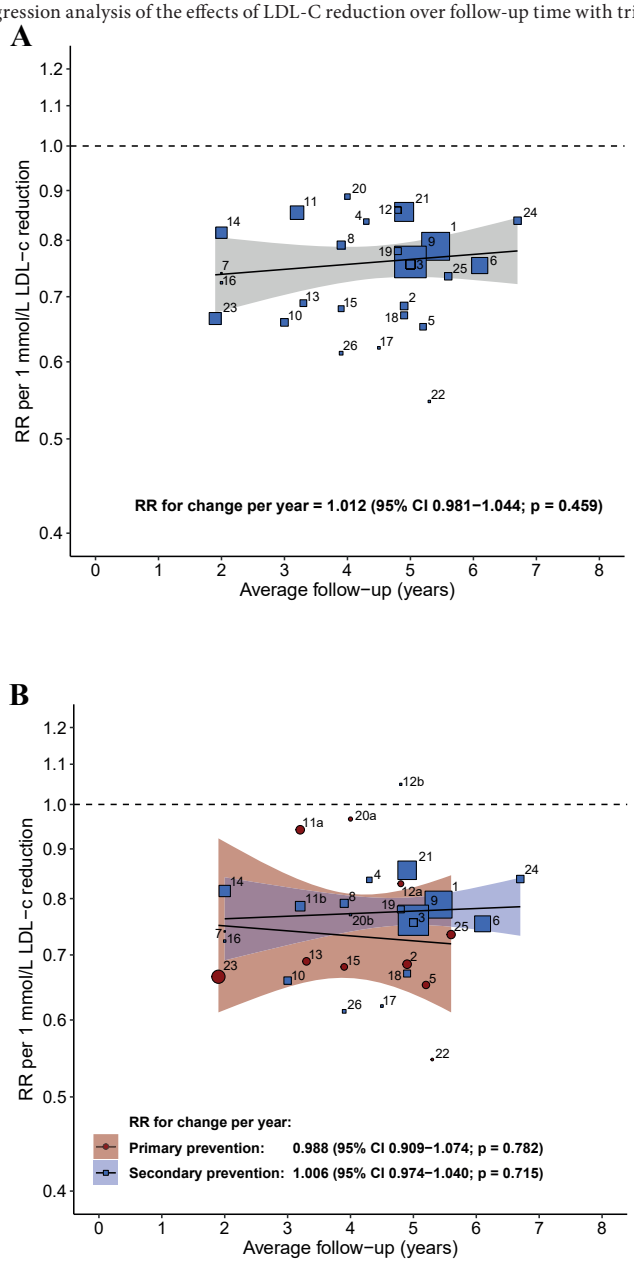


Random-effects meta-analyses of the effects of 1 mmol/L LDL-c reduction on major vascular events, with any type of lipid-lowering therapy, in primary prevention (A) and secondary prevention (B). If trials included both patients with and without a history of cardiovascular disease, the trial was included in both meta-analyses using the results of subgroup analyses presented in the original trials. Follow-up is either mean or median depending on what was presented in each trial. Age indicates the mean age during each trial. The size of the squares is proportional to the weight in the meta-analysis.

* The Coronary Drug Project was a multigroup trial that compared both fibrates and niacin to placebo, and is counted only once in the total number of trials.

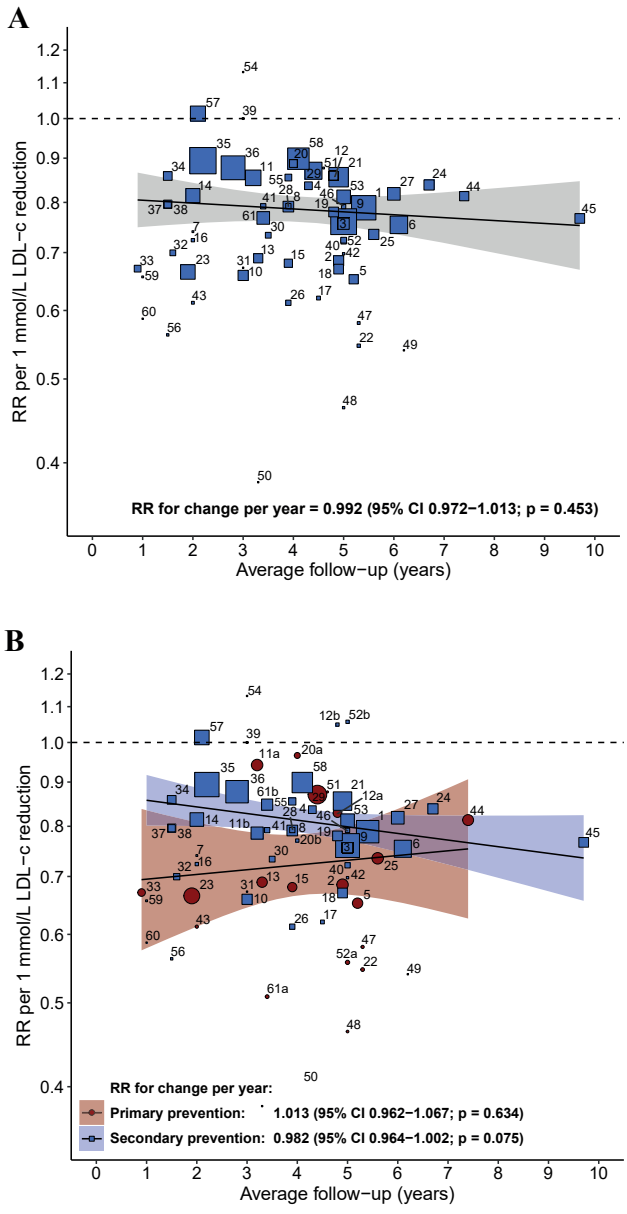
Abbreviations: CETP = cholesteryl ester transfer protein, CI = confidence interval, HR = hazard ratio, LDL-c = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin–kexin type 9.

Figure S3. Meta-regression analysis of the effects of LDL-C reduction over follow-up time with trials of statins only



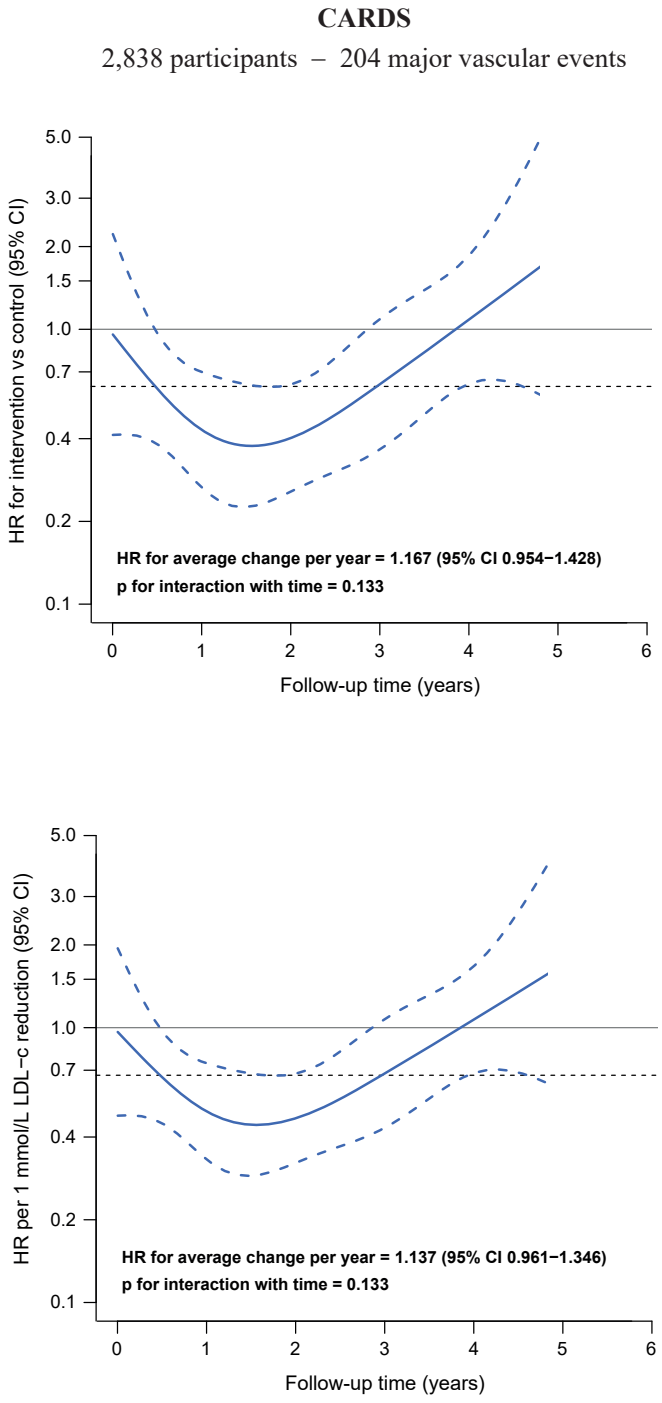
Random-effects meta-regression analysis of the HR for major vascular events per 1 mmol/L LDL-c reduction over follow-up time, using data of the 26 statin trials combined (A), and stratified for primary and secondary prevention (B). The shaded areas denote 95% confidence intervals. The size of the squares (and circles) is proportional to the weight in the meta-regression analysis. The numbers serve as identifiers for the individual trials and correspond to the number presented for each trial in Figure 2, Figure S1 & S2, and Table S1.
Abbreviations: CI = confidence interval, HR = hazard ratio, LDL-c = low-density lipoprotein cholesterol.

Figure S4. Meta-regression analysis of the effects of LDL-C reduction over follow-up time with trials of all lipid-lowering therapies



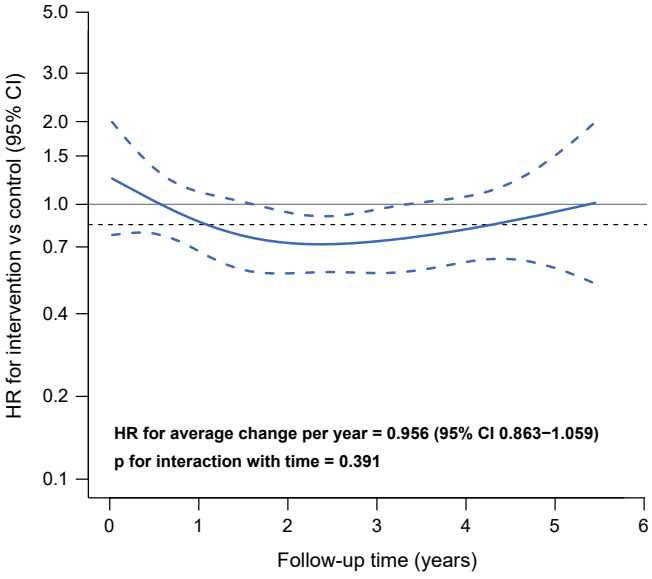
Random-effects meta-regression analysis of the HR for major vascular events per 1 mmol/L LDL-c reduction over follow-up time, using data of the 60 trials (61 comparisons) of all lipid-lowering therapies combined (A), and stratified for primary and secondary prevention (B). The shaded areas denote 95% confidence intervals. The size of the squares (and circles) is proportional to the weight in the meta-regression analysis. The numbers serve as identifiers for the individual trials and correspond to the number presented for each trial in Figure S1 & S2, and Table S1. Abbreviations: CI = confidence interval, HR = hazard ratio, LDL-c = low-density lipoprotein cholesterol.

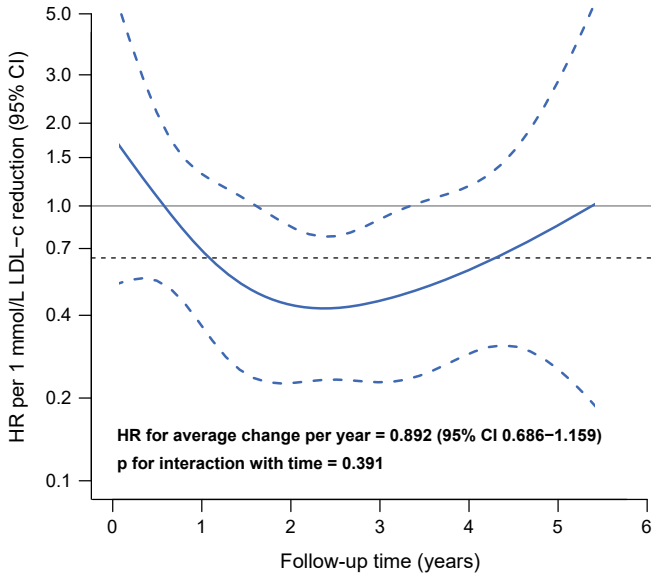
Figure S5. The effects of LDL-c reduction over follow-up time in the individual atorvastatin trials



ALLIANCE

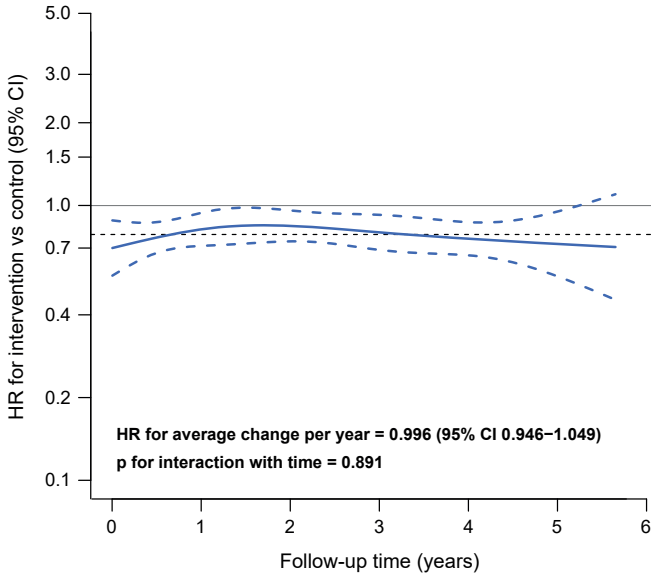
2,442 participants – 667 major vascular events

