Carotid Stenosis and Atrial Fibrillation as Targets for Individualised Prevention of Ischaemic Stroke

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Halsslagadervernauwing en boezemfibrilleren als aangrijpingspunten voor geïndividualiseerde preventie van herseninfarcten

(met een samenvatting in het Nederlands)

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Prologue

A not so uncommon conversation between a neurologist and a vascular surgeon

Neurologist
Oh hi there, a dissertation with research on asymptomatic carotid stenosis. Good heavens. What a surprise. I thought this subject was all sorted ages ago.

We occasionally see a symptomatic patient with contralateral asymptomatic carotid stenosis when performing a duplex ultrasound at our TIA service, but they are on medical therapy for their ipsilateral event regardless of the duplex findings.

Vascular surgeon
That is good news, because medical therapy will reduce the risk of vascular events, especially because ischaemic strokes related to carotid stenosis tend to be more disabling and are more often fatal. Preventive therapy is therefore mandated, but not all patients with asymptomatic carotid stenosis are on best medical therapy. On the contrary, in over half of patients with ischaemic stroke related to carotid stenosis there is considerable scope to improve preventive therapy.

Neurologist
It is good to hear your interest goes beyond the scalpel, my dear colleague. It seems we have work to do in improving primary prevention of ischaemic stroke in this specific group of patients. However, active tracing cases with asymptomatic stenosis in the population is like trying to find a needle in a haystack.

In addition, I am always worried that interventions to remove the carotid stenosis are routinely offered to patients with asymptomatic carotid stenosis. To me, it seems that medical therapy is sufficient – at least in most cases.

Vascular surgeon
You are right. Population-level screening is not cost-effective and will bring about many false-positive and false-negative cases. However, a screening targeted to those people at high risk might be another option and we could investigate whether that is worthwhile. This has also been suggested for atrial fibrillation – the other main cause of ischaemic strokes. Here an age criterion of 65 years and older is suggested as threshold for pulse palpation to detect irregular pulse.

With regard to the carotid interventions, it very much depends on the country you are consulting a medical doctor. The large majority of carotid interventions are performed on asymptomatic patients in for example the United States of America, whereas in Sweden these patients are not operated on at all. In the Netherlands, we are on the conservative side as well, with around 3% of carotid interventions performed on asymptomatic cases. So, it is far from routinely offered to asymptomatic patients in the Netherlands.

Medical therapy might well be sufficient in most cases with asymptomatic stenosis, but we hope we are able to select those patients with a net clinical benefit of intervention in addition to medical therapy. But it is clear that guidance for careful patient selection in contemporary practice is lacking.

Neurologist
Targeted screening is an interesting suggestion. This has not received much attention in the literature. An age criterion will surely improve the yield of screening because it is an important predictor, but you also want to detect stenosis early in younger people, because these can benefit longer from preventive therapy. How about combining several predictors together in a risk model?

Preventive therapy can be initiated or intensified in these early detected cases, but a net clinical benefit is crucial when offering an additional carotid intervention. The question remains, however whether it is at all possible in the contemporary era of good medical therapy with low stroke rates in medically treated cases to achieve a net clinical benefit?

Vascular surgeon
Risk prediction models can indeed be used to target screening to those at highest risk. These have been suggested for atrial fibrillation, but validation of these models is necessary before implementation.

It is surprising how little reliable evidence has been published about stroke rates in medically treated cases. This prevents us informing patients about the absolute gains they might receive from a carotid intervention. The stroke risk is presumably low for most patients, but the risk of developing a stroke might be high in a subgroup of these patients – possibly even higher than for some symptomatic patients to whom we offer a carotid procedure!

In this high-risk subgroup of patients, the risk might outweigh the hazards of an operation (while avoiding many operations that may be of only marginal clinical benefit). We should keep in mind that procedural hazards have declined over time as well and are not the same for each patient (and surgeon) either.

Neurologist
We have a rather important gap in evidence to guide contemporary clinical decision making for these patients. Ideally, we should predict who is at high risk of having carotid stenosis and atrial fibrillation combined with predicting who has the highest risk to develop ischaemic strokes and who has most benefit from intervention. That might identify a subgroup of patients with the highest absolute gains of prevention.

Vascular surgeon
Exactly, the net clinical benefit in contemporary practice. That is what we hoped to address in this dissertation. Maybe more timely than expected at first glance?

Neurologist
Absolutely! Let us crack on and get this sorted... definitely!

I

General Introduction, Areas of Uncertainty, and Thesis Outline and Objectives

General Introduction

Stroke is the second leading cause of death and disability worldwide.[1] Around 12 million people suffer a stroke annually and over 100 million people live with the consequences of a stroke resulting in stroke-related disability-adjusted life years. Stroke has two main causes that both result in disruption of the cerebral blood flow: ischaemia and haemorrhage. Ischaemia is caused by a lack of blood flow necessary to deliver oxygen and nutrients to the brain and haemorrhage is caused by excess of blood outside the blood vessels leading to compression of surrounding tissue. In approximately 80% of stroke the cause is ischaemic in nature and the remaining 20% is haemorrhagic. The main subtypes of brain ischaemia are thrombosis, embolism and systemic hypoperfusion.

Fifteen to twenty percent of ischaemic strokes are related to narrowing of the extracranial carotid artery, also known as carotid artery stenosis.[2] It is often classified, along with other pathologies, such as dissection, Takayasu arteritis, giant cell arteritis, and fibromuscular dysplasia, as large vessel disease of the extrancranial vessels. These pathologies are types of thrombotic strokes where blood clots are formed in the artery and block access to particular regions of the brain.

Another fifteen to twenty percent of ischaemic strokes is related to atrial fibrillation (AF), the most common cardiac arrhythmia.[3] In such cases, the thrombus is formed in the left atrial appendage of the heart and particles of debris are transported along the blood stream until they get stuck and also disrupt arterial blood flow. This subtype of ischaemic stroke is therefore often called cardioembolic stroke.

Ischaemic strokes related to carotid stenosis and AF tends to be more disabling or fatal compared with other ischaemic stroke subtypes.[4-6] In addition, the risk of recurrence is also higher with these subtypes.[5,6] This led to an interest in prevention strategies aiming to prevent the onset of ischaemic strokes (primary prevention) or reduce the impact after the ischaemic stroke occurred, i.e. stroke recurrence (secondary prevention). Primary and secondary prevention strategies aim to optimise modifiable risk factors. These include lifestyle changes and medical and interventional treatments.

Current guidelines for primary prevention of cardiovascular disease (CVD) have implemented risk prediction models to predict the incidence of CVD.[7,8] These models include patient characteristics that are associated with increased risks. They aim to tailor prevention strategies to individualized risk predictions. These risk prediction models do not include AF and carotid stenosis as predictors, since many people with these conditions go undetected. This is because these conditions can be asymptomatic or paroxysmal AF is not detected at the time of assessment. AF and carotid stenosis however warrant disease-specific interventions to prevent CVD.

Prevalence and sequelae of extracranial carotid artery stenosis

The prevalence of moderate (≥50%) and severe (≥70%) asymptomatic carotid stenosis in the general population has been estimated to be 1.5-2.0% and 0.5%, respectively.[9,10] The prevalence is higher in men and older people.[11] Other risk factors include smoking, hypertension, hypercholesterolaemia, diabetes mellitus and vascular disease in other arterial beds of the circulation.[12] In particular patients with lower-extremity arterial disease have a high prevalence of asymptomatic carotid artery stenosis.[13] People with carotid stenosis are at increased risk of ischaemic stroke,[14] myocardial infarction (MI) and premature death.[15]

The risk of ischaemic stroke and the best approach to prevent such strokes in patients with asymptomatic carotid stenosis provokes heated debates in the literature, especially about the role of carotid revascularisation. The risk of stroke has declined over the last decades presumably as a result of improved medical preventive therapy. This gave rise to disputes about the net benefit of carotid revascularisation in addition to medical therapy. We will further discuss this issue in chapter 12 of this disseration.

Primary and secondary prevention in patients with carotid stenosis

Prevention strategies in patients with carotid stenosis include lifestyle interventions, medical therapy and carotid revascularisation. The aim is to prevent strokes and MIs by controlling modifiable risk factors or removing the stenosis. Lifestyle interventions include a healthy diet, smoking cessation and physical activity and are indicated for patients with carotid stenosis, regardless of their symptomatic status. The net benefit of these additional prevention strategies is determined by the inherent risks of side effects of antithrombic therapy, i.e., haemorrhage, and procedural complications after carotid revascularization.

