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A new selection method to increase the health benefits of CVD prevention strategies

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Abstract

Background: Cardiovascular disease (CVD) prevention is commonly focused on providing individuals at high predicted CVD risk with preventive medication. Whereas CVD risk increases rapidly with age, current risk-based selection of individuals mainly targets the elderly. However, the lifelong (preventable) consequences of CVD events may be larger in younger individuals. The purpose of this paper is to investigate if health benefits from preventive treatment may increase when the selection strategy is further optimised.

Methods: Data from three Dutch cohorts were combined ($n = 47469$, men:women 1:1.92) and classified into subgroups based on age and gender. The Framingham global risk score was used to estimate 10-year CVD risk. The associated lifelong burden of CVD events according to this 10-year CVD risk was expressed as quality-adjusted life years lost. Based on this approach, the additional health benefits from preventive treatment, reducing this 10-year CVD risk, from selecting individuals based on their expected CVD burden rather than their expected CVD risk were estimated. These benefits were expressed as quality-adjusted life years gained over lifetime.

Results: When using the current selection strategy (10% risk threshold), 32% of the individuals were selected for preventive treatment. When the same proportion was selected based on burden, more younger and fewer older individuals would receive treatment. Across all individuals, the gain in quality-adjusted life years was 217 between the two strategies, over a 10-year time horizon. In addition, when combining the strategies 5% extra eligible individuals were selected resulting in a gain of 628 quality-adjusted life years.

Conclusion: Improvement of the selection approach of individuals can help to reduce further the CVD burden. Selecting individuals for preventive treatment based on their expected CVD burden will provide more younger and fewer older individuals with treatment, and will reduce the overall CVD burden.

Keywords

Cardiovascular disease, prevention, public health, risk prediction, burden of disease

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Introduction

One of the leading causes of mortality and morbidity worldwide is cardiovascular disease (CVD), with an expected burden of disease of 143 million disability adjusted-life years in 2020.[1,2] An important target of the World Health Organization (WHO) is to reduce the CVD burden by 30% before 2030.[3] A substantial part of this CVD burden can be prevented by positively influencing behavioural risk factors, e.g. blood

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pressure, smoking, diabetes and cholesterol, through preventive strategies.[4]

In the last decade, CVD risk prediction models have increasingly been used to predict individualised CVD risks. Based on their predicted 10-year CVD risk, several guidelines recommend the use of such prediction models to stratify individuals into risk categories, with a corresponding, recommended preventive treatment strategy. For example, cholesterol-lowering drug prescription is advocated in the case of a risk above the threshold of 7.5% risk of CVD events in 10 years according to the prediction model pooled cohort equations or above 10% risk according to the Framingham global risk score (FRS).[5,6] Over the years, many CVD risk prediction models have been developed, each with a specific risk threshold for 'high risk', implying that the classification of individuals who qualify for (preventive) treatment is, to say the least, not uniform. As different CVD risk prediction models may use different predictors and different coefficients, different models may classify different individuals as having a 'high risk'.[7] However, individuals have different health-related consequences of CVD, that is, loss in terms of life years due to (earlier) death, and health-related quality of life (QoL) due to non-fatal CVD events. Consequently, the health-related consequences of being classified as 'high risk' may differ per individual, depending on the current QoL and life expectancy. In addition, through combining the individual predicted risk of a CVD event with the expected consequences of this CVD event, it is possible to estimate the expected CVD burden of an individual. Aggregating these individual burden estimates can then provide an estimate of the total expected CVD burden in a specific population or group of individuals.

Inferences of the value and usefulness of current risk-based prevention strategies for CVD, however, are solely based on their ability to provide accurate risk estimations and do not include any consideration of the expected health loss due to the occurrence of the predicted CVD event(s). As a consequence, the selection of high-risk individuals, in whom preventive treatment is initiated, may include individuals at high risk but with a low expected CVD burden, for example due to high age. Similarly, young individuals with a relatively low CVD risk would not receive preventive treatment, even though their expected CVD burden (because they will lose life years due to the consequences of a non-fatal or fatal CVD event) could be substantial. For example, the overall expected burden due to fatal strokes may be higher in young individuals than in older individuals even though the risk of a stroke being fatal increases with age. Indeed, it has been shown that the estimated consequences in terms of health loss of having a CVD event vary widely with age.[8,9] This implies that selecting individuals for preventive treatment based on predicted risks only may not necessarily result in the most effective nor the most efficient strategy to reduce CVD burden on population or group level.