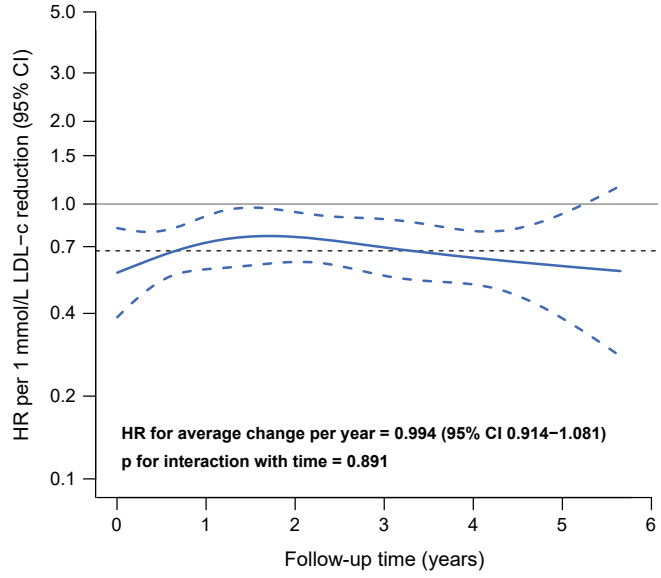




TNT

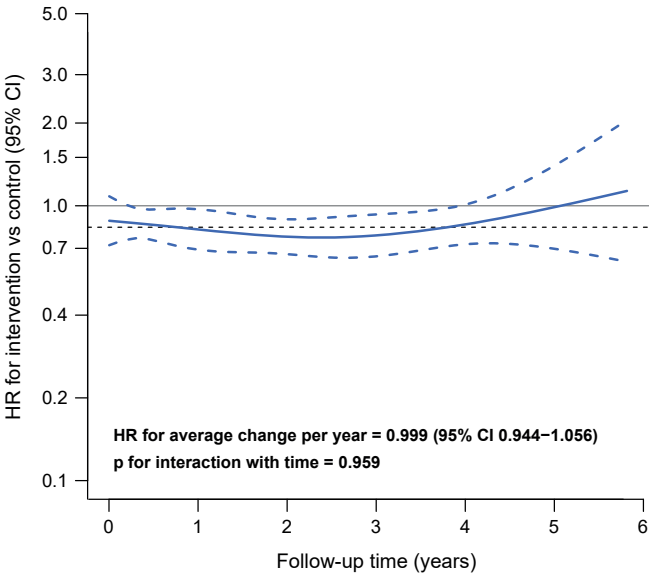
10,001 pa rticipants – 2,566 major vascular events

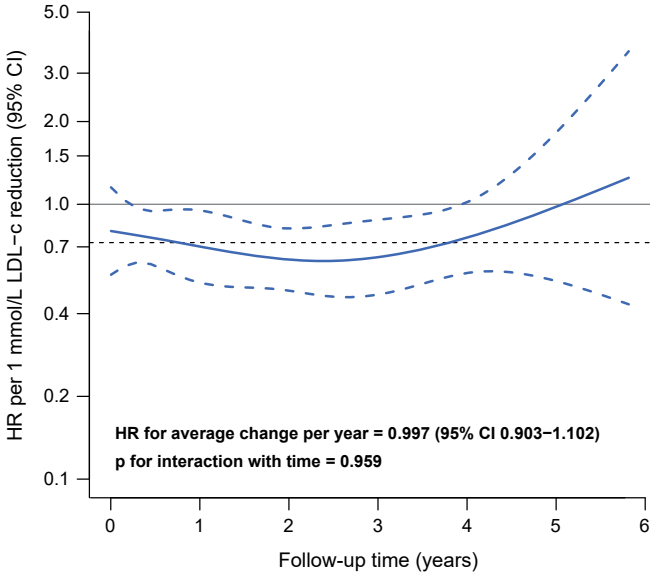


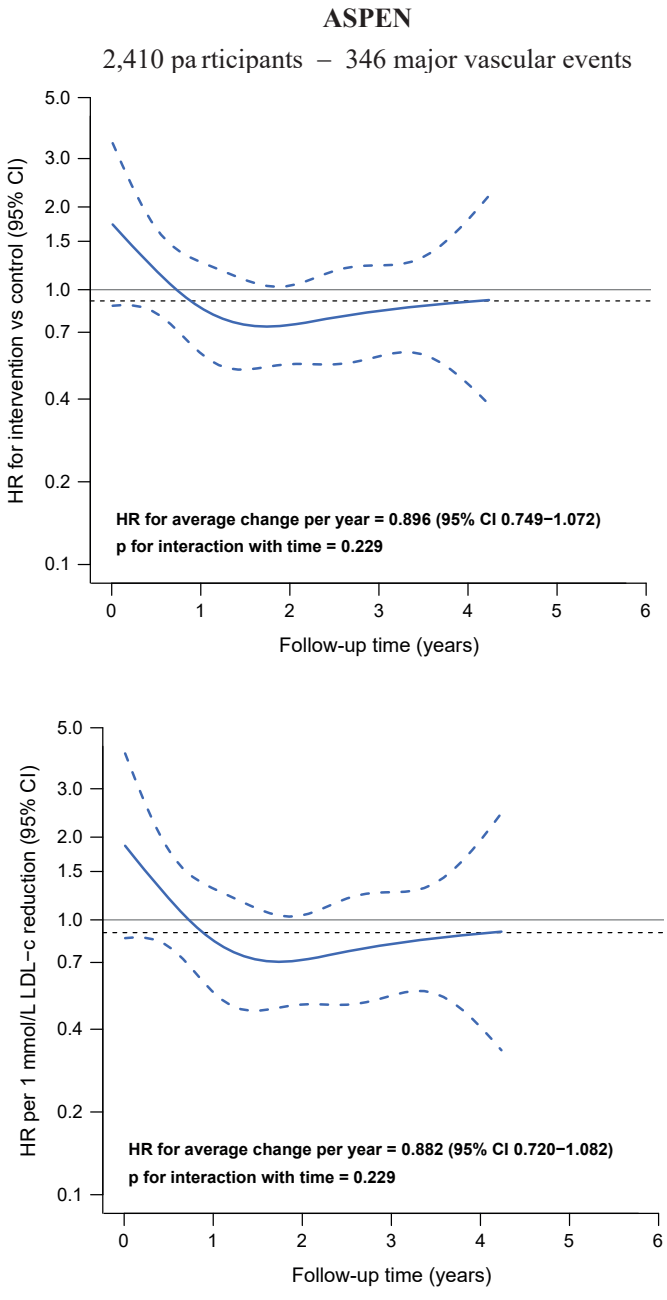


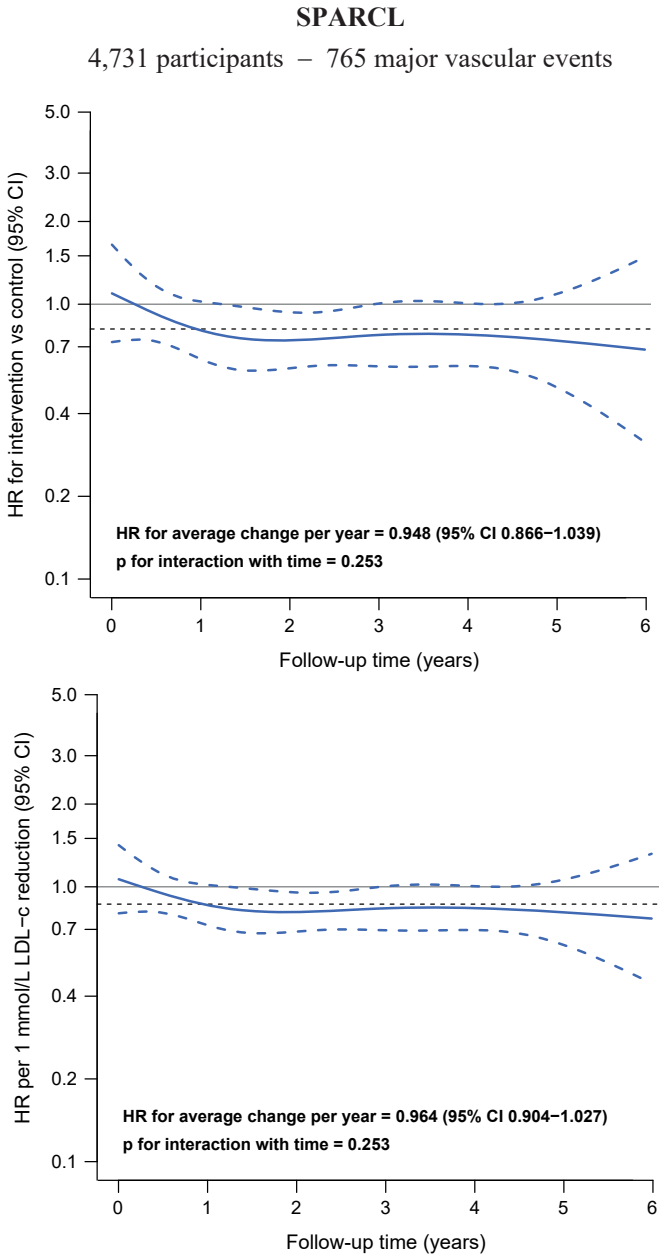
IDEAL

8,888 participants – 2,186 major vascular events



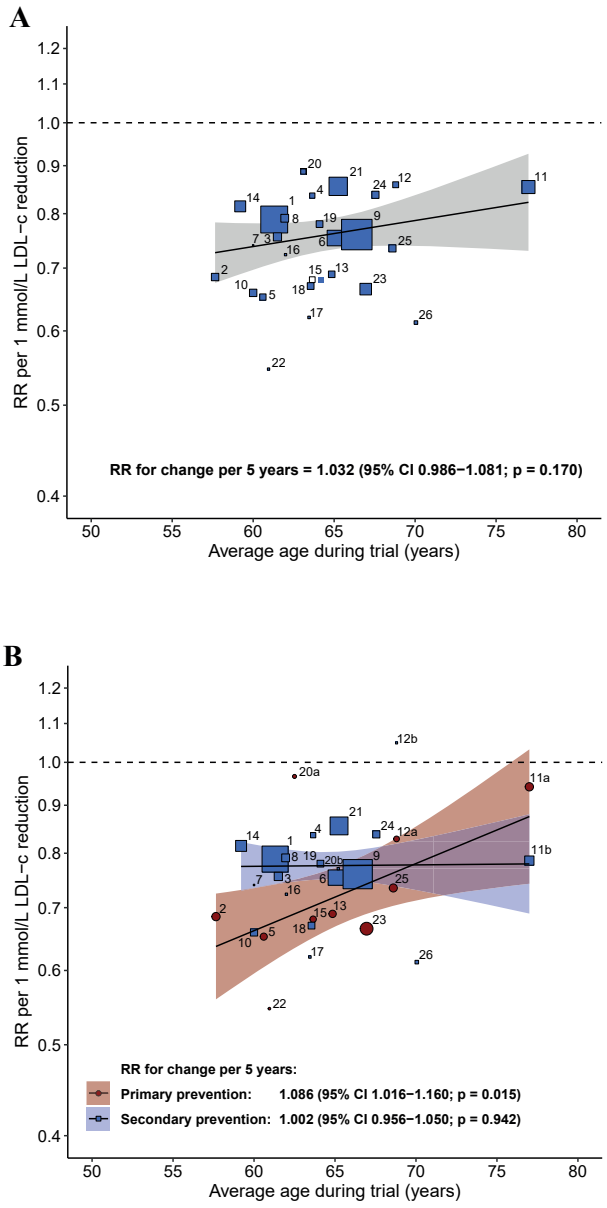



ASPEN
2,410 participants – 346 major vascular events
HR for intervention vs control (95% CI)
5.0
3.0
2.0
1.5
1.0
0.7
0.4
0.2
0.1
HR for average change per year = 0.896 (95% CI 0.749−1.072)
p for interaction with time = 0.229
0
1
2
3
4
5
6
Follow-up time (years)
HR per 1 mmol/L LDL−c reduction (95% CI)
5.0
3.0
2.0
1.5
1.0
0.7
0.4
0.2
0.1
HR for average change per year = 0.882 (95% CI 0.720−1.082)
p for interaction with time = 0.229
0
1
2
3
4
5
6
Follow-up time (years)



The HR for major vascular events for the intervention vs control (left side) and per 1 mmol/L LDL-c reduction (right side) over follow-up time, in the 6 individual atorvastatin trials for which individual participant data were available. The blue dotted lines denote 95% confidence intervals. The black dotted lines denote the overall trial hazard ratios. Abbreviations: CI = confidence interval, LDL-c = low-density lipoprotein cholesterol, HR = hazard ratio.

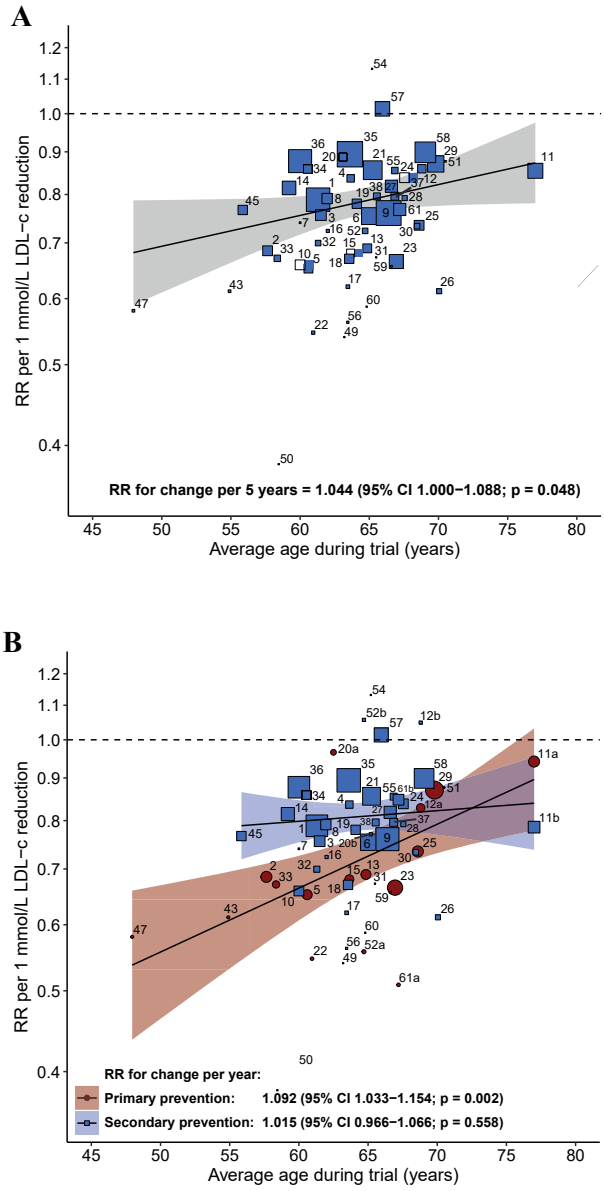
Figure S6. Meta-regression analysis of the effects of LDL-C reduction over age with trials of statins only



Random-effects meta-regression analysis of the HR for major vascular events per 1 mmol/L LDL-c reduction over age, using data of the 26 statin trials combined (A), and stratified for primary and secondary prevention (B). The shaded areas denote 95% confidence intervals. The size of the squares (and circles) is proportional to the weight in the meta-regression analysis. The numbers serve as identifiers for the individual trials and correspond to the number presented for each trial in Figure 2, Figure S1 & S2, and Table S1.

Abbreviations: CI = confidence interval, HR = hazard ratio, LDL-c = low-density lipoprotein cholesterol.