Anti-thrombotic therapy

In patients with asymptomatic carotid stenosis, antiplatelet therapy is currently recommended.[16] The preventive effect of aspirin was seen in the observational Asymptomatic Carotid Emboli Study (ACES),[17] but not in the Asymptomatic Carotid Bruit trial that randomised 372 patients between 375 mg enteric-coated aspirin daily versus placebo.[18] Antiplatelet therapy therefore provokes conflicting opinions in patients in whom asymptomatic carotid stenosis is the first manifestation of CVD and who have no indication for antiplatelet therapy because of CVD in other territories.

In patients with symptomatic carotid stenosis, secondary stroke prevention trials are used the determine optimal prevention strategies. In patients with an ischaemic stroke or TIA (not related to AF), antiplatelet drugs have been shown to reduce the risk of thrombotic events by approximately one quarter.[19] Different antiplatelet drugs have been studied in randomised clinical trials (RCTs).

Aspirin was compared to placebo and a reduction of around 15% was found in a meta-analysis of eleven trials.[20] It showed a net benefit when comparing the risk of haemorrhagic stroke to ischaemic stroke.[21] The dose of aspirin was associated with haemorrhagic complication rates.[22,23]

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial included over 19,000 patients with stroke, MI or PAD and showed that clopidogrel is more effective than aspirin in reducing risks of ischaemic events. A relative risk reduction of the composite of ischaemic stroke, MI or vascular death of 8.7% (95% CI 0.3%-16.5%; p=0.043) was found. The effect in the subgroup of stroke patients showed no benefit of clopidogrel, but subgroups of trials do not always provide a good basis to determine the benefit of treatment for individual patients.[24]

In the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) noninferiority trial, over 20,000 patients with non-cardioembolic ischemic stroke compared the combination of aspirin and dipyridamole to clopidogrel alone and showed comparable rates of recurrent stroke.[25]

Lipid-lowering therapy

No randomised trials have been performed on the effect of lipid-lowering therapy in patients with asymptomatic carotid stenosis. However, in the Asymptomatic Carotid Surgery Trial (ACST-1), the subgroup of patients who were on lipid-lowering therapy and allocated to deferral of CEA had a 10-year stroke risk of 13.4% versus 24.1% in patients who did not use lipid-lowering therapy. This might suggest that lipid-lowering therapy could reduce long-term stroke risk.

Recommendations for dose and/or intensity of lipid-lowering therapy are typically derived from primary and secondary cardiovascular disease prevention strategies.[26] These include high-intensity treatment goals of low-density lipoprotein (LDL) levels of <1.8 mmol/L or a 50% reduction of LDL by either 40-80 mg atorvastatin or 20-40 mg rosuvastatin.

Antihypertensive therapy

No RCTs have been performed on the effect of antihypertensive therapy in patients with asymptomatic carotid stenosis. Recommendations about antihypertensive therapy are also based on primary cardiovascular disease prevention strategies[27,28] and include treatment for patients with hypertension to maintain long-term arterial blood pressure <140/90 mmHg.

Carotid revascularisation

RCTs in the 1980s and 1990s showed that successful carotid revascularization by CEA reduced the long-term risk of stroke by approximately fifty percent in patients with asymptomatic or not recently symptomatic carotid stenosis (primary prevention)[29-32] and recently symptomatic carotid stenosis (secondary prevention).[33-36] The generalisability of these findings to contemporary

practice is limited, since the improvements of medical therapy affect the stroke risk in patients with carotid disease. This led to a decrease in absolute gains that individual patients might receive from CEA in addition to medical therapy.

For asymptomatic carotid stenosis, some have argued that the number of carotid-related strokes prevented by adequate medical therapy is too high to warrant additional carotid revascularisation, while others advocated that the residual ipsilateral stroke risk warrants carotid revascularisation. The identification of patients with a residual ipsilateral stroke risk and also a net clinical benefit of an additional CEA is of crucial importance, but limited progress has been made. We will further discuss this issue in Chapter 12 of this dissertation. For symptomatic patients, CEA is usually recommended for patients with severe 70-99% stenosis[37] and may also be beneficial in male patients with moderate 50-69% stenosis.[38]

The net clinical benefit depends not only on long-term reductions in stroke risk, but procedural hazards of carotid revascularisation should also be considered. These hazards have also declined since the recruitment of the aforementioned trials.[39] Current guidelines recommend to consider CEA in patients who have a risk of procedural stroke or death of less than 6% if the carotid stenosis caused symptoms recently and 3% in patients without recent symptoms and who also have a life expectancy of five years.[16] Operationalisation of these risks is however lacking and an attempt to quantify these risks by using risk prediction models will be investigated in this dissertation.

Furthermore, operator characteristics are increasing recognised as important determinants of procedural outcomes and further improve the net clinical benefit of intervention. Finally, an analysis of the timing and procedural stroke subtype helps inform safe discharge policies and may critically review reporting of in-hospital complication rates after CEA.

Prevalence and sequelae of AF

The prevalence of AF in the general population has been estimated to be around 3% in adults aged 20 years and older.[40] Risk factors include age, sex, hypertension, obesity, diabetes mellitus, heart failure, coronary artery disease, valvular heart disease, and chronic kidney disease. People with AF are at increased risk of ischaemic stroke[41-43] and premature death,[44] but also heart failure, left ventricular dysfunction, cognitive decline and vascular dementia.

It is clear that carotid stenosis and AF are so-called risk modifiers that mandate additional prevention strategies. We will describe the disease-specific prevention strategies in the next paragraphs.

Prevention of stroke in patients with AF

Antithrombotic treatment is the cornerstone of stroke prevention in patients with nonvalvular AF.[45] Warfarin and other vitamin K antagonists were the first anticoagulants used. More recently, non-vitamin K antagonist oral anticoagulants (NOAC) have shown to be suitable alternatives and their efficacy and safety is well established. Different types of NOACs have become available of which apixaban, dabigatran, rivaroxaban and edoxaban have been compared to warfarin in RCTs.

In the Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation (ARISTOTLE) randomised trial, patients were allocated to apixaban 5 mg twice daily or warfarin.[46] Apixaban showed a 21% reduction of stroke or systemic embolism. The risk of haemorrhagic stroke and intracranial haemorrhage were lower in patients using apixaban.

In the Randomized Evaluation of Long-Term Anticoagulation therapy (RE-LY) trial, patients were allocated to dabigatran 110 mg or 150 mg twice daily or warfarin.[47] Dabigatran 110 mg and warfarin showed similar rates of stroke and systemic embolism, but dabigatran showed lower rates of major haemorrhage. Dabigatran 150 mg showed lower rates of stroke and systemic embolism than warfarin but similar rates of major haemorrhage.

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) compared rivaroxaban 20mg once daily with warfarin.[48] The intention-to-treat analysis showed that rivaroxaban was non-inferior, while the per-protocol analysis showed a 21% reduction in stroke or systemic embolism.

Finally, the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Trombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial compared edoxaban 60mg daily (and 30 mg daily) to adjusted-dose warfarin.[49] Edoxaban 60 mg showed a 21% reduction of stroke or systemic embolism and a 20% reduction of major bleeding.

Oral anticoagulation should be initiated in man with AF and a CHA_2DS_2-VASc score of two or more and women with AF and a score of three or more.[50,51] Other treatment approaches for AF, such as left atrial appendage occlusion and exclusion as measures to prevent strokes in AF patient is beyond the scope of this dissertation.

Screening for undetected carotid stenosis

The importance of detecting asymptomatic carotid stenosis is stressed by a study that reported 387 patients with carotid-stenosis related TIAs. Less than half of patients were taking statins and

less than 60% were on antiplatelet therapy.[52] This represents potential missed opportunities for stroke prevention by initiation or intensification of medical therapy.

Population-level screening for undetected asymptomatic carotid stenosis with duplex ultrasound is not recommended in current guidelines.[16,53-55] Reasons include the low overall prevalence of asymptomatic carotid stenosis in the general population.