In this paper, we investigate if the selection strategy for preventive CVD treatment can be improved by considering a threshold based on expected CVD burden rather than on predicted CVD risk. We illustrate how selected individuals differ, and how this influences the effectiveness of a hypothetical preventive treatment strategy, in a combination of Dutch cohorts.

Methods

To illustrate if CVD preventive strategies can be improved by considering a burden threshold rather than a risk threshold, we combined different cohort datasets from The Netherlands. This resulted in a heterogeneous large dataset with different age groups and risks.

First, the MORGEN cohort was used.[10,11] The MORGEN cohort is a subset of the general population from Maastricht, Amsterdam and Doetinchem, including 20,423 men and women with baseline and follow-up data.[12,13] The second cohort (PROSPECT) is a cohort 16,401 women for whom baseline and follow-up data are available after linkage.[14] Finally, we used data from 10,645 patients with a history or recent diagnosis of manifest atherosclerotic disease enrolled in the Secondary Manifestations of ARTerial disease (SMART) Study between January 1996 and February 2014.[15] A reason to include individuals with a CVD history in the analysis was that these individuals were older, had more risk factors and a higher occurrence of CVD events.

Combined across these three cohorts 47,469 individuals were eligible for the analysis. The man to woman ratio was 1:1.92. Baseline information on the individuals per cohort is shown in Supplementary Appendix 1 Table 1.

Estimating CVD risk and CVD burden

The FRS is a widely used CVD risk prediction model containing easy to measure predictors, e.g. age, gender and systolic blood pressure (see Supplementary Appendix 1 Table 2).[5,15] The FRS prediction model was originally not developed to estimate the risk of a CVD event for individuals with a CVD history. Currently, there are multiple prediction models available for secondary risk estimations; for example, the SMART risk score.[16,17] Therefore, the FRS was used to estimate CVD risks of MORGEN and PROSPECT individuals and the SMART risk score was used to estimate CVD risks of SMART individuals.

As the FRS predicts the 10-year risk of CVD events (Supplementary Appendix 1 Table 3, columns 1–3), only events occurring within 10 years from baseline (start of cohort) were included in the event distribution and further analysis. Furthermore, for each cohort, the event distribution according to the FRS was determined and presented separately for men and women. The observed event distribution was determined per International Classification of Disease version 10 (ICD-10) code. The event distribution for men and women is shown per cohort in Supplementary Appendix 1 Table 3.

To conform to methodological guidelines in prediction modelling, the FRS prediction model was first recalibrated to each cohort, by updating the baseline hazard and linear predictor better to match each of the three separate cohorts.[18,19] Measures of the statistical performance after this recalibration, i.e. discrimination and calibration, were determined per cohort and separately for men and women. The statistical performance of the FRS after recalibration is presented in Supplementary Appendix 2. Note that the SMART risk score was originally developed on the SMART cohort, therefore recalibrating was not necessary and only the statistical performance of the FRS is presented.

To estimate each individual's expected burden of CVD, the individual's predicted risk was multiplied by the consequences of the events, i.e. multiplying the probability of having CVD events with the consequences of experiencing CVD events. The consequences of the occurrence of CVD events were estimated and expressed in quality-adjusted life years (QALYs) lost and determined per individual. The consequences were determined as a product of the observed event distribution, the impact on QoL following different CVD event types (utilities), and average life expectancy, representing years of life lost for fatal CVD events. The observed event distribution was determined separately for cohort, gender and age groups. The life expectancy of a (healthy) individual only depended on age and gender, and the impact of CVD events on QoL was assumed to be similar for all individuals, i.e. no separate values were used for cohort, gender, or age groups. Supplementary Appendix 3 presents more information on the impact of CVD events on QoL and the formula used to estimate CVD burden. In addition, Supplementary Appendix 3 also provides an example of the calculation of CVD burden per individual.

Description of the selection process

In this study, we compared four different scenarios of the selection of high-risk individuals for preventive strategies.

For scenario 1, risk-based selection, we investigated individuals at high absolute risk, according to the FRS, with a 10% risk threshold as recommended in the US guideline for CVD preventive strategies.[6] For consistency, we used one single threshold instead of two thresholds for each prediction model.