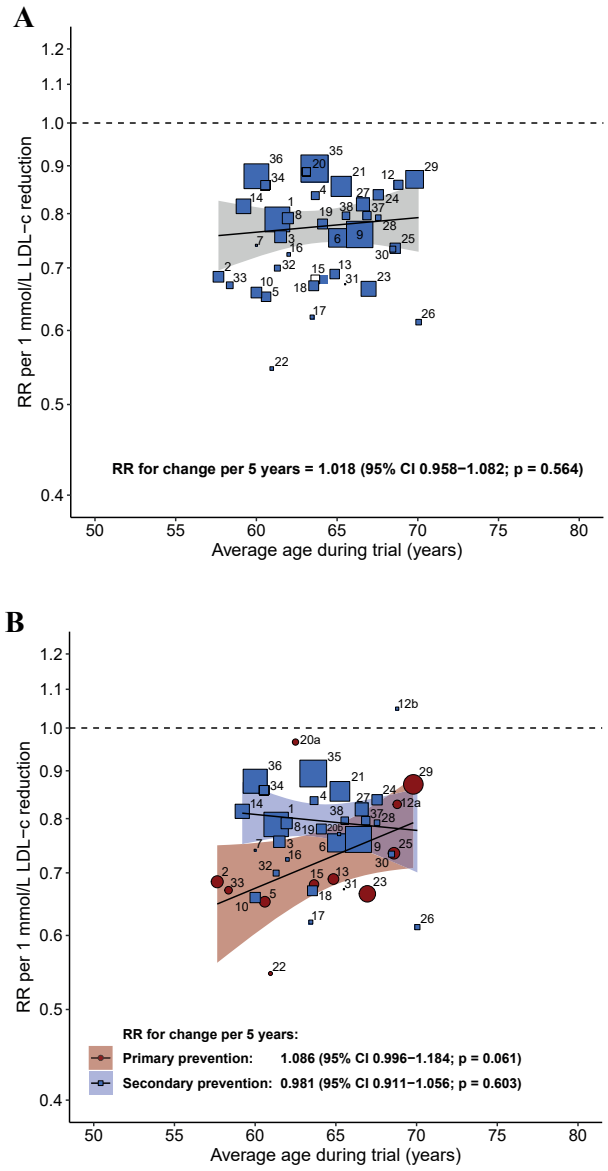
Figure S7. Meta-regression analysis of the effects of LDL-C reduction over age with trials of all lipid-lowering therapies



Random-effects meta-regression analysis of the HR for major vascular events per 1 mmol/L LDL-c reduction over age, using data of trials of all lipid-lowering therapies combined (A), and stratified for primary and secondary prevention (B). For some trials the average age was not available (Table S1), so these were not included in the analysis. The shaded areas denote 95% confidence intervals. The size of the squares (and circles) is proportional to the weight in the meta-regression analysis. The numbers serve as identifiers for the individual trials and correspond to the number presented for each trial in Figure S1 & S2, and Table S1.

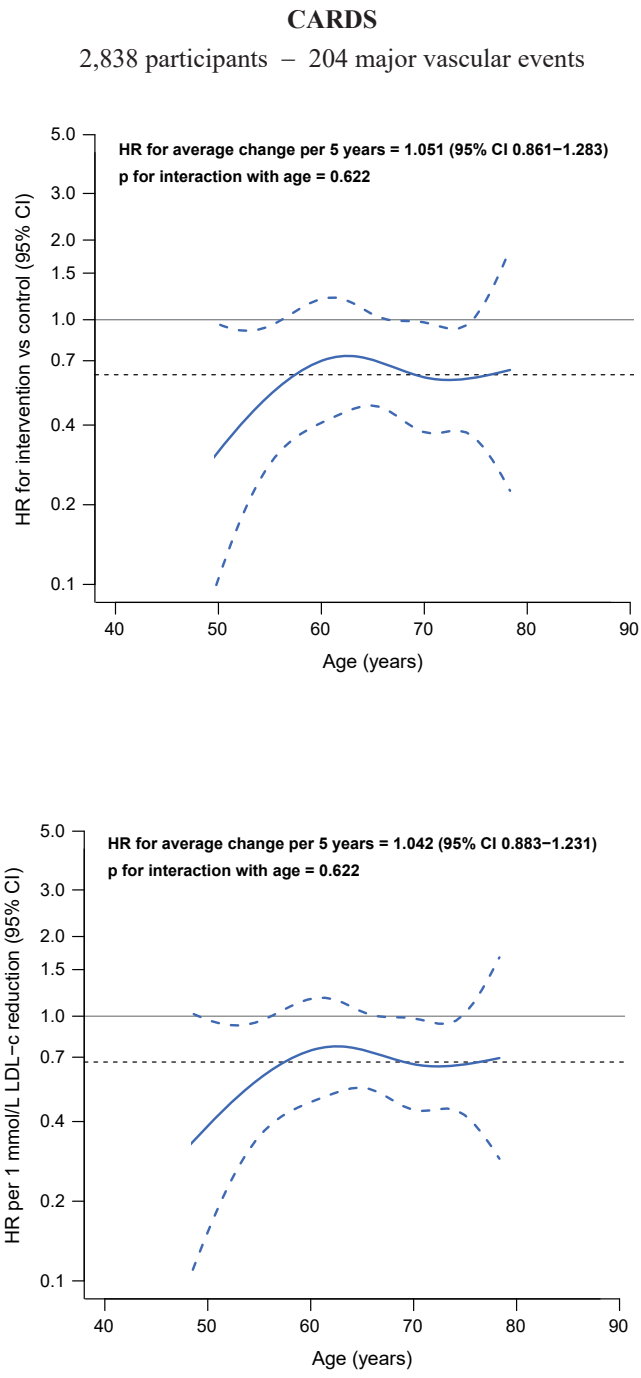
Abbreviations: CI = confidence interval, HR = hazard ratio, LDL-c = low-density lipoprotein cholesterol.

Figure S8. Meta-regression analysis of the effects of LDL-C reduction over age excluding the PROSPER trial



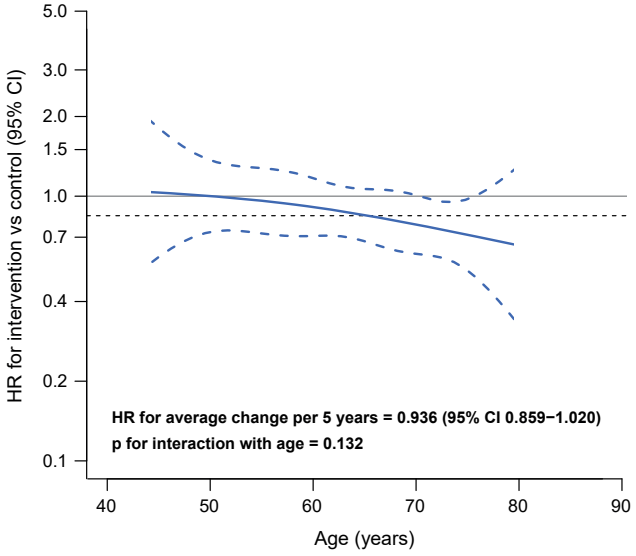
Random-effects meta-regression analysis of the HR for major vascular events per 1 mmol/L LDL-c reduction over age, using data of the trials of guideline-recommended therapies (i.e. statins, ezetimibe, and PCSK9 inhibitors) minus the PROSPER trial, for all trials combined (A), and stratified for primary and secondary prevention (B). The shaded areas denote 95% confidence intervals. The size of the squares (and circles) is proportional to the weight in the meta-regression analysis. The numbers serve as identifiers for the individual trials and correspond to the number presented for each trial in Figure 2, Figure S1 & S2, and Table S1.
Abbreviations: CI = confidence interval, HR = hazard ratio, LDL-c = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin–kexin type 9.

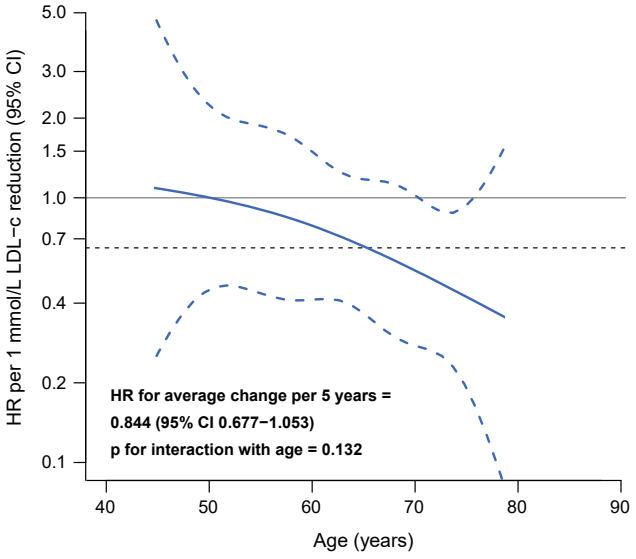
Figure S9. The effects of LDL-c reduction over age in the individual atorvastatin trials



ALLIANCE

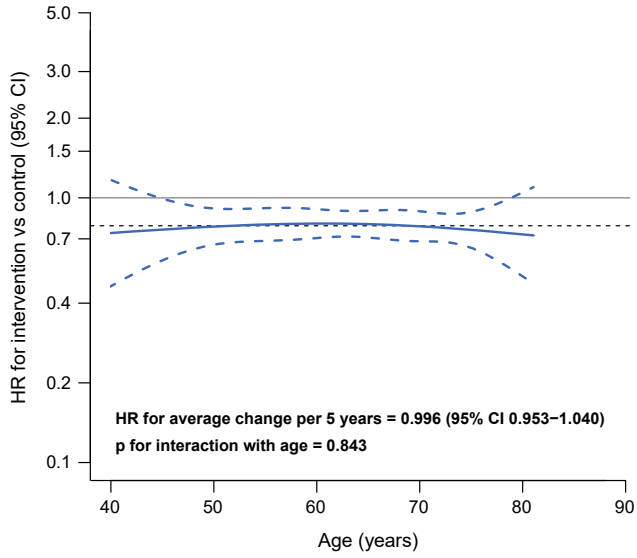
2,442 participants – 667 major vascular events

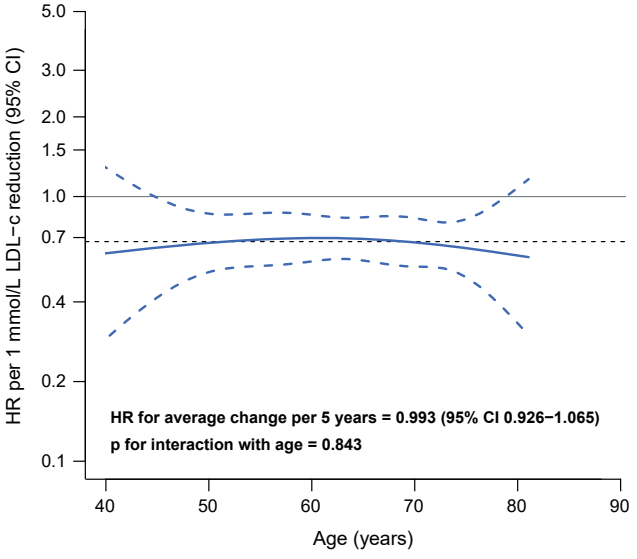




TNT

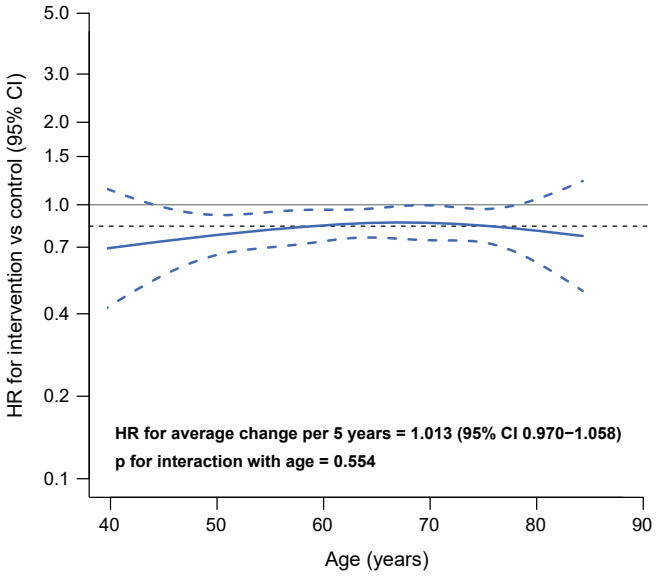
10,001 pa rticipants – 2,566 major vascular events

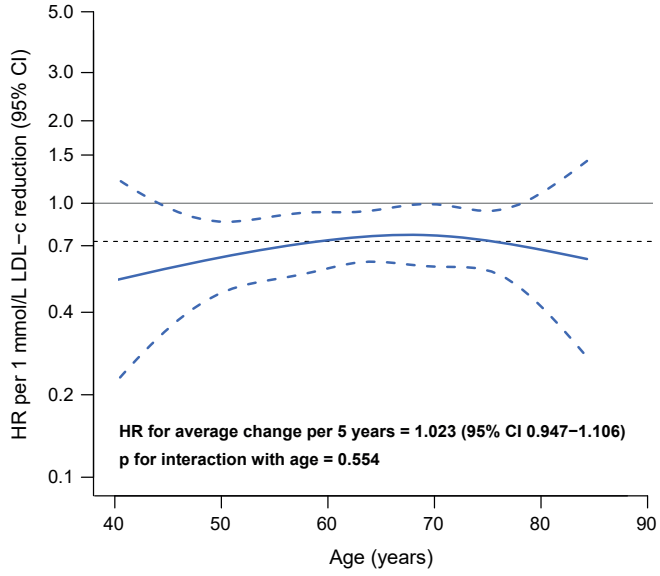




IDEAL

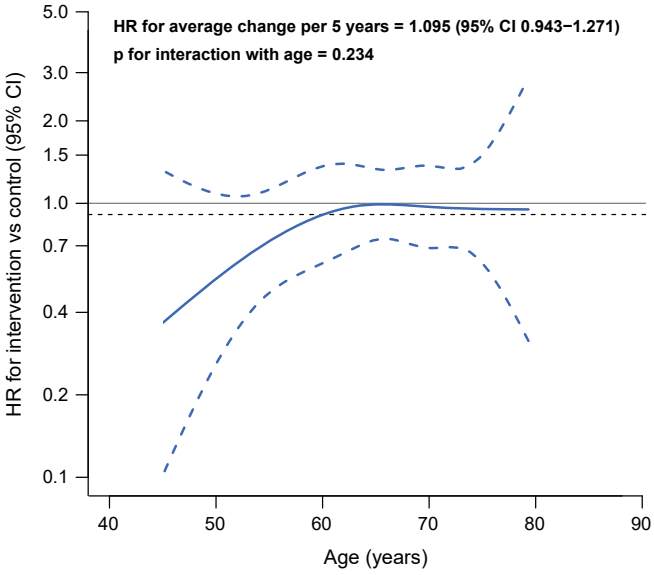
8,888 participants – 2,186 major vascular events