The United States Preventive Services Task Force (USPSTF) recommends against population-level screening because the low prevalence in the general population, but also absense of evidence of an incremental benefit of intensification of medical therapy and limited generalisability of trial findings to contemporary practice that leads to an overestimation of benefits of CEA.[56]

Recommendation for screening of subgroups at higher risk of asymptomatic carotid stenosis are inconsistent. The Society for Vascular Surgery (SVS) advise targeted screening of patients with multiple risk factors that include lower extremity arterial disease, people aged 65 years or above, or with a history of one or more of coronary heart disease (CHD), smoking or hypercholesterolemia.[55] The "14 Society" guidelines recommends that targeted screening in patients with symptomatic lower extremity arterial disease, coronary heart disease or atherosclerotic aortic aneurysm may be considered.[53] The European Society for Vascular Surgery (ESVS) advise targeted screening in patients with multiple vascular risk factors.[16] In contrast, the American Heart Association (AHA) recommends against screening.[54]

The prevalence of asymptomatic carotid stenosis in subgroups of patients with risk factors will be higher, but it is striking that only separate risk factors are used and not combinations. Risk prediction models use combinations of predictors and provide prevalences for subgroups with different risk factor profiles. These can be used to define a cohort of patients at higher risk of asymptomatic carotid stenosis. These risk prediction models enable targeted or selective screening of people at high risk and will therefore reduce the number needed to screen (NNS).

Screening for undetected AF

Studies show considerable scope for improvement of stroke prevention in patients with AF, since AF is often undetected.[40] AF is newly diagnosed at the time of the event in at least half of cases with cardioembolic strokes.[57,58]

Population-level screening for undetected AF in people without cardiovascular disease using electrocardiogram (ECG) is not recommended in current guidelines. The overall prevalence of AF in the general population and especially in younger people is considered too low to make population-level screening worthwhile.[50]

Screening populations at high risk of AF is advised by the European Society for Cardiology (ESC).[50] Opportunistic screening by pulse taking or ECG is recommended in people aged 65 years or above and systematic ECG screening may be considered in people aged 75 or above or those at high risk of stroke.[50] These recommendations are based on the SAFE trial that found a 60% improvement in AF detection with opportunistic or systematic screening compared with routine practice over a period of 12 months.[59,60] Implementation of systematic AF screening in people who are asymptomatic is not recommended by the USPSTF, because cost implications and lack of evidence that systematic screening is more effective than usual practice.[61,62]

Other selection criteria to target screening for undetected AF have been suggested, such as $CHADS_2$ and CHA_2DS_2-VASc, since this would allow a risk prediction model for prediction of AF diagnosis and risk stratification of outcomes, such as stroke or systemic thromboembolism.[63] This approach has shown to be particularly cost-effective.[64-66]

Areas of uncertainty

There remain several evidence gaps around the current understanding of the epidemiology of carotid artery stenosis and AF and the optimal prevention strategies to prevent ischaemic strokes.

While the prevalence and risk factors of asymptomatic carotid stenosis in the general population have been studied extensively,[9,11] the translation of these patterns into targeted screening for undetected asymptomatic carotid stenosis and AF in high risk populations by applying risk prediction modelling to contemporary large datasets is lacking. This might have contributed to inconsistent recommendations about screening in current guidelines. Risk prediction models might be used to target screening to those at high risk of asymptomatic carotid stenosis and AF, but risk prediction models need to be validated for discrimination and calibration in large contemporary datasets before implementation.

In patient in whom carotid artery stenosis is detected, it is currently unclear what antithrombotic regime is appropriate. There is also considerable disagreement around the net clinical benefit of carotid revascularisation in patients with asymptomatic carotid stenosis in contemporary practice with effective medical therapy. It has been suggested that medical therapy reduces the stroke risk to such an extent that carotid revascularization should not be offered at all or only in selected cases.[14,16] We will discuss the selection of those patients who may receive enough absolute benefit in terms of reduction of stroke risk to warrant carotid revascularisation in contemporary practice and the lack of validated risk prediction models to stratify such patients in the Chapter 12 of this dissertation.

Similarly, in patients with symptomatic carotid stenosis, substantial uncertainty exists whether carotid endarterectomy should be offered routinely to all symptomatic patients or whether symptomatic patients with low and intermediate risk of stroke should be managed with medical therapy.

The net clinical benefit however does not only depend on stroke (recurrence) risk, but also on procedural hazards. Procedural hazards have declined since the recruitment of the trials that determined the efficacy of CEA.[39] Hospital volume, operator volume, and operator speciality have also been suggested as predictors of procedural complications, but reported associations are inconsistent. These predictors might be important to consider by whom patients should be treated and can also inform credentialing processes in future RCTs that determine the efficacy of carotid revascularisation.

Before implementation measures to reduce the risk of procedural stroke or death after CEA, it is important to perform a detailed analysis of the timing of such events and stroke subtype. This

might inform clinicians when and how to reduce procedural strokes.[67] Such an analysis is also important for research purposes, because it might critically review the reporting of in-hospital complication rates after CEA and help inform safe discharge policies, since it is unclear whether in-hospital procedural hazards reflect true risks after CEA.

Risk prediction models might help inform patients about procedural hazard and possibly patient selection for CEA by providing individualised risk estimations by taking several patient and disease characteristics into account. Before implementation of such risk prediction models in clinical practice, it is essential to assess their predictive performance and clinical applicability. This validation to assess discrimination and calibration should be performed in generalizable external observational data with representative absolute procedural risks of patients who underwent CEA.

THESIS OUTLINE AND OBJECTIVES

In this thesis, the prevalence of carotid stenosis and AF, two main causes of ischaemic stroke, and the treatment of carotid stenosis is scrutinised.

Part 1 focuses on the prediction of asymptomatic carotid stenosis and comprises three chapters. Risk prediction models might identify individuals at higher risk of asymptomatic carotid stenosis, thereby enabling targeted screening. Early identification of asymptomatic carotid stenosis allows the initiation or intensification of preventive therapy to reduce risk of the CVD. In ***chapter 2***, a systematic review of published studies of prediction models for asymptomatic carotid stenosis is conducted and these models are externally validated in a large contemporary screened population. In ***chapter 3***, a novel risk prediction model to detect asymptomatic carotid stenosis in a large contemporary screened population is derived. In ***chapter 4***, a systematic review to identify established risk prediction models to detect asymptomatic carotid stenosis in patients with lower extremity arterial disease is conductced, a novel risk prediction model is developed and externally validated in two independent populations.

Part 2 focuses on identification of risk factors and prediction of AF and comprises two chapters. In ***chapter 5***, it is determined whether either body mass index or waist circumference alone, or in combination, better estimates the risk of AF in men and women. In ***chapter 6***, the utility of established models to predict prevalent AF in a large contemporary screened population is compared.

Part 3 focuses on combined prediction of the prevalence of AF and asymptomatic carotid stenosis to optimise risk stratification for primary prevention of CVD. In ***chapter 7,*** the yield and accuracy of screening along with the prediction of 10-year risk of cardiovascular disease using the pooled risk equations is assessed. This might identify individuals in whom disease-specific prevention strategies should be considered if AF or asymptomatic carotid stenosis is found and who benefit from closer follow-up to improve compliance.

Part 4 focuses on the identification of risk factors and prediction of procedural outcomes after treatment of carotid stenosis to improve the net clinical benefit. In ***chapter 8***, the relationship between operator and hospital volume and procedural outcomes after CEA and carotid artery stenting (CAS) is investigated. In ***chapter 9***, the relationship between operator speciality and procedural outcomes after CEA and CAS is analysed. In ***chapter 10***, the frequency and timing of procedural stroke and death in patients who underwent CEA for asymptomatic carotid stenosis is described. In ***chapter 11***, the predictive performance of risk prediction model to predict the risk of

procedural stroke and death after CEA in a large contemporary population, thereby enabling patient selection for CEA, is assessed.

The following objectives were formulated:

1) To identify established risk prediction models to detect asymptomatic carotid stenosis in the population and assess their performance (external validation) in a large contemporary screened population (Chapter 2)
2) To derive a novel risk prediction model to detect asymptomatic carotid stenosis in a large contemporary screened population (Chapter 3)
3) To identify established risk prediction models for asymptomatic carotid stenosis in patients with lower extremity arterial disease, then develop a new risk prediction model and, finally, validate this model in two independent populations (Chapter 4)
4) To determine precise estimates of the risk of AF by body mass index and waist circumference alone, or in combination in men and women (Chapter 5)
5) To systematically identify and compare the utility of established models to predict AF (Chapter 6)
6) To determine the yield and accuracy of screening for AF and carotid stenosis along with cardiovascular risk stratification using the pooled risk equations (Chapter 7)
7) To examine the association between operator or hospital volume and procedural outcomes of carotid revascularisation (Chapter 8)
8) To examine the association between operator speciality and procedural outcomes of carotid revascularization (Chapter 9)
9) To assess frequency and timing of procedural complications after CEA for asymptomatic carotid stenosis (Chapter 10)
10) To identify established risk prediction models for procedural stroke or death after CEA and assess their performance (external validation) in a large contemporary population of patients who underwent CEA (Chapter 11)

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Part I

Detection of Asymptomatic Carotid Stenosis

2

Validation of Risk Prediction Models to Detect Asymptomatic Carotid Stenosis

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Abstract

Background: Significant asymptomatic carotid stenosis (ACS) is associated with higher risk of strokes. While the prevalence of moderate and severe ACS is low in the general population, prediction models may allow identification of individuals at increased risk, thereby enabling targeted screening. We identified established prediction models for ACS and externally validated them in a large screening population.