For scenario 2, burden-based selection, individuals were ranked according to the individual expected CVD burden. Individuals with the highest burden were then selected, until exactly the same number of individuals was selected as when applying scenario 1. The CVD burden of the selected individual with the lowest CVD burden was defined as the burden threshold (i.e. all individuals with a burden exceeding this threshold were selected). Selecting exactly the same number of individuals in scenarios 1 and 2 allowed comparison of the expected benefits from preventive treatment across these two scenarios.

Scenario 3 combined the selection procedures of scenarios 1 and 2. Here, individuals were selected if they had a high predicted risk (scenario 1), a high expected burden (scenario 2) or both. It was expected that the two groups of selected individuals would largely overlap between scenarios 1 and 2 because 'high predicted risk' would often lead to 'high expected burden'. However, applying a burden-based selection as in scenario 2 might result in not selecting, and thus withholding treatment, from a small subgroup of individuals with a high CVD risk currently considered for preventive treatment (scenario 1). Scenario 3 thus reflects the notion that withholding relatively cheap and effective preventive medication from individuals with a high CVD risk but with a low expected burden may not be desirable.

Given selection on both risk and burden, scenario 3 will select a larger number of individuals for preventive treatment than scenarios 1 and 2. Therefore, comparison of outcomes between these scenarios is not possible. To assess the impact of combined selection, scenario 4 was defined as an extension of scenario 2, again selecting individuals on burden, but now selecting exactly the same number of individuals as in scenario 3.

In Supplementary Appendix 6, two figures are presented to show more details on the four investigated scenarios, where the marks represent the selected individuals according to the four scenarios.

Description of hypothetical treatment

For those individuals selected for preventive strategies in either of the four scenarios, hypothetical treatment was considered; for example, poly pill, blood pressure-lowering medication or aspirin. We assumed that all individuals adhered to this medication and that medication would lower the risk of CVD events by 35%,

similarly across all types of CVD events included in the composite endpoint.[20] As preventive CVD medication often has side effects, these were included in the analysis (for details see Supplementary Appendix 3 Table 2).

After preventive treatment, the risk reduction on CVD events was applied to each individual. For all four scenarios of selecting individuals, the number of selected individuals, average values of risk and burden, and average values of reduction in CVD burden after treatment were determined. The expected number of events was calculated by summing the estimated CVD risk of the selected individuals. After preventive treatment, the individual risk estimates were multiplied by 35% which resulted in a decrease of the average CVD risk and number of expected CVD events. Furthermore, the gain in QALYs was determined for scenarios 2–4 compared with scenario 1 (reference scenario). Scenarios were also compared among each other.

Results

Estimating CVD risk and CVD burden

Figure 1 (upper part) shows the barplot for the predicted CVD risks according to the FRS per age group and gender, with vertical lines representing the 5th and 95th percentile values. The risk estimates vary widely between men and women. As a consequence, men have on average a higher predicted risk compared to women. As expected, there was a trend towards higher CVD risk with increasing age, both for men and women.

The expected CVD burden increased up to the age of 75 years for men and women and decreased thereafter (Figure 1, lower part). In addition, the burden estimates were higher for men than for women for two reasons. First, CVD risk also partially determines CVD burden and CVD risks were higher for men. Second, there were differences in the observed event rates; for example, men more often experienced a fatal CVD event than women (Supplementary Appendix 4 Table 2). This was due to the high proportion of men in the SMART cohort. As this subgroup has the highest risk of fatal CVD, in the combined cohort the CVD risk for men exceeds that for women. This effect is therefore not apparent in the other cohorts.

The relation between CVD risk and CVD burden is shown in Supplementary Appendix 5 Figure 1.