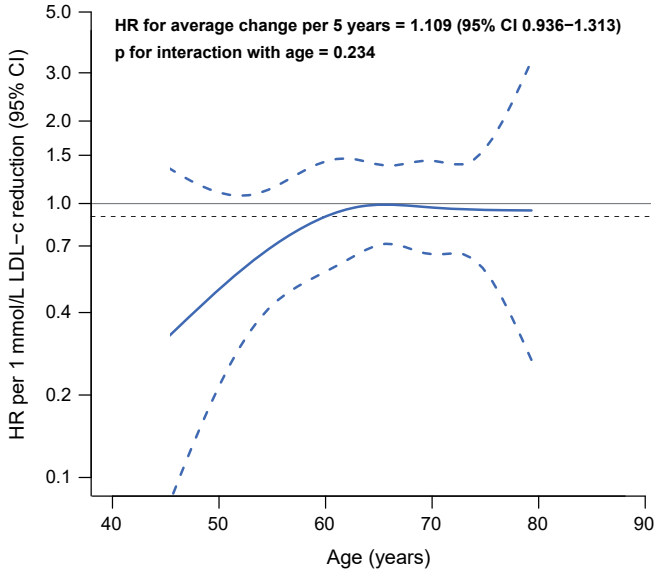


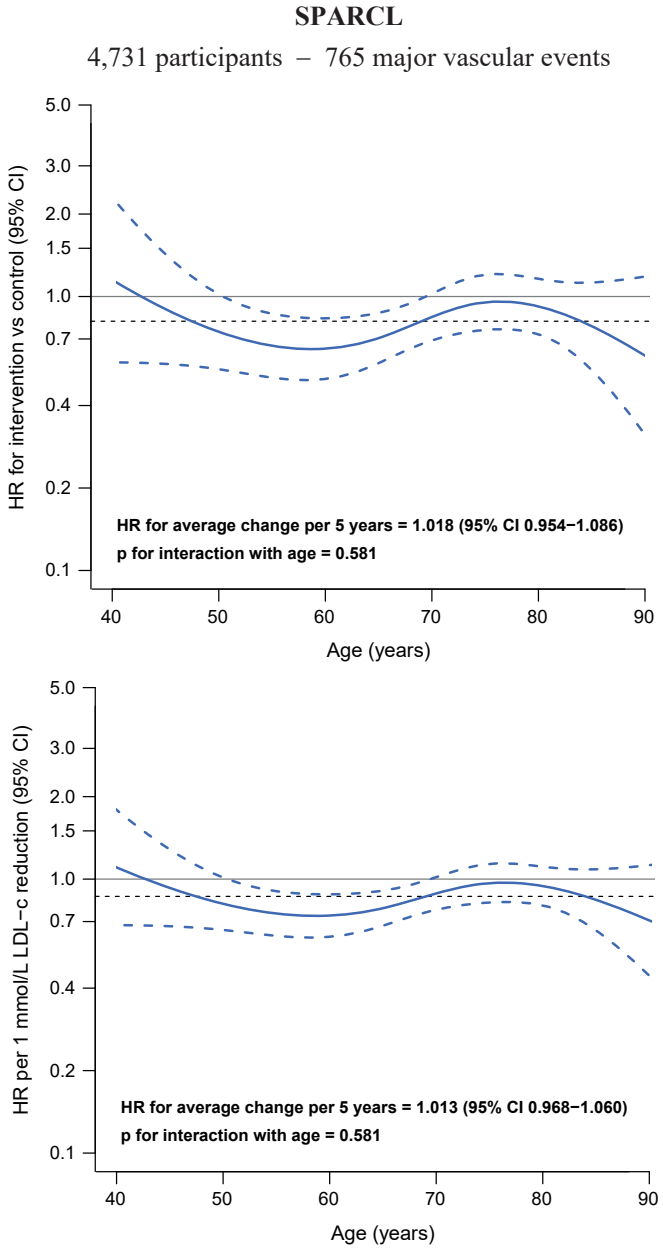


ASPEN

2,410 participants – 346 major vascular events







The HR for major vascular events for the intervention vs control (left side) and per 1 mmol/L LDL-c reduction (right side) over age, in the 6 individual atorvastatin trials for which individual participant data were available. The blue dotted lines denote 95% confidence intervals. The black dotted lines denote the overall trial hazard ratios. Abbreviations: CI = confidence interval, LDL-c = low-density lipoprotein cholesterol, HR = hazard ratio.

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Chapter 9.

General discussion

Cardiovascular disease (CVD), including atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF), remains a leading cause of morbidity and mortality worldwide.[1,2] Despite the routine use of lipid-lowering, blood pressure-lowering, and antithrombotic therapies in patients with ASCVD, and diuretics, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients with HF, many of these patients still have a high residual risk of CVD events and mortality.[3–5] CVD events impose a large burden on patients, as well as a huge economic burden.[2,6] Therefore, there is a great need to reduce this residual CVD risk in patients with ASCVD and HF. In this thesis, risk factors contributing to residual CVD risk were investigated (**Chapters 2–4**), models were derived to predict residual CVD risk for individual patients (**Chapters 5 & 6**), and individualized treatment effects of therapies reducing residual CVD risk were estimated (**Chapters 5–8**). The findings may have important implications for the management of patients with ASCVD and HF in clinical practice, and for future research.

Factors contributing to residual CVD risk

Before we can focus on reducing residual CVD risk in patients with ASCVD and HF, we first need to know what causes this excess risk in these patients. Among patients with established CVD, higher plasma concentrations of C-reactive protein (CRP), as a marker of systemic inflammation, are associated with an increased risk of future CVD events independent of conventional risk factors (**Chapters 2 & 3**). The association is consistent for patients with different types of CVD, i.e. coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral artery disease (PAD), and abdominal aortic aneurysm (AAA), and for various cardiovascular outcomes, i.e. myocardial infarction, stroke, major adverse limb events, incident HF, and cardiovascular and all-cause mortality. In addition, in patients with established CVD, the metabolic syndrome and insulin resistance are also associated with an increased risk of incident HF, independent of diabetes mellitus and other conventional risk factors (**Chapter 4**). Previous studies have already shown that the metabolic syndrome and insulin resistance are associated with an increased risk of ASCVD events in this population.[7,8] The findings from **Chapters 2–4** are supported by previous studies in people without a history of CVD.[9–13] But what distinguishes the studies in this thesis from previous studies, is that they were performed in patients with established CVD who mostly were already treated with conventional guideline-recommended lipid-lowering, blood-pressure lowering, and antithrombotic therapy.[14–16] This allowed us to directly assess the influence of CRP, the metabolic syndrome, and insulin resistance on the residual risk of CVD. In this population, we showed that both an elevated CRP concentration (above the median, i.e. >1.9 mg/L) and the presence of the metabolic syndrome considerably increased the risk of CVD on top of conventional risk factors such as diabetes mellitus, smoking, and

hypertension. These findings demonstrate that inflammatory and metabolic risk are two important pillars that contribute to residual CVD risk.

Role for inflammatory and metabolic risk factors in clinical practice

This raises the question: what should be done with inflammatory and metabolic risk factors in clinical practice? First of all, they should be measured. Guidelines recommend the routine measurement of cholesterol and blood pressure in all patients with or at high risk of CVD.[15,16] I would propose that in addition to these measurements, physicians also consider measuring CRP and the components of the metabolic syndrome in all patients with or at high risk of ASCVD or HF. As the associations between baseline measurements of these risk factors and cardiovascular outcomes were shown to be consistent over time, sometimes even beyond 15 years after the measurement, it may not be needed to measure these factors during each visit, but once every few years could suffice (**Chapters 2**–**4**).

Measuring CRP and the components of the metabolic syndrome could be important for two reasons. First, they could support identification of patients with a high residual CVD risk. Both an elevated CRP concentration (e.g. >2.0 mg/L) and presence of the metabolic syndrome indicate that a patient is likely to have a high residual CVD risk. The presence of either of these risk factors alone may already be a basis for starting intensified preventive treatment. But ideally these factors should be incorporated in clinical risk scores that predict an individual's CVD risk based on several patient characteristics. CRP has already been included in the European Society of Cardiology (ESC) guideline-recommended SMART2 risk score.[15,17] Future studies may assess the incremental value of adding the metabolic syndrome and its components to cardiovascular risk scores.

Second, measuring these factors may be important to identify potential treatment targets. If patients have an elevated CRP concentration, indicating a residual inflammatory risk, they may benefit from anti-inflammatory therapy to reduce their residual risk of CVD (**Chapter 6**). In recent years, anti-inflammatory treatment with low-dose colchicine was proven to effectively reduce CVD risk in patients with CAD.[18,19] Given that the association between inflammation (measured by CRP) and cardiovascular outcomes was consistent for patients with other types of CVD, i.e. CeVD, PAD, and AAA (**Chapter 2**), ongoing and future studies may reveal the efficacy of anti-inflammatory therapy in these patients as well.[20–22] If patients meet the criteria for the metabolic syndrome, indicating a residual metabolic risk, they may benefit from therapies targeted at components of the metabolic syndrome or the metabolic syndrome as a whole to reduce their residual CVD risk. For example, icosapent ethyl, a highly purified eicosapentaenoic acid (EPA) ethyl ester, has been shown to reduce both triglyceride levels and CVD risk in patients with or at high risk of

ASCVD (**Chapter 7**).[23] Sodium/glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists could also reduce metabolic risk, and have already been proven to effectively reduce CVD risk in individuals with diabetes mellitus, and for SGLT2 inhibitors, HF hospitalization and cardiovascular mortality risk in patients with HF.[24–26] Future trials may evaluate the efficacy of these drugs in ASCVD patients without diabetes mellitus and HF. Treatment modalities that improve insulin resistance or increase high-density lipoprotein cholesterol (HDL-c) may also have the potential to reduce residual CVD risk, although trials so far have shown contrasting results.[27–30] To target the metabolic syndrome as a whole, therapies aimed at reducing obesity such as diet and physical activity interventions, and bariatric surgery (if body-mass index is >35 kg/m^2) may be effective.[31–33] Future research should focus on whether existing and newly developed therapies aimed at inflammatory and metabolic risk factors can reduce residual CVD risk. It may also be evaluated if these therapies are effective in the prevention and/or treatment of HF.

Other drivers of residual CVD risk

Inflammatory and metabolic risk are not the only drivers of residual CVD risk. Other pathways that were largely not investigated in this thesis include residual cholesterol risk, residual thrombotic risk, and residual lipoprotein(a) risk.[34] However, the expected benefits of low-dose colchicine regularly exceed those of intensified low-density lipoprotein cholesterol (LDL-C) reduction, indicating that residual inflammatory risk likely has a larger contribution to the total residual CVD risk than residual cholesterol risk in patients already treated with a statin (**Chapter 6**). This is supported by a recent analysis of randomized controlled trials.[35]

Individualized prediction of residual CVD risk

Just measuring risk factors that contribute to residual CVD risk is not enough to determine an individual's risk or to guide treatment decisions. As residual CVD risk is determined by a combination of several patient characteristics, it is difficult for clinicians to make an assessment of an individual's risk based on risk factor measurements alone. Therefore, clinicians should make use of multivariable prediction models to estimate individual CVD risk in their patients.[15] For this purpose, the ESC guidelines recommend the use of the SMART2 risk score (10-year CVD risk) and SMART-REACH model (lifetime CVD risk) in all patients with ASCVD (**Chapters 6 & 7**).[15,17,36] However, existing models for patients with HF have several limitations.[37–40] They often include a large number of (not routinely available) predictors, lack external validation, are often not competing risk-adjusted, and only provide predictions for a limited time span. This may be an explanation for the fact

that, to date, there are no guideline-recommended risk scores for patients with HF.[41] The newly developed LIFE-HF model is a lifetime prediction model predicting the 2- and 5-year risk of HF hospitalization and mortality, as well as the HF hospitalization-free and overall life expectancy for individual patients with HF and reduced ejection fraction (HFrEF) (**Chapter 5**). This model overcomes the limitations of previous models by including only ten of the strongest routinely available predictors, being extensively validated in various trial and registry populations, making use of a separate function for non-cardiovascular mortality to adjust for competing risks, and by being the first model to predict lifetime risk in patients with HF.

Clinical implications of cardiovascular risk scores

The use of the SMART2 and SMART-REACH models for patients with ASCVD, and the LIFE-HF model for patients with HFrEF in clinical practice could have several important implications. First, physicians could use these tools to communicate an individualized prognosis to their patients. Patients often want to know what they can expect in the future, in terms of their risk of CVD events, and their anticipated (event-free) life expectancy. Especially for patients with HFrEF, who have a high mortality risk, it may be useful to quantify their life expectancy.[5] Second, the models could help to increase awareness among physicians and patients of the high residual risk that many of these patients with ASCVD and HF have, even when adequately treated with conventional therapies.[3,4,42] This is important as physicians may think that as long as patients with ASCVD reach their LDL-C and blood pressure targets, and patients with HF have stable and/or mild symptoms, there is no need to consider additional treatment options. That this may be the case is evident from the underwhelming uptake of novel therapies in clinical practice.[43–45] Also, patients may not see the value of adding new medications to several they may already be taking. By providing individualized predictions of residual CVD risk, the models could encourage physicians to optimize preventive treatment in patients with a high residual risk, and could promote a healthy lifestyle and treatment adherence in patients. Third, the risk predictions provided by the models could be used to guide treatment decisions. Intensive therapies could be prescribed to those patients with a high residual risk, i.e. the patients who need it most. For the reasons outlined above, I would propose that clinicians consider using the SMART2 and SMART-REACH model in patients with ASCVD, and the LIFE-HF model in patients with HFrEF, regularly during clinic visits, and when making treatment decisions.

Risk-based treatment in patients with ASCVD

When treatment decisions are based on risk predictions, with more intensified treatment options recommended for individuals with a higher risk, this is called 'risk-based treatment'.[46] The concept behind risk-based treatment is that individuals with a higher risk, benefit more from preventive therapy than those with a relatively low risk. This can be explained using a simple example: a treatment causing a 20% relative risk reduction will afford an absolute risk reduction (ARR) of 6% in a patient with a risk of 30%, as compared to an ARR of only 2% in a patient with a risk of 10%. This also means that less high-risk patients need to be treated to avoid one event, i.e. the number needed to treat (NNT) is lower in these patients (17 vs. 50 in the example). Risk-based treatment has already been widely recommended for the primary prevention of CVD for several years.[15,47–49] For this population, guidelines include specific recommendations for risk categories, divided based on the 10-year risk of CVD as predicted by the SCORE2 algorithm.[15,50] They follow the principle: the higher the risk category, the more intensive the recommended preventive therapy. In contrast, for patients with ASCVD, guidelines have traditionally used a 'one size fits all' approach, with all patients classified as being at very high risk of future CVD events.[16,47] However, there is a wide distribution of residual CVD risk in patients with ASCVD, with some patients being at very high risk of future events, while others have a relatively low residual risk under conventional therapy (**Chapters 6 & 7**). These findings support that a risk-based treatment approach would be advisable for patients with ASCVD as well. The latest ESC guidelines already recommend that estimates of an individual's residual CVD risk are taken into account in decisions on the initiation of intensified preventive therapies.[15] But for a risk-based treatment approach to be effectively implemented in clinical practice, it may be necessary to establish specific risk thresholds with corresponding recommendations for preventive treatment, as has been done for primary prevention. Future research may focus on determining the optimal combination between risk thresholds and treatment recommendations, in terms of effectiveness and cost-effectiveness, to support risk-based treatment for patients with ASCVD in clinical practice.

Risk-based treatment in patients with HF

Guidelines for patients with HFrEF also largely use a one size fits all approach.[41,51] The four pillars of HFrEF therapy, i.e. beta-blockers, ACE inhibitors/ARBs or angiotensin receptor-neprilysin inhibition (ARNI), mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors have class I recommendations for all patients with HFrEF. This while there are considerable differences in the risk of HF hospitalization and mortality between individual patients with HFrEF (**Chapter 5**). However, given the overwhelming efficacy of the abovementioned therapies demonstrated in clinical trials, and the fact that even the HFrEF patients at the lowest risk still have a substantial risk of HF hospitalization and

mortality, the class I guideline recommendations for all HFrEF patients should not be disputed. Nevertheless, several studies have shown that the uptake of ARNI, MRAs, and SGLT2 inhibitors in patients with HFrEF in clinical practice is lacking.[43,44,52] A risk-based treatment approach using the risk predictions of the LIFE-HF model, with even more stringent recommendations for patients in the higher risk categories could be useful to make sure that at least the high-risk patients will be more likely to receive comprehensive treatment with the four pillars of HFrEF therapy. Also, a risk-based approach could be useful for making decisions on the initiation of additional therapies such as vericiguat, digoxin, device therapies, or new therapies that may be developed in the future. Even if the risk predictions provided by the LIFE-HF model are not needed to inform treatment decisions, because therapies should be prescribed to all patients, they could still be useful for increasing risk awareness, and encouraging physicians to prescribe and patients to adhere to guideline-recommended therapies.