Methods and results: Prediction models for prevalent cases with ≥50% ACS were identified in a systematic review (975 studies reviewed and 6 prediction models identified [3 for moderate and 3 for severe ACS]) and then validated using data from 596 469 individuals who attended commercial vascular screening clinics in the United States and United Kingdom. We assessed discrimination and calibration. In the validation cohort, 11 178 (1.87%) participants had ≥50% ACS and 2033 (0.34%) had ACS ≥70%. The best model included age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, vascular and cerebrovascular disease, measured blood pressure, and blood lipids. The area under the receiver operating characteristic curve for this model was 0.75 (95% CI, 0.74–0.75) for ≥50% and 0.78 (95% CI, 0.77–0.79) for ≥70% ACS. The prevalence of ≥50% ACS in the highest decile of risk was 6.51%, and 1.42% for ≥70% ACS. Targeted screening of the 10% highest risk identified 35% of cases with ≥50% ACS and 42% of cases with ≥70% ACS.

Conclusions: Individuals at high risk of significant ACS can be selected reliably using a prediction model. The best-performing prediction models identified over one third of all cases by targeted screening of individuals in the highest decile of risk only.

Introduction

Transient ischemic attack (TIA) or ischemic stroke is the first presentation of cardiovascular disease in about 25% of the cases,[1,2] and 15-20% of ischemic stroke cases are associated with extracranial carotid artery stenosis.[3-5] Carotid stenosis is also a predictor for coronary events and vascular death.[6] The prevalence of moderate (≥50%) and severe (≥70%) asymptomatic carotid stenosis (ACS) in the general population has been estimated to be 2.0% and 0.5%, respectively.[7]

Due to this low overall prevalence, population-level screening for ACS with duplex ultrasound is not recommended in current guidelines.[8-11] However, targeted screening of high-risk individuals might be worthwhile,[11] and risk stratification tools or prediction models have been developed to provide individualized risk estimation for ACS. Before recommending targeted screening, risk prediction tools should be assessed for discrimination, calibration and likely ability to detect false positive and false negative cases in an independent external population. We conducted a systematic review of published studies of prediction models for ACS and then externally validated these models in a large contemporary population of screenees in the USA and UK.

METHODS

This systematic review and meta-analysis was conducted according to a predefined protocol that has been registered in an international registry for systematic reviews (PROSPERO): CRD42019108136. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations (Table S1) and the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist.[12,13]

Data sharing

Data from large population-based studies conducted by the Nuffield Department of Population Health can be shared with bona fide researchers on application to the principal investigators of this study. Details of the departmental data access policy can be found at https://www.ndph.ox.ac.uk/data-access.

Search strategy and eligibility criteria

We used comprehensive electronic strategies and incorporated a validated research search filter to search Medline (via PubMed interface) and EMBASE (via OVID EMBASE interface) on March 1, 2019 for studies reporting on development and validation of prediction models for risk of ACS in general or screened populations (Methods S1).[14] We included studies that: (1) addressed development and/or validation of diagnostic prediction models to detect ACS of 50% or greater; (2) assessed prediction models in both general and high-risk populations, but not in diseased populations at higher risk of ACS; (3) involved a cross-sectional study design; and (4) were published in peer-reviewed journals without any language restrictions.

Screening process and data extraction

Two authors (MHFP and MSM) independently screened all titles and abstracts of the retrieved references and subsequently independently reviewed full-text copies for final inclusion in this study. We performed backward citation searching using the bibliographies of included studies.

Two authors (MHFP and MSM) independently extracted the following data from the included studies reporting the development of a prediction model, based on the CHARMS checklist: source of data, setting study, geographic area (country and continent), study years, sample size, modelling method (eg, logistic model), number of participants with missing data, handling of missing data,

investigation of satisfaction of modelling assumptions, selection methods for predictor selection, shrinkage of predictor weights, number of outcome events, number of participants, degree of stenosis, number and type of predictors (diagnostic variables) used in the final model, number of outcome events per variable, presentation of model, model performance (calibration and validation). In studies that reported internal validation of prediction models, we extracted the following additional data: method of internal validation (e.g., cross-validation, bootstrap); whether the model was adjusted or updated after internal validation. In studies reporting external validation of a prediction model, we extracted the following additional data: type of external validation (e.g., geographical and/or temporal distinct population); whether authors of the external validation also developed the original model; performance of the model before or after model recalibration.

Critical appraisal

Prediction modelling studies were assessed for risk of bias and applicability using the Prediction model Risk Of Bias ASsessment Tool (PROBAST).[15] The assessment of risk of bias involved four domains: participants; predictors; outcome and analysis. Risk of bias was judged as low, high, or uncertain for each domain. The assessment of applicability involved three domains: participants; predictors and outcome. Applicability was judged as low, high, or uncertain for each domain. Each distinct model included in the article was evaluated separately.[16]

External validation cohort

A cohort of 0.6M self-referred and self-funded individuals who attended commercial vascular screening clinics between 2008 and 2013 in the United States and the United Kingdom was used for external validation. All individuals completed a standardized questionnaire including questions about their age, sex, height and weight, history of vascular disease (peripheral arterial disease, transient ischemic attack, stroke, coronary artery disease, and congestive heart failure), history of hypertension, history of diabetes mellitus, smoking history, and use of antiplatelet, antihypertensive, and lipid-lowering medication. Standard blood pressure cuffs and sphygmomanometers were used, with systolic pressure (SBP) measured using a Doppler probe, and peripheral arterial disease (PAD) was assessed with ankle-brachial pressure index assessment.

Most participants underwent carotid duplex screening, conducted by trained staff using dedicated vascular ultrasound instruments (GE LOGIQ e®). The highest peak systolic velocity (PSV) and end-diastolic velocities (EDV) of both the common carotid arteries and the internal carotid arteries were measured.

A blood sample was collected from a subset of participants for selected plasma biochemical measurements using point-of-care testing methods (Alere Cholestech LDX® system, Alere Inc, Waltham MA, USA). Plasma levels of total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglycerides were measured by enzymatic methods. Low-density lipoprotein-cholesterol (LDL-C) was estimated using the Friedewald formula (LDL = total cholesterol – HDL – triglycerides/5).

Predicted outcomes

We externally validated the prediction models for both moderate or severe ACS:

1) Moderate or severe ACS; i.e., estimated stenosis of ≥50% (based on peak systolic velocity (PSV) ≥125 cm/s at either side or 0 cm/s for occluded arteries); and

2) Severe ACS, i.e., estimated stenosis of ≥70% (based on PSV ≥230 cm/s at either side or 0 cm/s for occluded arteries).

Statistical analyses (external validation)

Selected characteristics of the external validation cohort were summarized using standard methods. We used the same external validation population for all external validation analyses to enable comparisons between different prediction models. Participants who provided a blood sample and had a duplex ultrasound performed were included in analyses. For most predictors, the percentage of participants with missing data was <12%, except for measured diastolic blood pressure (31.8%) (Table S2). Missing data were imputed using chained equations and 20 data sets with 200 iterations.[17] Total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL-ratio) was calculated before imputation.[18] Post-imputation rounding was applied for limited-range variables (SBP, diastolic blood pressure, TC/HDL-ratio, HDL-C, LDL-C, and height), if needed.[19]

The regression formula reported for each model was applied to the external validation cohort to calculate the probability of ≥50% and ≥70% ACS per participant. These individual probabilities

were used for assessing the predictive performance. We contacted authors to provide the regression formula if it was not reported. If the authors did not report or could not provide the regression formula, we calculated a sum score (total points) for each participant by summing the scores assigned to each predictor in the original reports (referred to as a 'score chart'). We used the sum score to assess the predictive performance.

We examined the performance of discrimination and calibration in the different prediction models. Discrimination is the ability of the prediction model to distinguish between participants with and without the disease outcomes, assessed using the area under receiver operating characteristic (AUROC) curve. AUROC curves values were calculated per imputed data set and results were subsequently pooled using Rubin's rules.[20,21]

Calibration is the agreement between predicted risk and observed risk and was assessed with calibration plots. For the models that provided the regression formula, we estimated the mean probability per participant across the 20 imputed data sets and subsequently we split the predicted risks in deciles. We then calculated mean predicted and observed probability with corresponding 95% confidence intervals (CI) per decile. In contrast, for the models that did not provide the regression formula, we used the predicted probability per sum score as reported in the original reports and we calculated the observed probability with corresponding 95% CI in the validation cohort.