Description of the selection process

In the combined cohort, applying the risk-based strategy to select individuals resulted in a selection of 32.1%

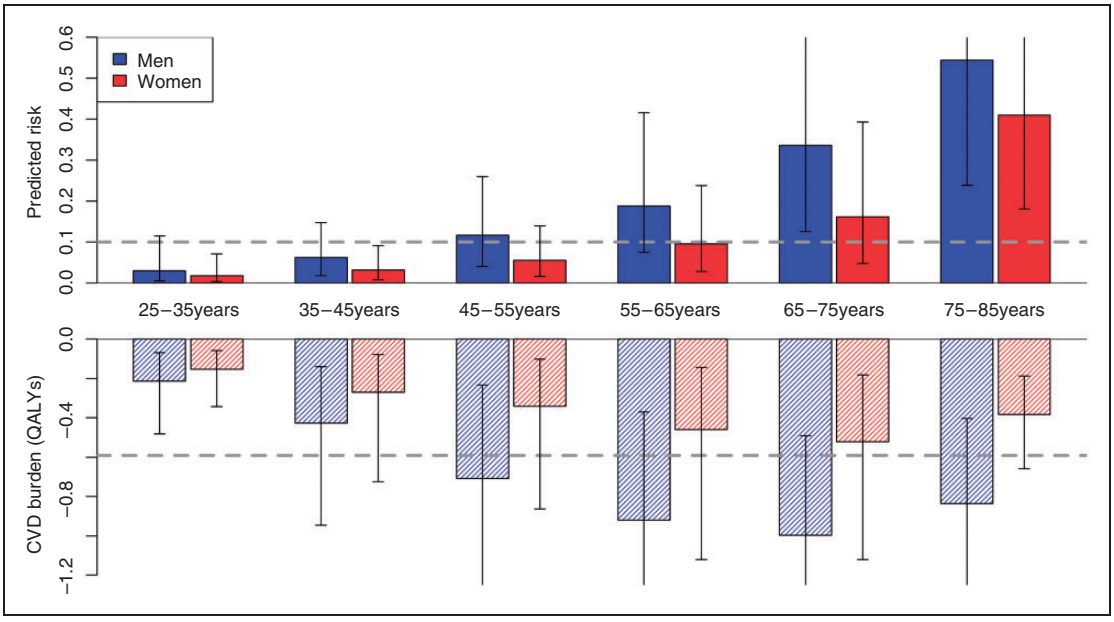

Figure 1. Bar plot of the average values for the predicted cardiovascular disease (CVD) risk (upper part) and for the expected CVD burden (lower part), per age group (for visual clarity, this figure is present with some limit values for the estimates of CVD risk and burden). The vertical lines represent the 5th and 95th percentile values of the predicted risks in each group and not the confidence intervals for the expected mean CVD risk estimates. Furthermore, the grey dotted lines represent the threshold with a risk threshold of 10% (upper part) and a burden threshold of 0.59 quality-adjusted life-years (QALYs) (lower part), with the lower part indicating that individuals with an expected lifelong health loss due to CVD (i.e. CVD risk multiplied by CVD event consequences) exceeding 0.59 QALYs would be eligible for preventive treatment.

Table 1. Overall impact of hypothetical preventive treatment when the selected individuals are based on estimates of CVD risk (threshold of 10%) or CVD burden (threshold of 0.59 QALYs) according to FRS.

	Selection				Impact		
	Total selected individuals (%)	Average CVD risk	Expected number of events	Estimated CVD burden (QALYs lost)	With preventive treatment (QALYs lost)	Expected number of events	Gain in QALYs
Scenario 1: risk-based strategy							
Men	8182 (50.4%)	0.24	1961	11320 (1.38)	7362 (0.90)	1275	3958 (0.48)
Women	7081 (22.7%)	0.19	1334	7191 (1.02)	4675 (0.66)	867	2516 (0.36)
Men and Women	15,263 (32.1%)	0.21	3295	18,511 (1.21)	12,037 (0.79)	2142	6474 (0.42)
Scenario 2: burden-based selection							
Men	8887 (54.7%)	0.23	2003	11937 (1.34)	7764 (0.87)	1302	4174 (0.47)
Women	6376 (20.4%)	0.19	1202	7195 (1.13)	4678 (0.73)	781	2517 (0.39)
Men and Women	15,263 (32.1%)	0.21	3205	19,133 (1.25)	12,441 (0.82)	2083	6691 (0.44)

CVD: cardiovascular disease; QALYs: quality-adjusted life-years.

of all individuals, i.e. 15,263 individuals had a predicted risk above the threshold of 10% (scenario 1). However, the percentage of selected men and women was not similar due to different risk estimates, 50.4% and 22.7% of all men and women were considered for the hypothetical treatment, respectively (Table 1, selection part). In addition, men were selected for treatment at a much earlier age than women, with about 50% of men over 45 years of age qualifying for treatment, while a similar percentage was reached only in women between 65 and 75 years of age.