Future directions for risk prediction in ASCVD and HF

Even though the SMART2, SMART-REACH, and LIFE-HF models have been developed in line with the most recent quality standards, they are not perfect and may be improved in the future.[53] First, geographical differences in baseline risk have only partially been taken into account by these models. Ideally, the models should be recalibrated to individual risk regions or countries, as was done for the SCORE2 algorithm.[50,54] This requires risk-/country-specific event rates and mean predictor levels, which are not yet available for patients with ASCVD and HF, but may become available in the future. Second, the SMART-REACH and LIFE-HF models predict lifetime risk, but validation has been performed for up to 10 years. Longer-term validation may be considered when data with longer follow-up duration become available. Third, in the future, the performance of prediction models may be improved through the use of artificial intelligence (AI) and machine learning techniques, although the incremental value of these techniques on top of conventional methods in risk prediction is yet to be demonstrated.[55] Fourth, the implementation of prediction models in clinical practice may be improved by integrating them in electronic health records. Finally, the LIFE-HF model only applies to patients with HFrEF. A similar model should be developed for patients with HF and mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF).

Individualized prediction of treatment effects

As discussed, the identification of residual risk markers and the prediction of individual CVD risk may have important clinical implications, but the ultimate goal is to reduce the residual risk in patients with ASCVD and HF. This requires an intensification of preventive therapy. It may not be feasible, nor (cost-)effective to prescribe intensified preventive therapies to all patients with ASCVD and HF. Rather intensive therapies should be prescribed to those patients who are most likely to benefit from such treatment, and in whom they are most cost-effective. Previously, we discussed a risk-based treatment approach, in which the most intensive therapies are prescribed to the patients with the highest residual risk, i.e. the greatest need for treatment. As discussed, this may be an effective way to increase the chances that intensified therapies are prescribed to patients with the largest benefit from treatment. However, as demonstrated in **Chapters 5-7**, high risk does not always equal high treatment benefit.

The risk and treatment benefit paradox

Previously, we discussed that a treatment causing a fixed relative risk reduction leads to larger absolute risk reductions in patients with a high as compared to a low residual CVD risk. However, treatment benefits are not only determined by an individual's CVD risk, but also by an individual's competing risk of non-cardiovascular death, and remaining life expectancy.[56,57] Patients with a high 5-year or 10-year CVD risk may appear to have a large potential treatment benefit. But as these patients are often older and have more comorbidities, they often have an increased risk of non-cardiovascular death and a shorter remaining life expectancy. A shorter remaining life expectancy leads to a shorter potential treatment duration. This leaves less time for the benefits of treatment to accumulate, which could lead to a smaller total treatment benefit over the patients' remaining lifetime. In contrast, patients with a low short-term CVD risk, who are often younger and in the earlier stages of the disease, may appear to have a limited potential treatment benefit. But as they will get older and the disease may progress over the years, they may have a high lifetime CVD risk. Due to their longer life expectancy, these patients can be treated over a longer period of time, potentially leading to larger lifetime treatment benefits. This paradox in which patients with a low short-term risk and small expected short-term treatment benefit regularly have a larger expected lifetime treatment benefit than patients with a high short-term risk, is illustrated by several examples throughout this thesis. First, among patients with HFrEF, the average expected lifetime benefit in terms of years gained in overall life expectancy from comprehensive treatment with an MRA, ARNI, and SGLT2 inhibitor, is largest for younger patients with a relatively low to moderate 5-year risk of mortality (**Chapter 5**). Second, in patients with chronic CAD, the average expected number of years

gained in CVD-free life expectancy from anti-inflammatory treatment with low-dose colchicine, is largest for younger patients, mostly irrespective of 10-year CVD risk (**Chapter 6**). Third, among patients with ASCVD, the average expected number of CVD-free life-years gained from icosapent ethyl is largest for patients within the lowest CVD risk quartile, and smallest for patients within the highest CVD risk quartile (**Chapter 7**).

Lifetime versus shorter-term risk and treatment benefit

The paradox described above, also shows the importance of the prediction of lifetime risk and lifetime treatment benefit in addition to conventional 10-year and other shorter-term estimates.[36,57–59] As in patients with ASCVD and HF, therapies are usually continued lifelong, lifetime benefits are a more complete representation of the total treatment benefit that can be expected in these patients. Relying solely on short-term estimates of CVD risk and treatment benefit may lead to undertreatment in younger patients in the earlier stages of the disease. Due to their relatively low short-term risk of CVD events, intensified treatment may not seem beneficial. But as discussed, they may in fact have a high lifetime risk, and as a result of the long potential treatment duration, may have a large lifetime treatment benefit. Older patients with more advanced disease may be overtreated when relying on short-term estimates. Intensified treatment may seem beneficial in these patients because of their high short-term CVD risk, but treatment benefits may in fact be limited as these patients may only be treated over a short period of time due to their relatively short life expectancy. I would therefore propose the use of both short-term and lifetime estimates of CVD risk and treatment benefit to guide treatment decisions in clinical practice, in line with the recommendations in the ESC CVD Prevention Guidelines.[15]

Heterogeneity of relative treatment effects

Besides differences in absolute treatment effects between individual patients, there may also be heterogeneity of relative treatment effects.[56,60,61] In trials, this is commonly assessed using subgroup analyses. However, these analyses have several limitations.[62,63] There is a high risk of chance findings, most trials are not adequately powered to detect subgroup differences, and only one characteristic is assessed at a time inducing a reference class problem. A recommended method that overcomes these limitations is evaluating the interaction between a treatment and individual baseline risk as predicted by a multivariable risk model.[56,60,61] Using this methodology, it was shown that the relative treatment effect of icosapent ethyl is numerically more favourable in the lower as compared to the higher CVD risk quartiles, but that the treatment-by-risk interaction is not significant (**Chapter 7**). Previously, treatment-by-risk interactions have been assessed for intensive blood pressure lowering and antithrombotic therapy in patients with ASCVD, and SGLT2 inhibitors in

patients with HFrEF, but not for other therapies.[61,64,65] Similarly, relative treatment effects may change over time. For example, the relative treatment effects of LDL-C reduction remain stable over time in the secondary prevention of ASCVD, but attenuate with increasing age in primary prevention (**Chapter 8**). To date, this has not been evaluated for other therapies in patients with ASCVD and HF. As variation of relative treatment effects due to differences in baseline CVD risk, and changes in these effects over time are important for the selection of patients for intensified therapies, and determining the optimal timing for the initiation of these therapies, I would propose that in the future heterogeneity of relative treatment effects due to baseline risk and time is routinely assessed in all clinical trials.

Hypothesis on the favourable relative treatment effects in younger lower-risk patients

A potential explanation for the finding that the relative treatment effects of icosapent ethyl were largest for patients in the lowest CVD risk quartile (**Chapter 7**), and those of LDL-C reduction attenuated with increasing age in primary prevention (**Chapter 8**), is that lowering risk factors such as triglycerides and LDL-C may be more effective in the earlier stages of atherosclerosis. In younger individuals with a relatively low CVD risk, in whom atherosclerosis is still absent or in an early stage, lowering these risk factors may prevent the development of clinically significant atherosclerosis leading up to major vascular events. Whereas in older individuals with a high risk of CVD, in whom atherosclerosis is already advanced, lowering triglyceride and LDL-C levels may halt its further development but may not cause reversal to a state in which there is no or only minimal atherosclerosis, leaving them at considerable risk of major vascular events. In addition, older individuals with a higher CVD risk often have other risk factors that may still cause CVD events, even when triglyceride and/or LDL-C levels are reduced. This hypothesis is supported by Mendelian randomization studies which showed that a genetically determined lower LDL-C from birth is associated with greater relative reductions in the risk of major vascular events per 1 mmol/L lower LDL-C than the same magnitude of LDL-C reduction achieved with statins later in life.[66–68] Future research should further explore this hypothesis, also for other risk factors and preventive therapies in patients with or at high risk of ASCVD.

Benefit-based treatment

The observation that there are important differences in both absolute (**Chapters 5-7**) and relative treatment effects (**Chapters 7 & 8**) between individual patients, and that these are not solely related to differences in residual CVD risk (high risk does not always equal high benefit), brings us back to the question: how do we select the right patients for intensified therapy? The primary aim of selecting patients for treatment is to be able to prescribe the

treatment to those patients with the largest treatment benefit. Therefore, instead of relying on risk estimates as a proxy for potential treatment benefit, i.e. risk-based treatment, it may be better to rely directly on estimates of an individual's treatment benefit, i.e. benefit-based treatment. The LIFE-HF model provides individualized estimates of short-term and lifetime treatment benefits from guideline-recommended therapies in patients with HFrEF (**Chapter 5**), while the SMART2 and SMART-REACH models provide such estimates for patients with ASCVD (**Chapter 6 & 7**). The estimates provided by these models could be used to guide treatment decisions, and as a basis for guideline recommendations. A previous study already showed that in patients with ASCVD, a lifetime benefit-guided treatment strategy resulted in more CVD-free life-years gained and more CVD events avoided than the conventional risk factor-based strategy, although at a higher cost per quality-adjusted life-year (QALY).[69] In this study, a treatment threshold of ≥1 year additional CVD-free life per therapy was chosen. Future studies should further explore the (cost-)effectiveness of benefit-based treatment strategies in patients with ASCVD and HF to determine the optimal treatment thresholds, and to allow the incorporation of benefit-based treatment in future guidelines.

Other clinical implications of individualized treatment effects

Even before a benefit-based treatment approach has been implemented, individualized treatment effects may already have important clinical implications. First, they could emphasize the sometimes substantial long-term benefits of intensified therapy in younger patients with less advanced disease, in whom treatment benefits may often be underestimated in current practice. Second, they could allow the weighing of treatment benefits against potential treatment harms, and costs. Third, they could help physicians to communicate treatment benefits to their patients, which could support shared decision-making, and promote treatment adherence.[70] In this way, individualized treatment effects could help to improve the currently lacking implementation of guideline-recommended therapies in patients with ASCVD and HF, leading to reductions in the residual risk of these patients.[43–45] I would therefore propose that clinicians consider predicting individualized treatment benefits, using the LIFE-HF model for patients with HFrEF, and the SMART2 and SMART-REACH models for patients with ASCVD, when making treatment decisions in clinical practice.

Choosing the right therapy for residual risk reduction

After the identification of patients who are likely to benefit from intensified therapy to reduce their residual CVD risk, another challenge arises: choosing the best therapy to reduce their risk with. For patients with ASCVD, several intensified prevention strategies are available and recommended by guidelines: LDL-C reduction to <1.4 mmol/L, systolic blood pressure reduction to <130 mmHg, dual antiplatelet therapy, dual pathway inhibition (aspirin + low-dose rivaroxaban), low-dose colchicine, and icosapent ethyl.[15,71] Low-dose colchicine may be expected to be more effective than intensified lipid- and blood pressure-lowering therapy in the majority of patients with chronic CAD already on conventional preventive treatment (**Chapter 6**). Icosapent ethyl leads to significant reductions in major vascular events across all quartiles of baseline residual CVD risk (**Chapter 7**). This supports a broader use of these therapies than currently recommended by international guidelines.[15,71] For low-dose colchicine, this has recently been supported by other studies.[35,72] However, some patients, with higher LDL-C and blood pressure levels, may be expected to benefit more from intensified lipid- and/or blood pressure-lowering therapy (**Chapter 6**). This shows that the choice of therapy for residual risk reduction should always be made on an individual level. As discussed previously, individuals with a high residual inflammatory risk may benefit most from low-dose colchicine, patients with a high residual triglyceride risk from icosapent ethyl, and patients with a high residual cholesterol risk from intensified lipid-lowering therapy (e.g. with a PCSK9 inhibitor), and so on.[34,35] To support the choice of the therapy that is likely to be most beneficial for an individual patient, individualized treatment benefits of all guideline-recommended treatment options can be predicted and compared using the online tools of the SMART2 and SMART-REACH models on www.U-Prevent.com.

For patients with HFrEF, MRAs, ARNI, and SGLT2 inhibitors are available to reduce their residual risk of HF hospitalization and mortality.[41,51] But as current guidelines include class I recommendations for these therapies for all patients with HFrEF, individualized treatment benefits predicted for these therapies by the LIFE-HF model (**Chapter 5**) may not be needed to select patients for intensified treatment, or choose which of these therapies to prescribe (all patients should be treated with all therapies). Nevertheless, the individualized treatment benefits predicted by the LIFE-HF model could be used to make decisions on the initiation of additional therapies such as vericiguat, digoxin, and if their effect estimates are added to the model in the future, device therapies. Also, they could help to improve the lacking uptake of the therapies with class I recommendations by emphasizing to physicians and patients, the absolute benefits of these therapies for all patients with HFrEF, including younger patients with stable and/or mild symptoms.[43,44,52]

Future directions for individualized prediction of treatment effects

As discussed the estimates of individualized treatment effects presented in this thesis, as well as the models that were used to derive these estimates, may already be useful in the management of patients with ASCVD and HF in clinical practice. Nevertheless, there is still room for improvement. The methodology applied in this thesis to predict individualized treatment benefits, can also be used to derive individualized estimates of treatment harms.[61,64] Models simultaneously predicting both treatment benefits and harms for individual patients with ASCVD and HF, would allow for the selection of patients with the most favourable benefit-harm balance for intensified treatment. Also, the impact of the use of clinical prediction tools such as the LIFE-HF model on guideline adherence, patient satisfaction, and cardiovascular outcomes in clinical practice could be evaluated, for example using a cluster-randomized trial design.

Concluding remarks

Despite the routine use of various preventive therapies, the residual risk of CVD events and mortality remains an important problem in patients with ASCVD and HF. Several risk factors, including inflammatory and metabolic factors, contribute to this risk. The major driver of residual risk varies between individual patients, as do the magnitude of this risk, and the benefit that may be expected from intensified therapies. Residual risk reduction in patients with ASCVD and HF therefore requires an individualized approach. Clinical prediction models, such as the ones developed and applied in this thesis, can provide estimates of an individual's short-term and lifetime CVD risk, as well as an individual's potential benefit from various preventive therapies. Many of these models are freely available on www.U-Prevent.com. Their use in clinical practice could allow physicians to select the patients with the largest expected benefit from intensified treatment, choose the right therapy for the right patient, and could support doctor-patient communication and shared decision-making. Altogether, this could help to improve the lacking implementation of novel therapies such as low-dose colchicine, icosapent ethyl, and PCSK9 inhibitors in ASCVD patients with a high residual risk and/or large predicted treatment benefit, and MRAs, ARNI, and SGLT2 inhibitors in all patients with HFrEF. In this way, the residual risk in patients with ASCVD and HF could be considerably reduced.