Differences between the prevalence of the predicted outcome in the development cohorts and the validation cohort are known to influence calibration. For this reason, we recalibrated the prediction models to the prevalence of the predicted outcome in the validation cohort by re-estimating the intercept.[22] We fitted a logistic model with a fixed calibration slope and the intercept as the only free parameter.[22]

STATA version 15.1 was used for all statistical analyses and R version 3.5.1 was used for constructing the figures.

Clinical application

Clinical application of the prediction model with the best discrimination was assessed using two approaches. The first approach assessed targeted screening of the 10% and 20% cases at highest

predicted risk of having significant ACS. For this, we calculated test characteristics for the highest decile and the highest two deciles of predicted risk. The second approach assessed targeted screening with a fixed level of sensitivity. For this, test characteristics were calculated for two levels of sensitivity (closest to sensitivity 80% and 90%).

Sensitivity analyses

We performed additional external validation of the prediction models: 1) in all available cases; 2) participants without a history of prior TIA or stroke using imputed data sets; and 3) participants without a history of prior cardiovascular disease (i.e., stroke, TIA, MI, and PAD) using imputed data sets.

Ethical approval

The University of Oxford Medical Sciences Inter-Divisional Research Ethics Committee approved the study. All individuals provided written consent for the data collected at the screening visit to be used for research purposes.

Role of the funding source

The study funders had no role in study design, data collection, analysis, or interpretation, drafting the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to publish the report.

RESULTS

We screened 923 unique reports identified by literature searching, assessed the full-texts of 102 reports for eligibility, and included five studies (Figure 1 and Table S3). Four studies involved model development studies, of which one performed additional external validation of an existing prediction model.[23-26] One study was an external validation study.[27] Overall, six prediction models for the prevalence of ACS were developed.[23-26] Characteristics of model development are provided in Table 1 and Table S4.

Three prediction models were developed to detect ACS ≥50%,[23,24,26] one model was developed to detect ACS ≥60%,[25] and two models were developed to detect ACS ≥70%.[23,26] The risk predictors included age, sex, smoking, hypertension, hypercholesterolemia, diabetes, myocardial infarction, stroke or TIA, height, measured blood pressure, and blood lipids. The number of predictors included in the prediction models varied from four to eight. Two models used clinical characteristics and four models used blood measurements in addition to clinical characteristics. An overview of the predictors used in prediction models is provided in Table S5. The number of cases used to develop the prediction models varied from 394 to 23,706; the number of events varied from 18 to 465, and the number of cases per predictor varied from 2.6 to 59.8.

The overall risk of bias was low in two models and high in four models. Concerns with the applicability of the prediction models was deemed low in three models, unclear in two models and high in one model. An overview of the risk of bias and the applicability per model is provided in Table S6.

Figure 1. Flowchart of literature review to identify the included studies

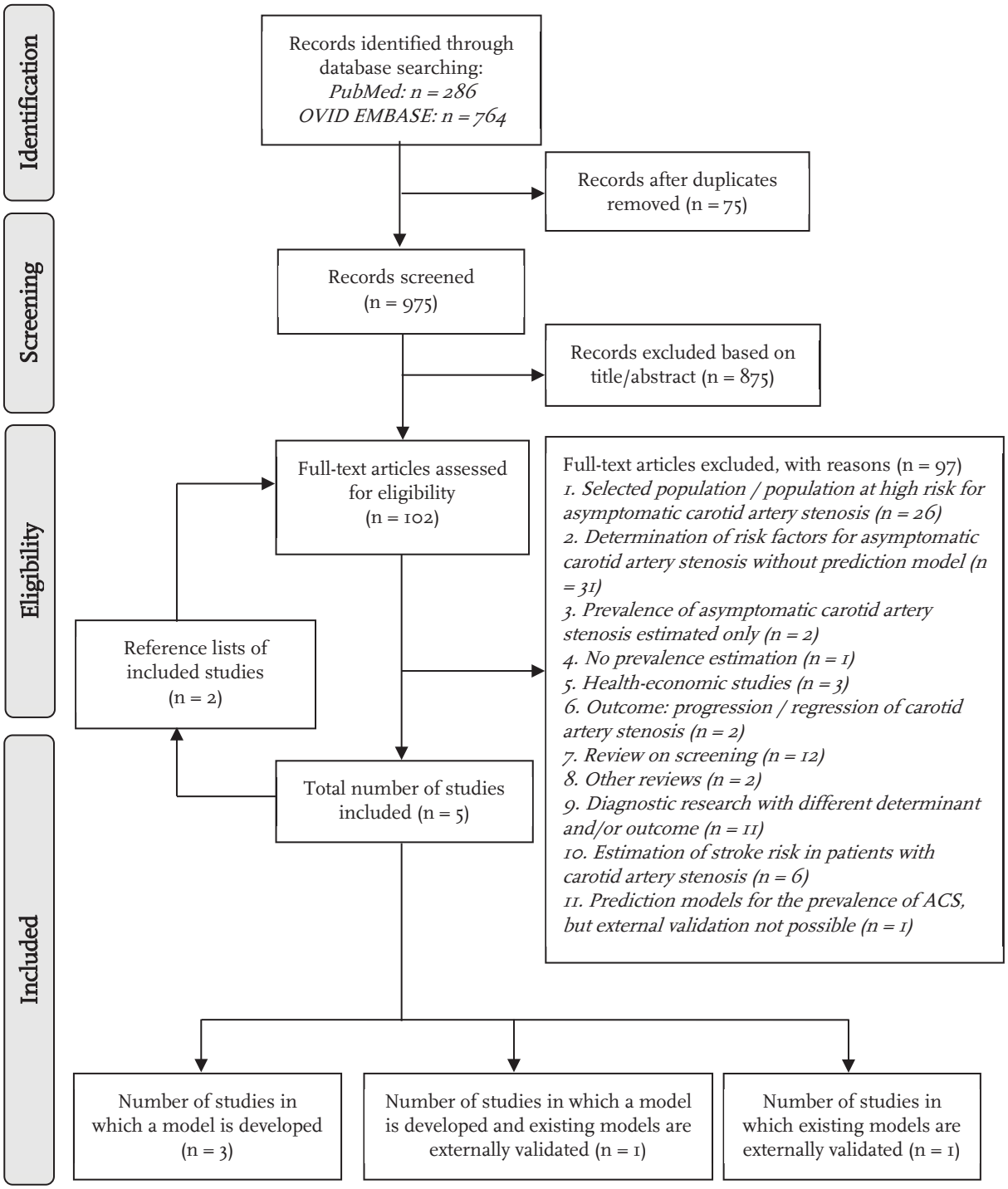


Table 1. Selected characteristics of studies assessing different risk *prediction models for ACS*

	Predicted outcomes	Data sources	Calendar year of recruitment	No. of cases / participants in derivation cohort	Number of included predictors	Number of events per predictor	First author, year of publication
1.	70-100% ACS	Renqiu Stroke Screening Study, China	2012	18 / 3006 (0.6%)	7	2.6	Yan et al, 2018[26] *Model 1*
2.	50-100% ACS			33 / 3006 (1.1%)	8	4.1	*Model 2*
3.	>70% ACS	Four observational studies: Sweden,	Tromsø: 1994-5; MDCS: 1991-6;	127 / 23,706 (0.5%)	8	15.9	De Weerd et al, 2014[23] *Model 1*
4.	>50% ACS	Norway, Germany, four communities in the US	CAPS: NA; CHS: NA.	465 / 23,706 (2.0%)	8	58.1	*Model 2*
5.	>50% ACS	Screening, NY, US	2001-2002	38 / 394 (9.6%)	4	9.5	Jacobowitz et al, 2003[24]
6.	≥60% ACS	Screening, NY, US	1997	239 / 1331 (18%)	4	59.8	Qureshi et al, 2001[25]

ACS indicates Asymptomatic carotid stenosis; CAPS, Carotid Atherosclerosis Progression Study; CHS, Cardiovascular Health Study; MDCS, Malmö Diet and Cancer Study; NA, not available; NY, New York; US, United States.