At the same proportion of selected individuals for scenario 2 (the burden-based strategy), the burden threshold was 0.59 QALYs. This indicates that, on an individual level, an expected lifelong health loss due to CVD (i.e. CVD risk multiplied by CVD event consequences) exceeding 0.59 QALYs would make individuals eligible for preventive treatment. Overall, 32.1% of all individuals had an expected CVD burden exceeding 0.59 QALYs and therefore were assigned to preventive treatment in scenario 2.

The total number of the selected individuals was, by definition, similar, the percentage of men and women changed across the selection strategies. In scenario 2, more men, and therefore fewer women, were considered compared to scenario 1 (Table 1, column 2). Although in scenario 2 the total number of selected individuals did not change, individuals were selected based on their estimated CVD burden rather than on their CVD risk. Consequently, certain individuals were selected in scenario 2 who were not selected in scenario 1 because their CVD risk was below the risk threshold of 10%, and vice versa. Supplementary Appendix 7 provides more details on the percentage of selected individuals per age group, separately for men and women, in each scenario. Comparing scenario 2 with scenario 1, on average the risk estimates were similar and burden estimates were higher. The difference in burden estimates was mainly caused by the fact that on average younger individuals qualify for treatment in scenario 2, compared to scenario 1. The lower part of Figure 1 shows that, for example, for the age group 35–45 years, the part of the percentile interval line above the threshold (grey dotted line) is larger than in the upper part of Figure 1. As an example of different implications of scenarios 1 and 2, 15.2% and 4.4% of the men and women between the age of 35 and 45 years were selected for preventive treatment in scenario 1, whereas many more individuals (28.6% and 13.9% of the men and women, respectively) were selected in scenario 2. Additional details on selected individuals and average values of risk and burden per age group and gender are provided in Supplementary Appendix 6.

Following scenarios 3 and 4, an additional 2351 individuals were selected, which resulted in a group that included 37.1% instead of 32.1% of all individuals (Table 2, selection part).

Description of the impact of hypothetical treatment

Treatment following a risk-based selection strategy (scenario 1) is estimated to yield 6474 QALYs, compared to no treatment. Treatment following the burden-based selection strategy (scenario 2) is estimated to yield 6691 QALYs (Table 1). Hence, without treating more individuals, 217 QALYs can be gained from switching to a burden rather than a risk-based selection strategy.

When comparing scenario 3 to scenario 1, the expected gain was 628 QALYs (Table 2). This difference in QALYs was due to the effect of treating the additionally selected individuals, hence comparison of

Table 2. Scenario analyses for four different selection strategies.

	Selection				Impact		
	Total selected individuals		Estimated CVD burden (QALYs lost)		Gain in QALYs		Gain in QALYs compared to scenario 1
	N	%	Total	Average	Total	Average	Total
Scenario 1: Risk-based strategy (risk ≥0.10)	15,263	32.1	18,511	1.20	6474	0.42	–
Scenario 2: Burden-based strategy (burden ≥0.59 QALYs)	15,263	32.1	19,133	1.24	6691	0.44	217
Scenario 3: Extended risk-based strategy (risk ≥0.10 or burden ≥0.59 QALYs)	17,614	37.1	20,310	1.15	7103	0.40	628
Scenario 4: Extended burden-based strategy (burden ≥0.51 QALYs)	17,614	37.1	20,426	1.16	7143	0.41	669

CVD: cardiovascular disease; QALYs: quality-adjusted life-years.

the current and new risk-based strategy is not directly informative. For a more informative comparison the burden-based strategy was extended (scenario 4) by also selecting 37.1% of the individuals as in scenario 3; this was achieved by decreasing the burden threshold by 0.08 QALYs to a threshold of 0.51 QALYs. After hypothetical treatment, the gain from scenario 4 compared to scenario 3 was 41 QALYs (Table 2, column 8).

Overall, the gain was 217 QALYs without treating additional individuals (scenario 2 vs. scenario 1) and 669 QALYs when additional individuals were selected based on their CVD burden (scenario 4 vs. scenario 1). Hence, scenario 2 has potential for greater health gain than scenario 1, and, likewise, scenario 4 has potential for greater health gain than scenario 3. As it may not be desirable to withhold preventive treatment from individuals currently eligible for preventive treatment (according to scenario 3), the opportunity loss of not implementing scenario 4, compared to scenario 3, is 41 QALYs.