Highlights of this thesis

- Higher plasma CRP, as a measure of chronic low-grade inflammation, is independently associated with an increased risk of a variety of cardiovascular events, and mortality in patients with CAD, as well as CeVD, PAD, and AAA (**Chapter 2**).
- In patients with established CVD, higher plasma CRP is independently associated with an increased risk of incident HF beyond 15 years after its measurement (**Chapter 3**).
- Among non-diabetic patients with established CVD, the metabolic syndrome including abdominal obesity and insulin resistance, are associated with an increased risk of incident HF, independent of conventional risk factors and future development of diabetes mellitus (**Chapter 4**).
- The newly developed LIFEtime perspective for Heart Failure (LIFE-HF) model can be used to reliably predict 2-/5-year risk of HF hospitalization and mortality, HF hospitalization-free and overall life expectancies, and (lifetime) treatment benefits from any combination of guideline-recommended therapies, for individual patients with HFrEF (**Chapter 5**).
- Based on individual treatment benefits estimated with the SMART-REACH model, the 10-year and lifetime benefits of anti-inflammatory treatment with low-dose colchicine vary between individuals, but are expected to exceed those of intensified LDL-C and SBP reduction in the majority of patients with chronic CAD treated with conventional preventive medication (**Chapter 6**).
- Among patients with ASCVD and elevated triglyceride levels, icosapent ethyl significantly reduces the risk of major vascular events across all quartiles of baseline residual CVD risk (**Chapter 7**).
- Based on a meta-analysis of 60 RCTs of lipid-lowering therapies, the relative treatment effects of LDL-C reduction remain stable over time in the secondary prevention of CVD, but attenuate with increasing age in the primary prevention of CVD (**Chapter 8**).

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Appendix

Summary

Cardiovascular disease (CVD) is the most common non-communicable disease, and the leading cause of mortality worldwide. Individuals who are at especially high risk of CVD events and mortality are patients with established atherosclerotic cardiovascular disease (ASCVD), and heart failure (HF). Over the years, several risk factors for future CVD events in these patients, such as smoking, hypercholesterolemia, and hypertension, have been identified. Therapies reducing these conventional risk factors, such as lipid- and blood pressure-lowering drugs, as well as renin-angiotensin system (RAS) inhibitors and beta-blockers to treat HF, are routinely used in all patients with ASCVD and HF in current clinical practice. Despite the routine use of these preventive treatments, many of these patients still experience recurrent CVD events. The CVD risk that remains after efforts have been made to institute conventional preventive treatment options to a maximum extent, is referred to as 'residual risk'. To be able to improve the prognosis of patients with ASCVD and HF, it is important to identify risk factors that contribute to this residual CVD risk, and to predict CVD risk and the effects of preventive treatment for individual patients, so that new treatment targets can be identified and additional therapies can be prescribed to patients with the largest need for/benefit from intensified treatment.

This thesis consists of two parts: **Part I** focuses on inflammatory and metabolic risk factors contributing to the residual risk of ASCVD and HF, while **Part II** focuses on the prediction of residual CVD risk and treatment effects in individual patients with ASCVD and HF.

Part I. Inflammatory and metabolic risk

Several risk factors have been suggested to potentially contribute to the residual risk of ASCVD and HF. Among these risk factors are obesity-related disturbances such as systemic inflammation, and the metabolic syndrome. With the growing burden of obesity, these factors may become increasingly important.

In **Chapter 2**, we showed that among patients with established CVD, a higher plasma concentration of C-reactive protein (CRP), as a marker of systemic inflammation, is independently associated with an increased risk of recurrent ASCVD events (hazard ratio [HR] per 1 mg/L 1.08; 95% confidence interval [CI] 1.05-1.10), and all-cause mortality (HR 1.10; 95% CI 1.08-1.12). **Chapter 3** added that in this same population, a higher CRP is also independently associated with an increased risk of incident HF (HR 1.10; 95% CI 1.07-1.13); both HF with reduced ejection (HFrEF: HR 1.09; 95% CI 1.04-1.14) and HF with preserved ejection fraction (HFpEF: HR 1.12; 95% CI 1.07-1.18). Patients with a CRP concentration exceeding the commonly used limits for low-grade inflammation (>10/>20 mg/L) are at

especially high risk of ASCVD events (compared to lowest CRP quintile: HR 1.90; 95% CI 1.58-2.29 for CRP >10 mg/L vs HR 1.60; 95% CI 1.35-1.89 for the highest CRP quintile ≤10 mg/L), and incident HF (compared to lowest CRP quartile: HR 2.49; 95% CI 1.74-3.56 for CRP >20 mg/L vs HR 2.22; 95% CI 1.76-2.79 for the highest CRP quartile ≤20 mg/L). In both analyses, the associations were independent of established CVD risk factors and medication use, were not modified by prior CVD location, and remained consistent beyond 15 years after the CRP measurement. These results indicate that inflammation is an important driver of residual CVD risk. Anti-inflammatory agents such as low-dose colchicine, which to date have only been tested and shown to reduce ASCVD events in patients with coronary artery disease (CAD), may also effectively reduce ASCVD risk in patients with other CVD locations (i.e. cerebrovascular disease, peripheral artery disease, and abdominal aortic aneurysm), and may have a role in the prevention of HF.

In **Chapter 4**, we demonstrated that among non-diabetic patients with established CVD, presence of the metabolic syndrome (MetS) defined according to the Adult Treatment Panel (ATP) III criteria was independently associated with an increased risk of incident HF (HR 1.32; 95% CI 1.04-1.68, HR per criterion 1.17; 95% CI 1.06-1.29). Of the individual MetS components, only higher waist circumference, as a measure of abdominal obesity, was independently associated with an increased risk of HF (HR per standard deviation [SD] 1.34; 95% CI 1.17-1.53). Insulin resistance quantified using the homeostasis model of insulin resistance (HOMA-IR) was also associated with an increased HF risk (HR per SD 1.15; 95% CI 1.03-1.29). All associations were independent of established risk factors, medication use, and the development of diabetes mellitus (DM) during follow-up, and were similar for HFrEF and HFpEF. These results, combined with previous literature showing an association between MetS and recurrent ASCVD, show that metabolic disturbances largely related to abdominal obesity are another important driver of residual CVD risk, even in the absence of DM. This supports the potential benefits of weight loss in patients with established CVD. In addition, it suggests that therapies targeted at (components of) the MetS, such as icosapent ethyl, and drugs that to date have mainly been tested in individuals with DM, such as sodium/glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, may also have the potential to reduce ASCVD and HF events in these patients.

Part II. Individualized prediction of risk and treatment effects

Just knowing which factors contribute to residual CVD risk is not enough to find out the risk of an individual patient, as this is usually determined by a combination of risk factors. As risk factor levels vary considerably between patients, there is a wide distribution of residual risk, with some patients being at very high risk of future CVD events, whereas

others have a relatively low residual risk under conventional therapy. Differences in residual risk as well as remaining life expectancy between individuals also lead to heterogeneity of treatment effects. Patients with a high residual risk or a long remaining life expectancy (who can be treated over a long period of time) may have a large benefit from intensified treatment, whereas in patients with a low residual risk or a limited remaining life expectancy, the benefits of adding more treatments may not outweigh the costs and risk of adverse events. So, estimates of an individual's residual CVD risk and expected benefit from treatment are important as they form a fundamental basis for treatment decisions. For patients with ASCVD, the guidelines of the European Society of Cardiology (ESC) therefore recommend that decisions on the initiation of intensified preventive therapies are based on an individual's predicted (lifetime) CVD risk and expected treatment benefit, as estimated by the SMART2 risk score and SMART-REACH lifetime prediction model.

However, there are currently no guideline-recommended risk scores for patients with HF. Existing scores are limited by the large number of (not routinely available) predictors, the lack of external validation and competing risk adjustment, the short-term predictions (mostly 2-year risks), and the fact that they do not allow the prediction of individual treatment benefits. In **Chapter 5**, we developed and externally validated the LIFEtime perspective for Heart Failure (LIFE-HF) model. The LIFE-HF model can be used to predict the 2- and 5-year risk of all-cause mortality ± HF hospitalization, as well as an overall and HF hospitalization-free life expectancy for individual patients with HFrEF, based on ten routinely available predictors. As demonstrated by the validation in multiple trials and cohorts of HFrEF patients from various geographic regions, the model's discriminative ability is similar or better than that of existing models, with c-statistics of 0.65-0.74, and the model's calibration is excellent for up to at least a 10-year period. In addition, the model was combined with HRs from trials to allow the prediction of individual treatment benefits from any combination of guideline-recommended therapies for HFrEF. This showed the heterogeneity of absolute treatment benefits in patients with HFrEF: combined treatment with a mineralocorticoid receptor antagonist (MRA), SGLT2 inhibitor, and angiotensin receptor–neprilysin inhibitor (ARNI) was estimated to afford a median of 2.5 additional years of overall survival, with an interquartile range (IQR) of 1.7-3.7 years. Use of the LIFE-HF interactive tool in clinical practice could help physicians to identify patients with the greatest need for/benefit from intensified treatment, and to communicate risks and treatment benefits to patients, supporting both personalized medicine and shared decision-making. This could improve the lacking implementation of novel guideline-recommended therapies, and reduce the high residual risk of hospitalization and mortality in patients with HFrEF.

For patients with ASCVD, the ESC Guidelines include a list of intensified (step 2) prevention strategies that may be considered after conventional (step 1) preventive therapy has been instituted, to reduce residual CVD risk. Among these intensified strategies is anti-inflammatory therapy with low-dose colchicine, but the list also includes low density lipoprotein-cholesterol (LDL-C) reduction to <1.4 mmol/L, and systolic blood pressure (SBP) reduction to <130 mmHg. Estimating individual treatment benefits of these three strategies could help to decide which therapy is the most effective approach to reduce residual CVD risk in each patient. In **Chapter 6**, we used the SMART-REACH model to predict the individual lifetime benefits of low-dose colchicine, and compare them to those of LDL-C reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg, in a large population of patients with chronic CAD. This showed that low-dose colchicine affords a median of 2.0 (IQR 1.6-2.5) additional years of CVD-free survival, as compared to 1.2 (IQR 0.6-2.1) years for intensified LDL-C reduction, and 0.7 (IQR 0.0-2.3) years for intensified SBP reduction. It was estimated that the lifetime benefits of low-dose colchicine exceed those of intensified LDL-C reduction in 70%, and those of intensified SBP reduction in 68% of patients. As in **Chapter 5**, this analysis also shows that absolute treatment benefits vary considerable between patients, and that treatment decisions including the choice of therapy should therefore be tailored to the individual. In general, the findings of this chapter suggest that anti-inflammatory therapy with low-dose colchicine is a more effective approach to reduce residual CVD risk than intensified LDL-C or SBP reduction in the majority of patients with chronic CAD.

Another intensified preventive treatment that can be used to reduce residual CVD risk in patients with ASCVD is icosapent ethyl, a highly purified eicosapentaenoic acid (EPA) ethyl ester that lowers triglycerides. The ESC Guidelines recommend that icosapent ethyl may be considered in patients with ASCVD and triglycerides >1.5 mmol/L who have a high residual risk. This raises the question as to how the effects of icosapent ethyl are influenced by baseline residual risk. In **Chapter 7**, we showed that icosapent ethyl significantly reduces major adverse cardiovascular events (MACE) across all quartiles of SMART2-estimated baseline CVD risk, with an HR that ranged from 0.62 (95% CI 0.43-0.88) in the lowest to 0.78 (95% CI 0.63-0.96) in the highest risk quartile. Despite the numerical attenuation of the relative treatment effect, the absolute risk reduction increased across risk quartiles, i.e. ranged from 3.9% (95% CI 1.0-6.8%) in the lowest to 5.6% (95% CI 1.3-10.0%) in the highest risk quartile. These results indicate that icosapent ethyl can be used to effectively reduce residual CVD risk in all patients with ASCVD and elevated triglyceride levels irrespective of the size of their residual risk. This may support a broader use of icosapent ethyl than currently recommended in the ESC Guidelines.

Besides that treatment effects can be influenced by an individual's CVD risk and remaining life expectancy, they may also change over time. For example, it is conceivable that a preventive treatment is more effective in the first two years after the CVD event than in the fifth or tenth year of treatment, or when patients are young as compared to when they get older. This is important as cardiovascular preventive therapies are usually continued lifelong. Knowing how treatment effects change over time may have important implications for the timing of the initiation (or discontinuation) of preventive therapy, and the prediction of individual long-term treatment effects like in **Chapters 5-7**. In **Chapter 8**, we performed a meta-analysis of all relevant trials of LDL-C lowering therapies conducted to date, to establish the course of the relative treatment effects of a 1 mmol/L LDL-C reduction on CVD risk over time. This showed that in the secondary prevention of CVD, the effects of LDL-C reduction are stable over time, i.e. both follow-up time (up to at least ~7 years) and age. In primary prevention, the effects of LDL-C reduction were shown to significantly attenuate with higher age. These findings may indicate that in the primary prevention of CVD, physicians should strive towards early initiation of LDL-C lowering therapy in younger individuals at high risk of CVD. In secondary prevention, the current practice of starting LDL-C lowering therapy shortly after the first CVD event and then continue this therapy lifelong remains desirable. When the long-term effects of LDL-C reduction are predicted in individuals without a history of CVD, the use of an age-dependent treatment effect should be considered.

Concluding remarks

Systemic inflammation and obesity-related metabolic disturbances are important drivers of residual CVD risk. Existing and future therapies targeted at these risk factors may have an important role in reducing this risk. When making decisions on the initiation of intensified preventive treatment, the heterogeneity of treatment effects related to interindividual differences in risk factor levels, residual CVD risk, remaining life expectancy, and changes in treatment efficacy over time should be taken into account. Ideally, clinical prediction models accounting for all of these factors to estimate an individual's residual CVD risk and expected benefit from a variety of treatment options should be used to support clinical and shared decision-making. This has the potential to improve the implementation of intensified preventive therapies in patients with the largest need for/benefit from treatment, which could reduce the future burden of CVD in patients with ASCVD and HF.

Samenvatting (voor niet-ingewijden)

Hart- en vaatziekten zijn de meest voorkomende niet-besmettelijke ziekten en de belangrijkste doodsoorzaak wereldwijd. Mensen die een bijzonder hoog risico hebben op hart- en vaatziekten en vroegtijdig overlijden zijn mensen die in het verleden al eens een vorm van hart- en vaatziekten hebben doorgemaakt, zoals een hartinfarct, beroerte of hartfalen. Door de jaren heen zijn er verschillende risicofactoren ontdekt die het risico op hart- en vaatziekten verhogen, zoals roken, een hoog cholesterolgehalte in het bloed en een hoge bloeddruk. Tegenwoordig krijgen daarom bijna alle patiënten met een voorgeschiedenis van hart- en vaatziekten levenslang cholesterol- en bloeddrukverlagende medicijnen en bloedverdunners voorgeschreven met als doel om toekomstige hart- en vaatziekten te voorkomen. Bij patiënten met chronisch hartfalen worden hier vaak nog een aantal medicijnen aan toegevoegd die ervoor zorgen dat de belasting op het hart wordt verminderd, de pompfunctie verbetert, en het lichaam minder vocht vasthoudt. Ondanks al deze medicijnen zijn er nog steeds veel patiënten met hart- en vaatziekten die een hoog risico blijven houden op het krijgen van nieuwe hart- en vaatziekten en op vroegtijdig overlijden. Het risico wat overblijft nadat de optimale reguliere behandeling (zoals hierboven beschreven) is opgestart, wordt 'residuaal risico' genoemd. Om de prognose van patiënten met hart- en vaatziekten te kunnen verbeteren, is het belangrijk dat er risicofactoren worden geïdentificeerd die bijdragen aan dit residuaal risico. Deze risicofactoren zouden namelijk aangrijpingspunten kunnen vormen voor aanvullende en nieuwe behandelingen. Daarnaast is het belangrijk om het residuaal risico en de effecten van aanvullende behandelingen te kunnen voorspellen voor individuele patiënten, zodat een intensievere behandeling vooral kan worden voorgeschreven aan patiënten die dit het hardste nodig hebben (patiënten met het hoogste residuaal risico) en hier het meeste baat bij hebben (patiënten met het grootste verwachte behandeleffect).