Predictive performance

Discriminative performance, as assessed by the AUROC curves varied from 0.81 to 0.88 in the derivation cohorts, and from 0.71 to 0.87 in the internal validation cohorts, respectively (Figure 2).[23-27] Only one study provided calibration plots.[26]

In two studies, ten external validation analyses were performed.[26,27] In Yan et al, six external validation analyses were performed using both ≥50% and ≥70% ACS as outcomes.[26] The number of cases used for external validation in their study was 5,010, of which 64 (1.3%) had ≥50% ACS, and 38 (0.8%) had ≥70% ACS. The AUROC curve ranged from 0.63 to 0.68. No (re)calibration was performed. A cohort from China used for external validation was geographically and temporally distinct from the derivation cohorts. In Suri et al, four external validation analyses were performed using ≥50% and ≥75% ACS as predicted outcomes.[27] The number of cases used for external validation in their study was 5,449, of which 227 (4.2%) had ≥50% ACS and 52 (1.0%) had ≥75% ACS. The AUROC curve ranged from 0.56 to 0.60. No (re)calibration was performed. The validation cohort was from the US as were the derivation cohorts of the validated models and the data of validation cohort were older than the derivation cohorts.

External validation

The validation cohort consisted of 596,469 participants, of whom 11,178 (1.87%) participants had ≥50% ACS and 2,033 (0.34%) participants had ≥70% ACS. Baseline characteristics of the validation cohort are provided in Table 2.

Table 2. Selected characteristics of participants in the external validation cohort, by severity of ACS

	Participants with <50% ACS (n = 585,291)	Participants with 50-69% ACS (n = 9,145)	Participants with ≥70% ACS (n = 2,033)†	All Participants (n = 596,469)
Age (y)	62.0 ± 10.0	68.7 ± 8.9	68.3 ± 8.8	62.2 ± 10.1
Sex (male)	208,285 (35.6%)	3442 (37.6%)	1009 (49.6%)	212,736 (35.7%)
Current or former smoker	207,329 (40.0%)	4,865 (61.0%)	1,245 (69.2%)	213,439 (40.4%)
Never smoker	311,192 (60.0%)	3,112 (39.0%)	555 (30.8%)	314,859 (59.6%)
Hypertension	202,768 (36.0)	5,185 (58.9%)	1,166 (60.6%)	209,119 (36.4%)
Diabetes mellitus	44,986 (8.2%)	1,577 (18.3%)	312 (16.4%)	46,875 (8.4%)
Coronary heart disease*	26,997 (5.1%)	1,262 (14.9%)	344 (18.6%)	28,603 (5.3%)
Stroke/TIA	17,154 (3.3%)	758 (9.0%)	274 (15.0%)	18,186 (3.4%)
Peripheral arterial disease	16,370 (2.8%)	1,184 (13.4%)	424 (21.8%)	17,978 (3.1%)
Height (m)	1.68 ± 0.1	1.67 ± 0.1	1.69 ± 0.1	1.68 ± 0.1
SBP (mmHg)	132 ± 19.5	142 ± 21.8	146 ± 23.5	132 ± 19.6
DBP (mmHg)	78 ± 9.8	76 ± 10.2	78 ± 11.5	78 ± 9.8
HDL-C (mmol/L)	1.4 ± 0.5	1.3 ± 0.5	1.3 ± 0.4	1.4 ± 0.5
LDL-C (mmol/L)	3.0 ± 0.9	3.0 ± 1.1	3.0 ± 1.1	3.0 ± 0.9
TC/HDL-ratio	4.0 ± 1.6	4.2 ± 1.7	4.4 ± 2.0	4.0 ± 1.6

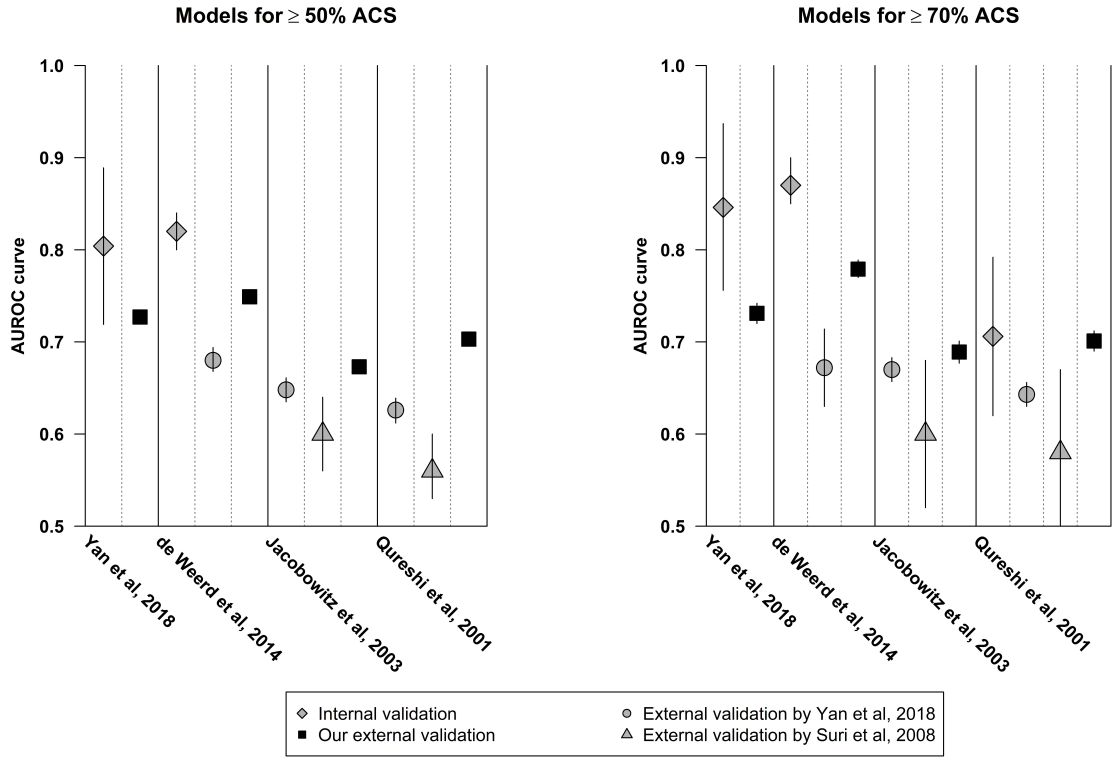
Values are mean ± SD for continuous variables and n (%) for categorical variables
DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack.
* Coronary heart disease is defined as previous myocardial infarction or a coronary intervention (bypass, angioplasty, or stenting). † In this group, 500 participants had a presumed occlusion.

Discrimination for outcome ≥50% ACS: The model with the best discrimination showed an AUROC curve of 0.749 (95% CI 0.744-0.753).[23] The discriminative performance was fair in three other models with AUROC curve of 0.727 (95% CI 0.722-0.732), 0.704 (95% CI 0.700-0.709) and 0.703 (95% CI 0.699-0.708).[25,26] The discriminative performance was poor in one model with AUROC curve of 0.673 (95% CI 0.668-0.678).[24]

Discrimination for outcome ≥70% ACS: The model with the best discrimination showed an AUROC curve of 0.779 (95% CI 0.770-0.789).[23] The discriminative performance was fair in three other models with AUROC curve of 0.759 (95% CI 0.749-0.770), 0.731 (95% CI 0.721-0.742) and

0.701 (95% CI 0.690-0.712).[25,26] The discriminative performance was poor in one model with AUROC curve of 0.689 (95% CI 0.677-0.701)[24] (Figure 2 and Table S7).

Figure 2. Discriminative performance of risk prediction models



The symbols represent the AUROC curves of the included prediction models and the vertical bars represent the 95% CIs. The values of the AUROC curves and 95% CIs are provided in Table S7.
The models of Jacobowitz et al, 2003[24] and Qureshi et al, 2001[25] were originally developed for >50% ACS and ≥60% ACS, respectively. Suri et al, 2008 used ≥50% ACS and ≥75% ACS as outcomes for the external validation.[27]
The AUROC curves of two external validations for ≥50% ACS in the models developed for ≥70% ACS by de Weerd et al, 2014[23] and Yan et al, 2018[26] and two external validations for ≥70% ACS in the models developed for ≥50% ACS by the same authors are omitted in this figure.
ACS indicates asymptomatic carotid artery stenosis; AUROC curve, Area under receiver operating characteristic curve, CI, confidence interval.