The analysis on the combined dataset is also performed on the different cohorts separately, the results are presented in Supplementary Appendix 8.

Discussion

This study illustrates how health benefits from preventive hypothetical treatment increase when the selection of individuals qualifying for preventive intervention changes rather than the intervention itself. Our study results illustrate that the current risk-based selection mainly targets older individuals, because CVD risk rapidly increases with age. Furthermore, when exactly the same number of individuals was selected based on their CVD burden, both old and young individuals are selected, with the selected young individuals having a low absolute risk but potentially a high health loss with a corresponding high expected burden when a CVD event would occur. As individuals selected on their expected CVD burden have, on average, a higher expected burden than individuals selected on their predicted risk, burden-based selection increases the health benefits of preventive treatment. When both selection strategies are combined, the yield of preventive treatment increases further without the need to withhold preventive treatment in older individuals at (relatively) high risk.

Furthermore, aggregating the individual estimates of CVD burden provides an estimated total CVD burden in a specific population, which can also be interpreted as the maximum theoretical health gain achievable by any preventive strategy in this population. When assessing and comparing CVD prevention strategies, the extent to which they would be able to reduce the CVD burden on population or group level should be the primary 'effectiveness' outcome of an impact assessment, as it better matches the targets set by the WHO and other organisations.[21]

Clinical impact

Many western countries have implemented a risk-based selection strategy to select individuals who should use medication to prevent CVD. Following this strategy, many older persons use such medication. This study illustrates how a new selection method may increase the health benefits from CVD preventive treatment. However, in clinical practice the results may vary. A switch from a risk-based to a burden-based strategy

implicates earlier intervention with preventive strategies in younger individuals. This raises the question of whether the prescription of medication is desirable for these individuals because they have to take lifelong medication which may complicate and lower adherence. A lifestyle intervention may be more appropriate for this group.[22] Furthermore, communication is key here because young individuals have a low absolute risk but their relative risk may be high. For example, a 2.6% risk for a 30-year-old woman may not seem very threatening, but as this risk falls in the highest risk quintile, it is very high compared with the risk of peers.

Another implication of the switch from risk to burden-based strategies is the withdrawal of preventive medication for some using or currently starting with preventive medication. This is particularly the case in older people with a low expected burden. The exact benefits are still under debate, however, as multiple studies have investigated the added value of medication, for example statins, in older individuals. Han et al. concluded that there was no benefit in giving pravastatin in primary prevention for all-cause mortality or coronary heart disease events among adults aged 65 years and older.[23] In addition, Thompson et al. showed that the pay-off time of using statins in primary CVD prevention lengthened when the direct treatment disutility of medication increased.[24] In 2012, the American Geriatrics Association recommended that clinicians should balance the benefits and harms of interventions in older individuals.[25] For example, the benefits of most medication are long term, i.e. decreased CVD risk, while the harms are short term, e.g. muscle weakness in elderly people. Balder et al. showed a large discrepancy between CVD risk guidelines and the current practice of statin prescription in The Netherlands, i.e. a large group of individuals had no discernible cause for statin treatment.[26]

Strengths

This study provides a transparent and detailed illustration of different strategies to select individuals for a preventive CVD intervention rather than improving the intervention itself. Risk-based selection compresses the individualised characteristic of the patient into one single number. Moreover, individuals with a similar high predicted CVD risk can be significantly different. As there is no direct relation between risk and burden estimates, similar risk estimates may result in varying health consequences of the disease and health benefits of preventive treatment. However, burden-based selection accounts for patient age and gender, in addition to predicted risk. Individuals with a similar burden may also be different, but the impact of preventive treatment will not vary significantly when expressed as a reduction of this burden. Furthermore, this way of considering individuals for preventive strategies is a move into the direction of more individualised care and increasing the effectiveness of a preventive strategy without (possibly) increasing costs, as similar numbers in a population use preventive medication.[27] The dataset used consists of individuals from a broad age range with relatively young individuals, whereas studies on CVD prevention often only include older individuals. However, the power in this young age group is low due to a low number of observed CVD events.