Dit proefschrift bestaat uit twee delen: **Deel I** richt zich op risicofactoren die bijdragen aan het residuaal risico op hart- en vaatziekten, waar **Deel II** zich richt op het voorspellen van het residuaal risico en de effecten van aanvullende behandelingen voor individuele patiënten met hart- en vaatziekten.

Deel I. Risicofactoren die bijdragen aan het residuaal risico op hart- en vaatziekten

Er zijn meerdere risicofactoren waarvan wordt gedacht dat ze mogelijk bijdragen aan het residuaal risico op hart- en vaatziekten. Onder deze risicofactoren zijn factoren die samenhangen met overgewicht, zoals laaggradige ontsteking en het metabool syndroom (een verzamelnaam voor een aantal verstoringen in het bloed en vetweefsel die plaats

kunnen vinden bij mensen met overgewicht). Met de wereldwijde toename van overgewicht en obesitas zouden deze factoren wel eens steeds belangrijker kunnen gaan worden.

In **Hoofdstuk 2**, hebben we het verband tussen C-reactief proteïne (CRP), een eiwit in het bloed dat de mate van ontsteking in het lichaam aangeeft, en het optreden van nieuwe hart- en vaatziekten onderzocht. Hieruit kwam naar voren dat het hebben van een hoge CRP concentratie in het bloed, en dus een grotere mate van ontsteking in het lichaam, in verband staat met een hoger risico op het krijgen van nieuwe hart- en vaatziekten zoals een hartinfarct of beroerte, en op vroegtijdig overlijden. In **Hoofdstuk 3**, hebben we hieraan toegevoegd dat een hoge CRP waarde ook in verband staat met een hoger risico op het ontwikkelen van hartfalen. Het kwart van de patiënten met het hoogste CRP had een anderhalf tot tweeënhalf keer zo hoog risico op toekomstige hart- en vaatziekten dan het kwart van de patiënten met het laagste CRP. Het verband tussen CRP en hart- en vaatziekten was onafhankelijk van reeds bekende risicofactoren (zoals cholesterol en bloeddruk), medicatiegebruik en het type hart- en vaatziekten, en bleef constant tot meer dan 15 jaar nadat het CRP was gemeten. Deze resultaten laten zien dat laaggradige ontsteking een belangrijke drijvende factor is van het residuaal risico op hart- en vaatziekten. Dit zou kunnen betekenen dat ontstekingsremmende medicijnen, zoals bijvoorbeeld colchicine, een belangrijke rol zouden kunnen spelen in het voorkomen van nieuwe hart- en vaatziekten in patiënten waarbij het risico niet genoeg wordt teruggebracht met de reguliere behandeling.

In **Hoofdstuk 4**, hebben we het verband tussen de aanwezigheid van het metabool syndroom en het optreden van hartfalen onderzocht. Men spreekt van het metabool syndroom op het moment dat een patiënt voldoet aan minimaal drie van de volgende vijf criteria: vergrote buikomtrek, verhoogde bloeddruk, verhoogde vetzuren in het bloed, verlaagd HDL-cholesterol (het "goede" cholesterol) in het bloed, en een verhoogd suikergehalte in het bloed. Ons onderzoek wees uit dat het hebben van het metabool syndroom in verband staat met een 32% hoger risico op hartfalen. Van de individuele componenten van het metabool syndroom bleek het met name de vergrote buikomtrek te zijn die bijdraagt aan dit hogere risico. Ook dit verband was onafhankelijk van reeds bekende risicofactoren en medicatiegebruik. Daarnaast was het verband ook onafhankelijk van het ontwikkelen diabetes (suikerziekte), hetgeen nog wel eens wordt gezien als de belangrijkste link tussen overgewicht en hart- en vaatziekten. Dit hoofdstuk laat zien dat verstoringen in het bloed en vetweefsel die samenhangen met overgewicht ook een belangrijke bijdragende factor zijn aan het residuaal risico op hart- en vaatziekten. Dit ondersteunt het belang van gewichtsverlies in patiënten met hart- en vaatziekten. Daarnaast suggereert het dat behandelingen die aangrijpen op (componenten van) het metabool syndroom ook een rol zouden kunnen spelen in het voorkomen van nieuwe hart- en vaatziekten in patiënten met een hoog residuaal risico. Voorbeelden van dergelijke behandelingen zijn het bloedvet-

verlagende medicijn icosapent ethyl en recent ontdekte medicijnen die onder andere het suikergehalte in het bloed verlagen maar tot op heden met name worden gebruikt in mensen met diabetes.

Deel II. Geïndividualiseerde voorspellingen van residuaal risico en behandeleffecten

Enkel weten welke factoren bijdragen aan het residuaal risico op hart- en vaatziekten is niet voldoende om het exacte risico van een individuele patiënt in te schatten, omdat dit risico door een combinatie van veel verschillende risicofactoren wordt bepaald. Aangezien er grote verschillen zitten in risicofactoren tussen patiënten, bestaat er ook een grote spreiding in het residuaal risico, waarbij sommige patiënten een heel hoog risico lopen op toekomstige hart- en vaatziekten, terwijl anderen slechts een heel laag risico hebben onder reguliere behandeling. Door deze grote verschillen in risico, zijn er ook grote verschillen in de effectiviteit van behandelingen tussen patiënten. Als voorbeeld: een medicijn dat het risico op hart- en vaatziekten met 20% verlaagt, leidt in een patiënt met een 10-jaarsrisico van 15% tot een absolute risicodaling van 3% (van 15% naar 12%), terwijl ditzelfde medicijn in een patiënt met een 10-jaarsrisico van 50% leidt tot een absolute risicodaling van wel 10% (van 50% naar 40%). In het eerste geval zul je 33 van dergelijke patiënten gedurende 10 jaar moeten behandelen om bij een van hen hart- en vaatziekten te voorkomen, terwijl dit in het tweede geval maar 10 patiënten zijn. Met andere woorden, de effecten van een behandeling zijn in principe het grootst in patiënten met het hoogste risico. Tegelijkertijd is de behandelduur ook van invloed op het totale behandeleffect. Een jonge patiënt met een lange resterende levensverwachting, kan over een lange periode behandeld worden en dus ook lang profiteren van de positieve effecten van de behandeling. Hierdoor is het totale behandeleffect vaak groter dan bij een oude patiënt met een zeer korte levensverwachting. Bij patiënten met een laag residuaal risico of een korte levensverwachting kan het dus zijn dat de voordelen van een aanvullende behandeling niet opwegen tegen de nadelen, zoals de bijwerkingen en kosten van de behandeling. Daarom is het dus belangrijk om geïndividualiseerde schattingen te hebben van het residuaal risico en het te verwachten effect van behandelingen, zodat op basis hiervan behandelbeslissingen kunnen worden gemaakt door de arts in samenspraak met de patiënt. Dergelijke schattingen kunnen worden gemaakt met behulp van een voorspelmodel, een soort formule die op basis van patiëntkenmerken iemands risico op hart- en vaatziekten uitrekent. Voor patiënten met hart- en vaatziekten als een hartinfarct of beroerte bestaan er reeds dit soort modellen, zoals de SMART2 risicoscore voor 10-jaarsvoorspellingen en het SMART-REACH model voor levenslange voorspellingen. Het gebruik van deze modellen wordt aanbevolen door de Europese richtlijnen voor cardiologen.

Echter, voor patiënten met chronisch hartfalen bestonden er nog geen voorspelmodellen die werden aanbevolen door de Europese richtlijnen. In **Hoofdstuk 5**, hebben wij daarom het LIFE-HF model ontwikkeld. Dit model kan worden gebruikt om op basis van een aantal patiëntkenmerken (leeftijd, geslacht, medische voorgeschiedenis, bloeddruk, hartfunctie en nierfunctie) het risico op overlijden in de komende 2 jaar en 5 jaar te voorspellen voor een individuele patiënt. Daarnaast voorspelt het ook de levensverwachting van de patiënt. Tevens kan het model het risico op een ziekenhuisopname door toenemend hartfalen voorspellen. Door het model te testen in grote aantallen patiënten hebben we laten zien dat het model goed onderscheid kan maken tussen patiënten met een hoog en een laag risico en dat het risico dat wordt voorspeld door het model meestal erg in de buurt komt van het daadwerkelijke risico van een patiënt. Naast risico's, kan het LIFE-HF model ook de effecten van verschillende behandelingen voor hartfalen voorspellen. Hiervoor hebben we de behandeleffecten die zijn vastgesteld in grootschalige geneesmiddelenonderzoeken toegevoegd aan het model. Op deze manier kan het model voorspellen met hoeveel procent het risico zal dalen en met hoeveel jaar de levensverwachting zal stijgen indien een bepaalde behandeling gestart wordt. Het LIFE-HF model zou hiermee als hulpmiddel kunnen dienen voor artsen om patiënten te selecteren die het meeste baat hebben bij een aanvullende behandeling. Ook zou het artsen kunnen helpen om de prognose van de ziekte en de effecten van behandeling beter te communiceren naar hun patiënten, waardoor het mogelijk wordt om samen met de patiënt behandelbeslissingen te maken. Dit zou ertoe kunnen leiden dat nieuwe bewezen effectieve behandelingen meer gaan worden toegepast en de prognose van patiënten met hartfalen wordt verbeterd.

In de Europese cardiologie richtlijnen is een lijstje opgenomen met aanvullende behandelingen die kunnen worden overwogen in patiënten met een hoog residuaal risico op hart- en vaatziekten. Op dit lijstje staan onder andere het ontstekingsremmende medicijn colchicine (in een lage dosis), maar ook het nog intensiever verlagen van het cholesterol en de bloeddruk. De vraag is dan welke behandeling het meest effectief is voor de individuele patiënt. In **Hoofdstuk 6**, hebben we het SMART-REACH model gebruikt om in een grote populatie van patiënten met een hartinfarct of hartoperatie (dotter of omleiding) in de voorgeschiedenis voor iedere patiënt het effect van lage-dosis colchicine, aanvullende cholesterolverlaging en aanvullende bloeddrukverlaging te voorspellen en met elkaar te vergelijken. Het effect van de behandelingen werd uitgedrukt in het aantal gewonnen levensjaren zonder nieuwe hart- en vaatziekten. Hieruit kwam naar voren dat lage-dosis colchicine naar schatting gemiddeld leidt tot 2.0 gewonnen vaatziektevrije levensjaren, ten opzichte van 1.2 en 0.7 vaatziektevrije levensjaren met respectievelijk aanvullende cholesterolverlaging en aanvullende bloeddrukverlaging. Het voorspelde behandeleffect van lage-dosis colchicine was groter dan dat van aanvullende cholesterolverlaging in 70% en aanvullende bloeddrukverlaging in 68% van de patiënten. Deze resultaten laten zien dat

welke behandeling het meest effectief is in het verlagen van het residuaal risico op hart- en vaatziekten verschilt per patiënt en dat de keuze voor het type behandeling dus moet worden afgestemd op het individu, bijvoorbeeld door gebruik te maken van het SMART-REACH model. In het algemeen, wijst dit onderzoek uit dat in de meeste gevallen het toevoegen van de ontstekingsremmer lage-dosis colchicine meer oplevert dan het intensiveren van de cholesterol- en bloeddrukverlagende behandeling.

Een andere behandeling die ook in de Europese richtlijnen genoemd wordt als optie om te overwegen als aanvulling op de reguliere behandeling van patiënten met hart- en vaatziekten is icosapent ethyl. Dit medicijn bevat een hoge dosis omega-3 vetzuren, een gezond vetzuur dat ook veel zit in vis en plantaardige oliën, en wat het gehalte van "slechte" vetten in het bloed verlaagd. De richtlijnen schrijven voor dat dit medicijn met name overwogen dient te worden in patiënten met een zeer hoog residuaal risico. Dit roept de vraag op of het effect van icosapent ethyl inderdaad afhankelijk is van de hoogte van iemands risico, of dat het wellicht ook effectief kan zijn in patiënten met een minder hoog risico. In **Hoofdstuk 7**, hebben we aangetoond dat icosapent ethyl het risico op nieuwe hart- en vaatziekten met 38% verlaagd in patiënten met een laag uitgangsrisico, en met 22% in patiënten met een hoog uitgangsrisico. De absolute risicodaling over een periode van ongeveer 5 jaar was 3.9% in laag-risico patiënten en 5.6% in hoog-risico patiënten. Met andere woorden, de relatieve risicovermindering door behandeling met icosapent ethyl is groter in laag-risico patiënten, waardoor de absolute risicovermindering in deze patiënten, ondanks hun lage uitgangsrisico, toch substantieel is en in de buurt komt van die in hoog-risico patiënten. Dit betekent dat icosapent ethyl ingezet kan worden voor het voorkomen van nieuwe hart- en vaatziekten in zowel patiënten met een hoog residuaal risico, als patiënten met een wat lager risico. Wellicht dus dat dit medicijn breder zou moeten worden ingezet dan op dit moment wordt aanbevolen door de Europese richtlijnen.

Naast dat de effecten van een behandeling kunnen afhangen van het risico en de resterende levensverwachting van een patiënt, kunnen ze ook veranderen over de tijd. Dit is relevant voor behandelingen van hart- en vaatziekten aangezien deze vaak voor een lange periode (meestal levenslang) moeten worden doorgebruikt. Weten of en hoe de effecten van een behandeling veranderen over de tijd is belangrijk voor het bepalen van het juiste start- en stopmoment en voor het voorspellen van de langetermijneffecten zoals in de **Hoofdstukken 5-7**. In **Hoofdstuk 8**, hebben we de resultaten van alle belangrijke onderzoeken die tot op heden zijn verricht naar de effectiviteit van cholesterolverlagende behandelingen gecombineerd, om het verloop van de effecten van cholesterolverlaging op het risico op hart- en vaatziekten over de tijd te analyseren. Hieruit kwam naar voren dat in patiënten met een voorgeschiedenis van hart- en vaatziekten, het effect van cholesterolverlaging niet verandert over de tijd, in ieder geval niet gedurende de eerste zeven jaar van de behandeling. Echter,

in mensen met risicofactoren voor hart- en vaatziekten (zoals diabetes of hoge bloeddruk) maar die nog niet eerder een vorm van hart- en vaatziekten hebben doorgemaakt, nam het effect van cholesterolverlaging af met het toenemen van de leeftijd. Dit betekent dat artsen er naar zouden moeten streven om zo vroeg mogelijk te starten met cholesterolverlagende behandeling in jonge mensen die een hoog risico lopen om later hart- en vaatziekten te krijgen. Voor patiënten die al hart- en vaatziekten hebben doorgemaakt, suggereren deze resultaten dat het voordelig is om de cholesterolverlagende behandeling levenslang voort te zetten.