Calibration: In the model with the best discrimination, predicted probabilities (after recalibration with adjusting the intercept) showed very good concordance between the predicted prevalence calculated with the prediction model and the observed prevalence in the external validation cohort. The predicted and observed prevalence of ≥50% ACS in the highest decile was 6.4% and 6.5%, respectively (Figure 3A).[23] The predicted and observed prevalence of ≥70% ACS was 1.7% and 1.4%, respectively (Figure S1). Other calibration plots are provided as Figure S1 & Figure S2 for the outcomes ≥70% ACS & ≥50% ACS, respectively.

Application of the prediction model with the best discrimination

Application for outcome ≥50% ACS: First, we assessed targeted screening in the highest decile and highest two deciles of predicted risk. Prevalence of ≥50% ACS in the highest decile of predicted risk was 6.5% with an NNS of 15. Targeted screening of the highest decile identified 34.8% of cases with ≥50% ACS. Prevalence in the two highest deciles of predicted risk was 4.8% with an NNS of 21. Targeted screening of the two highest deciles identified 55.0% of cases with ≥50% ACS (Figure 3B and Table S8).

Secondly, we assessed targeted screening with fixed levels of sensitivity. For this, test characteristics were calculated for two levels of sensitivity (approximately 80% and 90%). Observed prevalences of ≥50% ACS were 2.78% and 3.38% for the sensitivity of 90.0% and 79.5%. The corresponding specificity was 40.0% and 56.6%, respectively (Table S8).

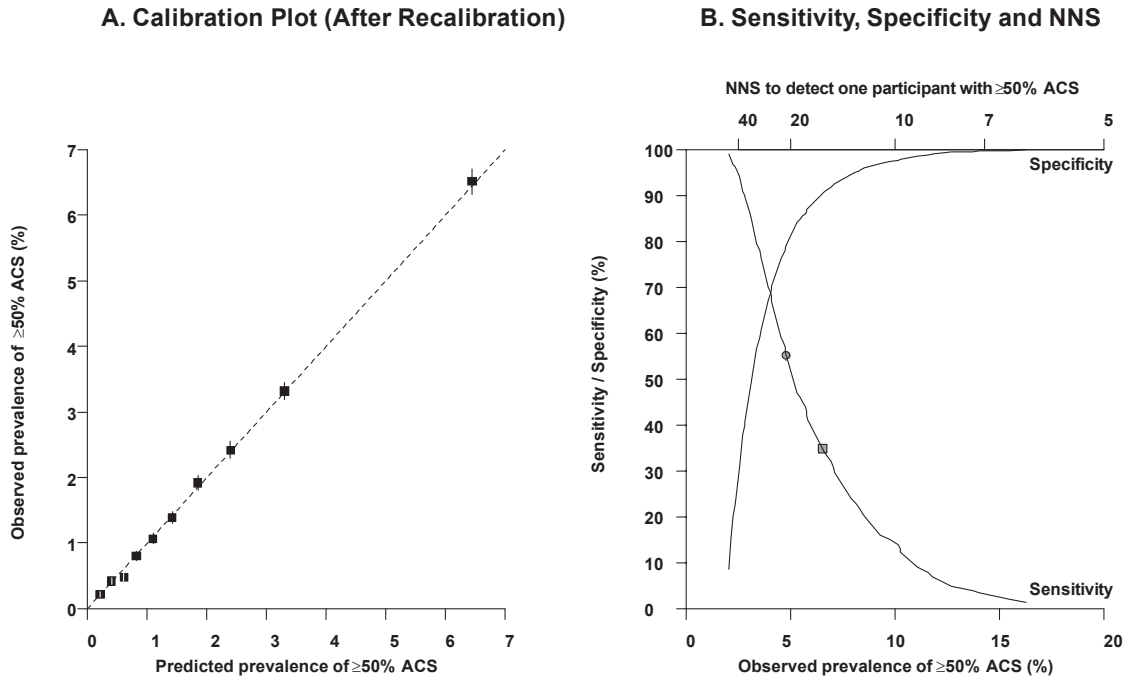
Application for outcome ≥70% ACS: Prevalence of ≥70% ACS in the highest decile of predicted risk was 1.4% with an NNS of 70. Targeted screening of the highest decile identified 41.7% of cases with ≥70% ACS. Prevalence in the two highest deciles of predicted risk was 0.98% with an NNS of 102. Targeted screening of the two highest deciles identified 62.1% of cases with ≥70% ACS (Figure S3 and Table S8).

Using fixed levels of sensitivity (approximately 80% and 90%), observed prevalences of ≥70% ACS were 0.8% and 0.5% for the sensitivity of 76.8% and 92.0%. The corresponding specificity was 65.1% and 40.0%, respectively (Table S8).

Sensitivity analysis

Validation in subsets with complete cases, cases without a history of TIA or stroke showed comparable results. Validation in the subset of cases without a history of cardiovascular disease showed a lower AUROC (Figure S4 and Table S9).

Figure 3. Clinical application of the prediction model of de Weerd et al, 2014 for ≥50% ACS



3A. Calibration plot of external validation of the prediction model developed by de Weerd et al, 2014.[23] It shows the predicted and observed prevalence of ≥50% ACS (after recalibration with adjusting the intercept). The boxes represent one decile of predicted risk and the vertical lines represent the 95% confidence intervals.
3B. Graph showing the sensitivity and specificity and corresponding observed prevalence and number needed to screen to detect one participant with ≥50% ACS using the prediction model developed by de Weerd et al, 2014.[23] The square corresponds to targeted screening of participants in the highest decile of predicted risk. The prevalence in this decile is 6.5% with a number needed to screen of 15 and sensitivity is 34.8%. The circle corresponds to targeted screening of participants in the highest two deciles of predicted risk. The prevalence in these deciles is 4.8% with a number needed to screen of 21 and sensitivity of 55.0%.
ACS indicates asymptomatic carotid artery stenosis; NNS, Number needed to scan.

Discussion

The present study validated prediction models in an external population to identify a cohort of individuals at high risk of asymptomatic carotid stenosis (ACS). In the model with the best discrimination, the observed prevalence of ACS in the decile at highest risk was 6.5% (≥50% ACS) and 1.4% (≥70% ACS) with an NNS of 15 and 70, respectively. Targeted screening of individuals in the highest decile of risk reliably identified 35% of cases with ≥50% ACS and 42% of cases with ≥70% ACS.

Early identification of ACS cases allows the initiation or intensification of cardiovascular risk management using triple medical therapy (i.e. antithrombotic, antihypertensive and lipid-lowering medication) to decrease the risk of cardiovascular disease. Carotid intervention might further decrease the risk of stroke in selected cases. Clinical and imaging features associated with an increased risk of stroke in patients with medically treated ACS, such as silent brain infarction, contralateral stroke or TIA, plaque echolucency, intraplaque hemorrhage, microemboli, and reduced cerebrovascular reserve, have been identified.[10,28] Risk stratification tools, using a wide range of predictors, have been developed to estimate long-term stroke and cardiovascular disease risk in cases with ACS, but these have not been validated with current medical treatment.[29,30] Reliable and validated risk stratification tools might help further refine the use of targeted screening for ACS by identifying cases at higher risk for stroke and cardiovascular disease.

We found that discrimination was less for participants without cardiovascular disease, but targeted screening could also include participants with a history of cerebrovascular or cardiovascular disease, since not all of these participants were taking adequate preventive treatments. Annual ipsilateral risk of stroke in ACS cases on medical therapy in previous RCTs varied between 1.4% and 2.4%.[31-33] More recent studies have reported lower risks due to improving risk factor management.[29] Annual risk of ipsilateral ischemic stroke and TIA in cases with >50% ACS and a history of TIA or minor stroke in another territory with consequent use of secondary prophylaxis was as low as 0.34% and 1.78%, respectively.[34]

The discrimination of the best model was fair and calibration very good, despite differences between the original derivation and our validation cohort. Differences in duplex protocols, (e.g. unilateral or bilateral screening), and differences in the methods of measurement of degree of stenosis between populations may have contributed to lower external performance in this large external validation cohort. Duplex screening does not assess intracranial stenosis and extracranial calcified vessels can hamper reliable assessment. Different criteria for assessment of stenosis are available, but validity of duplex ultrasound performed by experienced sonographers is good,[35] and PSV, whilst it is a simple measurement, may be useful as a screening tool to identify cases for more intensive evaluation.

The present study had several strengths. We conducted an extensive literature search to identify existing models and previous external validation according to a prespecified protocol. We used a large cohort for external validation and all models were validated using the same participants, allowing us to directly compare their predictive performance. Missing data in the validation population were limited for most variables and our findings were unaffected by missing values. Multiple imputation was used to handle missing data, which is preferred to complete-case analysis. A direct match between predictors in the models and the external validation cohort was available for all predictors of externally validated models. Bilateral examination of the carotid arteries was performed and stenoses of either side were used as outcome. Our sensitivity analyses showed that exclusion of participants with previous stroke or TIA and exclusion of participants with previous CVD did not influence the findings of the main analysis substantially.