Limitations

As the main focus of this study is to illustrate a proof of concept, our data may not accurately represent the population of The Netherlands. Preferably, we would have used one large cohort consisting of individuals aged from 20 to 90 years with a follow-up time of 15 years or longer. Unfortunately, such a cohort is not available in The Netherlands, and probably not even worldwide, therefore we used and combined three existing cohorts. Although our approach may yield slightly different results in population cohorts from other countries, the analysis itself is generalisable across other populations or can be repeated in a large population cohort whenever data are available.

In this study, only first CVD events are taken into account, although in practice individuals may experience more CVD events in a 10-year period. This simplification may lead to an underestimation of the burden estimates but was necessary because the registration of sequential events in individuals was not always very accurate in the cohorts included. Should we have had more data on follow-up and/or the sequence of CVD events within individuals, the expected burden would probably have been greater. Consequently, the absolute differences in QALYs gained between scenarios would have been different but the relative differences would still be marginal. As this study is an illustration of a proof of concept, we had to make a choice on the treatment effect and possible side effects of the preventive treatment. In our analysis only a single overall effectiveness estimate of event reduction was applied; however, the treatment effect of the medication may be different per age group because the observed CVD event rates differ for sex and gender. Furthermore, in practice different treatments (e.g. statins, antihypertensive drugs, or both) will be likely to be provided to different individuals depending on their risk profile. Along with a large variation in individuals' baseline risks, the expected risk reduction of preventive treatment in practice will vary substantially across individuals. The impact of assuming no variation could be assessed, for example, in a patient-level model with separate risk reduction estimates for each individual, or in deterministic sensitivity

analyses based on a range of plausible risk reductions. However, this would further complicate the analyses and is therefore mainly of interest when either the average risk reduction in groups of individuals deviates substantially from 35%, or when absolute outcomes of selection scenarios are appraised rather than differences between scenarios, as in our analysis. As our purpose was merely to demonstrate a proof of concept and not to evaluate absolute outcomes or real-world implementation of burden-based selection strategies, we chose not to account for individual variation of treatment effectiveness. A concrete application of this burden-based selection strategy requires detailed information on the effectiveness and consequences of the medication, the risk of the associated side effects, and should account for sequences of CVD events within individuals.

The results show that after hypothetical treatment the burden-based selection strategy provides more QALYs prevented compared to the risk-based strategy. However, the gain in QALYs was not equally distributed for men and women. The reduction in CVD burden according to the burden strategy was mainly caused by selecting more men and consequently fewer women. In other words, women had to sacrifice health benefits such that men had more health benefits from preventive treatment. Although this is a disadvantage of the burden-based strategy, the analyses can easily be performed for men and women separately; for example, with a gender-specific burden threshold. To investigate this matter further, we applied both selection strategies on the cohorts separately (see Supplementary Appendix 8). The results showed that more women were selected according to the burden strategy compared to the risk strategy. In other words, the switch in selected individuals was in the opposite direction. For the combined dataset, this means that the reduction in CVD burden may be biased due to a cohort effect because PROSPECT only consists of women. In addition, the imbalance in gender was already present in the risk-based strategy in which a larger proportion of men was selected compared to women. The effect of risk selection was enhanced because the health consequences of CVD events, e.g. more severe CVD events, were greater in men. The imbalance in health benefits from preventive treatment for men and women is undesirable; however, it is logical because our present goal was to maximise the number of QALYs to be gained from preventive treatment. Furthermore, the unfavourable effects are resolved in the extended selection strategy in which currently selected individuals retained their preventive treatment. The additionally selected individuals were mostly men, hence the QALY gain is caused by giving men preventive medication only now without withdrawing women from preventive medication.

Although in our analysis we fixed the burden threshold value to select the exact same number of individuals for preventive treatment as in traditional risk-based selection, in practice different burden thresholds can be set, and thresholds could also vary across subgroups of individuals. For example, in a formal health economic analysis the optimal value of the burden threshold for preventive treatment may be determined, even separately for men and women, or depending on comorbidities of individuals, if such distinctions are deemed socially and ethically acceptable. Similarly, for consistency we used one single risk threshold because different thresholds may have complicated the analysis and interpretation of the results.