Conclusie

Laaggradige ontsteking en aan overgewicht gerelateerde verstoringen in het bloed en vetweefsel zijn belangrijke drijvende factoren van het residuaal risico op hart- en vaatziekten. Bestaande en toekomstige behandelingen gericht op deze risicofactoren zouden een belangrijke rol kunnen spelen in het verlagen van dit risico. Bij het maken van beslissingen over het starten van aanvullende behandelingen in patiënten met hart- en vaatziekten, moet rekening worden gehouden met de risicofactoren, het residuaal risico en de levensverwachting van de individuele patiënt. Idealerwijs, zouden modellen die rekening houden met al deze factoren om het residuaal risico en de te verwachten effecten van aanvullende behandelingen te voorspellen voor individuele patiënten moeten worden gebruikt om behandelbeslissingen en het gesprek hierover tussen arts en patiënt te ondersteunen. Dit heeft de potentie om ervoor te zorgen dat aanvullende bewezen effectieve behandelingen meer zullen worden toegepast in die patiënten die daar het meeste baat bij hebben, wat de prognose van patiënten met hart- en vaatziekten sterk zou kunnen verbeteren.

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A

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feestjes tijdens vascuweekenden was jij dan ook altijd de laatste die naar huis wilde, mits je geen trein hoefde te halen natuurlijk. Ook het atten van de 0,5 liter slagroom was een van de hoogtepunten uit het van Geuns. Eline, wat was ik blij dat er een mede-Houtenaar in de groep zat. Beetje jammer dat je Houten eigenlijk helemaal niet leuk vond… Desondanks bracht je heel veel sfeer in de groep, en liet je niet alleen ons, maar ook de rest van de mensen in het van Geuns meegenieten van je harde, zeer aanstekelijke lach. Wat ik ook heb gewaardeerd is dat wij af en toe samen lekker konden zeuren op alles en iedereen, en de hele wereld. Dit luchtte vaak enorm op. Ik hoop dat je ooit bij zinnen komt, ontdekt dat Houten toch best leuk is, en dat we elkaar daar dan weer tegenkomen. Maria, jij was zo'n belangrijk onderdeel van de groep dat het bij mij weken heeft geduurd voordat ik door had dat jij helemaal niet bij de vascu promoveerde. Je was altijd vrolijk en positief en zorgde vaak voor een gezonde dosis meligheid met je oneindige stroom aan slechte woordgrappen. Wist je even geen woordgrap meer te bedenken, dan zette je gewoon het liedje 'Ik wil ook zo'n broek met van die zakken aan de zijkant' op, en dan was de sfeer ook weer helemaal goed. Ook fijn dat we elkaar konden helpen met, c.q. konden huilen over, onze eeuwig durende predictieprojecten. Helena, ik bewonder jouw empathie, en hoe jij altijd interesse toont in andere mensen. Je zegt wel eens dat je nog moet wennen aan de Hollandse directheid, maar misschien moeten wij Hollanders gewoon wat overnemen van jouw Deense vriendelijkheid. Fijn dat we elkaar konden helpen bij ingewikkelde lifetime predictie zaken. Het naleven van jouw motto 'stop whining, start shining' lukte hierbij alleen niet altijd… Tot slot denk ik dat er weinig moeders zijn die zo'n coole party trick in huis hebben. Marga, als jij in het van Geuns was, werd er een tikkeltje minder gewerkt, maar een heleboel meer gelachen. Vooral als je in de andere kamer ging zitten om je te "concentreren" om vervolgens wel om de haverklap koffie te komen halen in onze kamer en gezellig te kletsen. Jij was onze onbetwiste chef snacks. Ik hoefde nooit bang te zijn, want wij hadden een vrijwel identieke smaak in snacks, dus als ik jou liet kiezen, wist ik zeker dat ik kreeg wat ik lekker vond. Bedankt voor alle oreo's die je voor me hebt gekocht. Zonder deze beloningen na iedere afgeronde analyse of paragraaf van een manuscript, was dit proefschrift er waarschijnlijk nooit gekomen. Ook fijn dat toen een docent tijdens een saai epi college vroeg of ze de boel dan maar snel moest afronden, jij gewoon zonder gemute microfoon keihard "Ja, graag!" zei. Nadia, jij liet promoveren eruit zien alsof het je totaal geen moeite kostte, jij had altijd alles onder controle. En als dat even minder dreigde te worden, dan maakte je gewoon snel een mega overzichtelijk to-do lijstje en een perfect doordachte mappenstructuur voor je project, en dan was alles weer goed. Hier heb ik heel veel bewondering voor. Wat wel relatable was voor mij en ook fijn, was dat wij allebei figuren maakten in PDF en daar dan dingen in gingen aanpassen, ondanks protesten van collega's (amateurs). Jij bent altijd super aardig tegen iedereen, volgens mij komen woorden als conflict en ruzie niet eens in jouw woordenboek voor. Dat siert jou enorm. Alhoewel ik één keer een lichtelijk gefrusteerde, strenge versie van Nadia naar boven heb zien komen. Dit was voldoende om te weten dat

ik die nooit tegen me wil hebben. Iris, wat ik bijzonder vind aan jou is hoe ongekend makkelijk jij contact legt met mensen. Er is denk ik niemand op deze wereld waarmee jij niet even een gezellig small talk gesprekje of serieuze discussie over politiek of klimaat zou kunnen hebben. Daarnaast viel je organisatietalent op, ook al mocht je dit van sommige mensen op een gegeven moment niet meer doen… Multitasken kon je ook als de beste: jij bent de enige onderzoeker die ik ken die op het ene scherm een analyse in R kon draaien, terwijl je op het andere scherm keek naar schattige kattenfilmpjes, een goed restaurant voor die avond, of een nieuwe plek om met de paarden naartoe te gaan. De kattenfilmpjes kon ik ook wel waarderen, en leuk dat we af en toe over onze eigen katten konden praten. Nog sorry voor onze gebrekkige orthopedische kennis waardoor we je een weekend lang op een gebroken voet door Lissabon hebben laten lopen. Katrien, nog zo'n unieke persoonlijkheid, en eentje die echte Brabantse gezelligheid bracht in de groep. Wat ik het grappigste vind aan jou is jouw taalgebruik. Het lijkt wel alsof jij een soort eigen taal hebt ontwikkeld die een mengeling is van Brabants, Engels, straattaal, oud-Hollandse spreekwoorden en Spaans. Ik bewonder jouw perfectionisme en super uitgebreide medische kennis. Je vroeg nog wel eens of je mijn brein mocht lenen. Nou, ik zou je adviseren het jouwe te houden. Lukas, wat kwam er met jou een bom aan energie het van Geuns binnen. Ik dacht dat ik jong was, maar naast jou in Lissabon voelde ik me haast bejaard. Hier maakten we ook kennis met een andere eigenschap van jou: jij raakt altijd kwijt. Deels komt dit doordat jij, waar je ook bent, altijd bekenden tegenkomt. Waarschijnlijk ben je tijdens het lezen van dit stukje alweer 3 keer gestopt om iemand gedag te zeggen. Hoe kan het dat de enige persoon uit onze groep die in Groningen heeft gestudeerd, zoveel mensen kent in Utrecht?! Dit laat zien hoe sociaal jij bent. Wat ik ook mooi vond is dat als wij aan het klagen waren over iets, of iets totaal afbrandden, jij steevast zei: "oh dat valt toch wel mee, ik vind het wel leuk". Dit kenmerkt jouw enthousiasme en positiviteit. Joris, alsof Lukas het energieniveau in het van Geuns nog niet genoeg had opgekrikt, was jij daar ineens. Maar wat een aanwinst ben jij gebleken voor onze groep. Je brengt enorm veel sfeer in de groep met je goeie grappen en gekke stemmetjes/typetjes. Ik ken niemand die zo gezellig is op feestjes op alleen maar ginger ales en ice teas. Daarnaast vond ik de R skills en kennis van statistiek die jij van begin af aan liet zien, bizar. Al maakte je hierbij wel graag gebruik van ChatGPT, als het op medische kennis aankwam leek je zelf af en toe wel een wandelende AI-bot. Wel vind ik het bijzonder dat jij iedere dag een kaassoufflé eet bij de lunch terwijl je dit thuis nooit eet (gratis tip: koop een airfryer), en dat iemand met zo veel kwaliteiten woont in een huis zonder ramen. Als ik voor wat voor rede dan ook een vraag niet kan beantwoorden tijdens mijn verdediging, is er niemand aan wie ik dit meer zou toevertrouwen dan aan jou. Bedankt dus dat je mijn paranimf wil zijn.

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Ten eerste de leden van D4E. Wat ben ik blij dat wij meer dan 10 jaar na de middelbare school nog steeds zo'n hechte vriendengroep zijn. Eigenlijk zijn we meer dan een vriendengroep, een soort community, met onze eigen tradities, spelletjes en humor. Ik hoop dat we onze maandelijkse activiteiten en jaarlijkse vakantie nooit zullen opgeven! Even een persoonlijke noot voor jullie allemaal. Tim, wij kennen elkaar al 22 jaar, hebben van groep 3 tot en met 6 VWO bij elkaar in de klas gezeten en zijn altijd goeie vrienden geweest en gebleven. Ik hou van je soms goeie, en soms ook gewoon hele rare humor. Ook vind ik het mooi hoe jij je volledig op iets kunt storten om daar de beste in te worden, wat tot zowel frustratie als trots van mij dan ook eigenlijk altijd lukt. Luuk, ook we go way back, weet je nog toen we de jongensdubbel tot en met 10 jaar wonnen op de clubkampioenschappen? Als jij om iets lacht, wordt het automatisch twee keer zo grappig (vooral als je een van ons uitlacht). Ook bewonder ik hoe jij doelen voor jezelf stelt en er vervolgens alles aan doet om die te bereiken, of het nou is in de sport of in studie/werk. Léon, als ik aan jou denk, denk ik als eerste aan je woordgrappen (van wisselende kwaliteit) en onze legendarische FIFA carrières (Crouch en kast Jones in de spits bij Stoke City met Kuyt op rechts, en natuurlijk het eeuwige talent Embolo bij iedere club waarmee we speelden). Ik vind het mooi om te zien hoe jij bent uitgegroeid van een jongen op de middelbare school die eigenlijk geen vak echt leuk vond en nergens echt voor ging, tot iemand die zich volledig geeft voor zijn eigen onderneming(en) en daarmee ook nog iets goeds doet voor andere mensen en de wereld. Erik, wat ik het mooiste vind aan jou is hoe oneindig fanatiek jij bent, tot op het roekeloze af (ik zie je nog door de lucht vliegen op die kartbaan in Duitsland). Met dit fanatisme weet jij altijd het beste uit jezelf te halen, zowel bij dingen waar je overduidelijk talent voor hebt, als ook bij dingen waar je ogenschijnlijk totaal niet voor gemaakt bent. Je bent altijd de eerste aanwezige bij onze activiteiten en altijd enthousiast om nieuwe ideeën te bedenken voor onze vriendengroep. Dan de Peters, van groot (2 meter) naar klein (1,94 meter). Peter

G, de manier waarop jij als de meest relaxte man op aarde door het leven lijkt te surfen vind ik bizar. Dit was al zo op de middelbare school: jij maakte je niet druk, leek ook niet echt je best te doen en van het woord plannen had je sowieso nog nooit gehoord, maar uiteindelijk lukte alles altijd alsnog. Nu twee studies en een toonaangevende baan verder en dit is nog steeds zo. Bovendien zorg je met jouw bulderende lach en geweldige kookkunsten voor heel veel sfeer in onze groep. Peter V, er is niemand op deze wereld die zo ontzettend lekker kan balen als jij: het zij om een blikje knakworsten wat niet open gaat, een gemiste put bij minigolf of een ballon die je maar niet opgeblazen krijgt. Maar wat jou zo'n sterk persoon maakt is dat jij nooit opgeeft. Ongeacht de tegenslagen die jij te verwerken krijgt, jij staat altijd weer klaar voor de volgende (spreekwoordelijke) bal. Dit heeft jou veel succes gebracht en gaat jou ook nog veel succes brengen in de sport (triatlon en dergelijke) en je werk.

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naar Atalanta), de tennisleraaropleiding, en alle dubbeltoernooien en competitiedagen, tot uitjes naar vele bierbrouwerijen, de vakantie naar Malaga, en de werkelijk ontelbare game-avonden. Op deze avonden doen we al jaren exact hetzelfde (FIFA spelen en bier drinken in willekeurige volgorde en het liefst tegelijk), maar toch gaat het nooit vervelen. Je kunt ons op een willekeurige plek op aarde droppen, wij hebben altijd lol en zullen altijd blijven lachen om elkaars slechte grappen. Ik wil je bedanken voor onze vriendschap en voor dat je mijn paranimf wil zijn tijdens mijn verdediging.

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Curriculum Vitae

Pascal Burger was born on August 30th, 1995 in Utrecht, the Netherlands. After graduating cum laude from College de Heemlanden in Houten in 2013, he studied Medicine at Utrecht University. During the first year of his study he also used his experience as a tennis player, having followed a 'Toptennis' programme and having played in national youth ranking tournaments in the past, to get his license as a tennis coach. During the next few years, outside study hours, he gave tennis lessons to kids and adults at several tennis clubs throughout the Utrecht region. His first experience with research came with a research internship at the Nederlandse Obesitas Kliniek, studying the effects of bariatric surgery on obesity-related comorbidities, under the supervision of Dr. Jan Westerink. Soon after, a second research internship at the Department of Internal Medicine of the UMC Utrecht followed, studying the outcomes of second opinions in general internal medicine, under the supervision of Dr. Jan Westerink and Dr. Bram Vrijsen. These research internships resulted in his first two scientific publications (not included in this thesis), and a first congress presentation at the 2019 International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) congress in Madrid. After a senior internship at the Department of Internal Medicine of the UMC Utrecht, he obtained his medical degree in early 2020.

In March 2020, he started working on this PhD thesis at the Department of Vascular Medicine of the UMC Utrecht, under the supervision of Prof. Frank Visseren, Dr. Jannick Dorresteijn, Dr. Stefan Koudstaal, and Dr. Arend Mosterd. During his PhD candidacy, he presented several of his works at national and international congresses: the 2021 Werkgroep Cardiologische centra Nederland (WCN) congress (Chapter 6), the 2022 Nederlandse Vereniging voor Cardiologie (NVVC) congress (Chapter 6), the 2022 European Society of Cardiology (ESC) congress (Chapters 2 & 6), and the 2023 ESC congress (Chapters 7 & 8). The LIFE-HF project (Chapter 5) was presented as late-breaking science at the 2022 ESC congress in Barcelona. He combined his PhD research with a Postgraduate Master in Clinical Epidemiology, and obtained this degree in the summer of 2022. Since writing this thesis, as of December 2023, he has started working as a medical doctor at the Department of Internal Medicine of the Diakonessenhuis in Utrecht.