Conclusion

For decades, risk-based prevention has been applied to optimise the selection of individuals eligible for preventive interventions from a perspective in which risk reduction is seen as the ultimate goal. With the increasing emphasis on the actual health outcomes of patients, and on the improvements in these health outcomes provided by (preventive) interventions, it is now time to add a burden component to selection strategies. This is straightforward and easily implementable in clinical practice, and can efficiently improve the health benefits from preventive interventions.

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Author contribution

GAdW, GRL, HK and KGMM contributed to the conception and design of the work. All authors contributed to the acquisition and interpretation of data for the work, and GRL and HK contributed to the analysis of the data. GAdW, GRL, HK and KGMM drafted the manuscript. All authors critically revised the manuscript and gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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References

1. Atlas of CHD. Global burden or coronary heart disease. www.who.int/cardiovascular_diseases/en/cvd_atlas_13_coronaryHD.pdf?ua=1 (accessed 7 January 2018).
2. CVD Atlas of Stroke. Global burden of stroke. www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf?ua=1 (accessed 7 January 2018).
3. Mendis S. Global progress in prevention of cardiovascular disease. *Cardiovasc Diagn Ther*. 2017; 7(Suppl 1): S32–S38.
4. World Health Organization (WHO). Cardiovascular Diseases. www.who.int/mediacentre/factsheets/fs317/en/ (accessed 7 January 2018).
5. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129: S49–S73.
6. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women – 2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011; 57: 1404–1423.
7. van Giessen A, de Wit GA, Smit HA, et al. Patient selection for cardiac surgery: time to consider subgroups within risk categories? *Int J Cardiol* 2016; 203: 1103–1108.
8. Bots SH, Peters SAE and Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Global Health* 2017; 2: e000298.
9. Leening MJ, Ferket BS, Steyerberg EW, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. *BMJ* 2014; 349: g5992.
10. Beulens JW, Monninkhof EM, Verschuren WM, et al. Cohort profile: the EPIC-NL study. *Int J Epidemiol* 2010; 39: 1170–1178.
11. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Pub Health Nutr* 2002; 5: 1113–1124.
12. Verschuren WM, Blokstra A, Picavet HS, et al. Cohort profile: the Doetinchem Cohort Study. *Int J Epidemiol* 2008; 37: 1236–1241.
13. Blokstra A, Smit HA, Bueno de Mesquita HB, et al. *Monitoring of risk factors and health in the Netherlands (MORGEN cohort), 1993–1997*. Report no. 263200008. Bilthoven, The Netherlands: RIVM, 2005.
14. Boker LK, van Noord PA, van der Schouw YT, et al. Prospect–EPIC Utrecht: study design and characteristics of the cohort population. European Prospective Investigation into Cancer and Nutrition. *Eur J Epidemiol* 2001; 17: 1047–1053.
15. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117: 743–753.
16. Dorresteijn JA, Visseren FL, Wassink AM, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart* 2013; 99: 866–872.
17. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of estimated 10-year risk of recurrent vascular events and residual risk in a secondary prevention population. *Circulation* 2016; 134: 1419–1429.
18. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010; 21: 128–138.
19. Harrell FE. *Regression Modeling Strategies*. New York: Springer, 2001.
20. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013; 1: CD004816.
21. Dehmer SP, Maciosek MV, Flottemesch TJ, et al. Aspirin for the primary prevention of cardiovascular disease and colorectal cancer: a decision analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016; 164: 777–786.
22. Aeschbacher S, Bossard M, Ruperti Repilado FJ, et al. Healthy lifestyle and heart rate variability in young adults. *Eur J Prev Cardiol* 2016; 23: 1037–1044.
23. Han BH, Sutin D, Williamson JD, et al. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT–LLT Randomized Clinical Trial. *JAMA Intern Med* 2017; 177L: 955–965.
24. Thompson A, Guthrie B and Payne K. Using the payoff time in decision-analytic models: a case study for using statins in primary prevention. *Med Decision Making: An international journal of the Society for Medical Decision Making* 2017; 272989X17700846.
25. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. *J Am Geriatr Soc* 2012; 60: E1–E25.
26. Balder JW, de Vries JK, Mulder DJ, et al. Time to improve statin prescription guidelines in low-risk patients? *Eur J Prev Cardiol* 2017; 24: 1064–1070.
27. Piepoli MF, Hoes AW, et al.; Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and other societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016; 23: NP1–NP96.