The present study also had several limitations. Firstly, even though the external validation data were prospectively collected, it was not primarily designed for research purposes. Secondly, participants were self-referred and self-funded, which may limit the generalizability to other (screened) populations. In addition, some predictors were not included in established risk prediction models, such as social status, possibly hampering reliable prediction in specific groups of patients. Thirdly, data on medical history and height were assessed by self-reporting and, hence,

may be susceptible to recall bias. Fourthly, data from duplex measurement of the internal carotid artery and common carotid artery were not recorded separately.

Risk prediction models with good calibration are needed to improve the efficiency of targeted screening programs by identifying those at greatest risk, but future research should determine the long-term predictors of stroke and cardiovascular disease and determine the number of events that could be prevented by using more intensive medical treatment.

In conclusion, the present study showed that most prediction models had modest discrimination, but could reliably identify a cohort of cases at high risk of ACS. The prevalence of ACS in the decile(s) at highest predicted risk of ACS was considerably higher than the population prevalence, thereby substantially reducing the number of individuals needed to screen to detect ACS. Further research should determine the optimum thresholds required for a targeted screening by considering the number needed to screen, the diagnostic yield, the absolute reduction of stroke risk by prophylactic treatment, and cost-effectiveness of different approaches.

Contributors

AH, RB and SL obtained the data and considered the clinical applicability of Life Line Screening. MHFP designed the study. MHFP, PS and RaC cleaned the data. MHFP designed the search strategy, performed literature searches and removed duplicates. MHFP and MSM screened titles and abstracts and assessed full-text articles and reference lists of included studies. MHFP performed the statistical analyses, supervised by MSM, PS and SL. The manuscript was drafted by MHFP. All authors interpreted the data, contributed to revision and editing of the manuscript and approved the final version of the manuscript for submission for publication. MP, AH, MSM and PS contributed equally to this work. RB and SL are co-senior authors.

Declaration of interests

The authors declare no conflicts of interest. This study was designed, conducted and reported independently of Life Line Screening and all funding sources.

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Supplementary material

Methods S1: Search strategy

Table S1: PRISMA Checklist

Table S2: Missing data per variable

Table S3: Full-text evaluation

Table S4: Characteristics of included model derivation and /or internal validation studies

Table S5: Predictors (diagnostic variables) used in the prediction models

Table S6: Risk of bias assessment using PROBAST

Table S7: Discrimination of each prediction model in the original cohort and validation cohorts

Table S8: Clinical application of the prediction model with the best discrimination

Table S9: Sensitivity analyses

Figure S1: Calibration plots for outcome ≥70% ACS

Figure S2: Calibration plots for outcome ≥50% ACS

Figure S3: Clinical application of the prediction model with the best discrimination

Figure S4: Sensitivity analyses

Supplementary material can be found at the journal website:
https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014766

Supplementary material is attached to this dissertation and can be found here

3

Development and Internal Validation of a Risk Score to Detect Asymptomatic Carotid Stenosis

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Abstract

Objective: Asymptomatic carotid stenosis (ACS) is associated with an increased risk of ischemic stroke. Risk scores have been developed to detect individuals at high-risk of ACS, thereby enabling targeted screening, but previous external validation showed scope for refinement of prediction by adding additional predictors. We aimed to develop a novel risk score in a large contemporary screened population.

Methods: We developed a prediction model for moderate (≥50%) and severe (≥70%) ACS using data from 596,469 individuals who attended screening clinics. Variables which predicted the presence of ≥50% and ≥70% ACS independently were determined using multivariable logistic regression. Internal validation was performed using bootstrapping techniques. We assessed discrimination using area under the receiver operating characteristic curves (AUROC) and agreement between predicted and observed cases using calibration plots.

Results: Predictors of ≥50% and ≥70% ACS were age, sex, current smoking, diabetes mellitus, prior stroke/TIA, coronary artery disease, peripheral arterial disease, blood pressure, and blood lipids. Models discriminated between participants with and without ACS reliably, with AUROC of 0.78 (95% CI, 0.77-0.78) for ≥50% ACS and 0.82 (95% CI, 0.81-0.82) for ≥70% ACS. The number needed to screen in the highest decile of predicted risk to detect one case with ≥50% ACS was 13, that of ≥70% ACS was 57. Targeted screening of the highest decile identified 41% of cases with ≥50% ACS and 51% with ≥70% ACS.

Conclusions: Our novel risk model predicted the prevalence of ACS reliably and classified better who has and who does not have ACS compared with previous models. Targeted screening amongst the highest decile of predicted risk identified around 40% of all cases with ≥50% ACS. Initiation or intensification of cardiovascular risk management in detected cases might help to reduce carotid-related complications.

Introduction

Around 15-20% of ischaemic strokes are caused by extracranial carotid stenosis,[1] and such stenoses are also associated with an increased risk of coronary events and vascular death.[2,3] Appropriate use of triple medical therapy (ie, lipid-lowering medication, anti-platelet drugs and blood pressure lowering agents) in patients with clinically significant asymptomatic carotid stenosis (ACS), ie ≥50% luminal narrowing, can help prevent strokes and heart attacks. A study reporting 387 patients with carotid-stenosis related transient ischaemic attacks (TIAs) showed that less than half of patients taking statins and less than 60% were on antiplatelet therapy.[4] This represents potential missed opportunities for stroke prevention.

The overall prevalence of moderate (≥50%) and severe (≥70%) ACS in the general population is low, with estimates of 2.0% and 0.5%, respectively, hence population-level screening for ACS with duplex ultrasound is not recommended in current guidelines.[5-9]

Risk scores to enable targeted screening of cases in populations with an elevated risk of ACS have been developed.[10-14] A previous external validation of these established risk scores showed that the prediction model with the best predictive performance identified a group of cases at high risk of ACS with a number needed to screen (NNS) of 21 to detect one case with ≥50% ACS when people in the highest decile of predicted risk were screened only.[15] However, their data were based on participants who were recruited over two decades ago and important predictors of ACS, such as peripheral arterial disease, were not included in their model. We now aimed to develop a new risk score (the Prevalence of Asymptomatic Carotid Artery Stenosis [PACAS] risk score) in a large contemporary screened population to predict the presence of ACS and to further reduce the NNS by targeted screening of those at highest risk of ACS.

METHODS

Study Population

We used individual participant data from volunteers who attended commercial vascular disease screening clinics (run by Life Line Screening) between 2008 and 2013 in the USA and the UK. All individuals completed a standardized questionnaire, including questions about age, sex, height and weight, history of vascular disease (TIA, stroke, coronary heart disease [CHD]), hypertension, diabetes mellitus (DM), smoking status, and use of antiplatelet, antihypertensive, and lipid-lowering medication. Standard blood pressure cuffs and sphygmomanometers were used, with systolic pressure (SBP) measured using a Doppler probe, and peripheral arterial disease (PAD) was assessed with ankle-brachial pressure index assessment.

Carotid duplex screening was conducted by trained staff using dedicated vascular ultrasound instruments (GE LOGIQ e®). Participants underwent bilateral examination of the carotid arteries with measurement of the highest peak systolic velocity (PSV) and end-diastolic velocities (EDV) of each common carotid artery and internal carotid artery.

A blood sample was provided by a subgroup of participants to measure plasma biochemistry using point-of-care testing methods (Alere Cholestech LDX® system, Alere Inc, Waltham MA, USA). Plasma levels of total cholesterol and high-density lipoprotein (HDL) were measured by enzymatic methods.

Predicted Outcomes

We used two predicted outcomes:

1) Moderate or severe ACS, ie, estimated stenosis of 50-100% (≥50%), based on PSV ≥125 cm/s at either side or 0 cm/s for occluded arteries; and

2) Severe ACS, ie, estimated stenosis of 70-100% (≥70%), based on PSV ≥230 cm/s at either side or 0 cm/s for occluded arteries.

Mean degree of stenosis was determined according to the NASCET classification. If both sides showed ACS, patients were classified according to the greatest percent stenosis.

Statistical analysis

Model Development

Participants who provided a blood sample and who underwent duplex ultrasound of the carotid arteries were included in the present analyses. Age was categorized in four groups (<50, 50-59, 60-69, and ≥70 years), SBP in eight groups (<125, 125-139, 140-159, ≥160 mmHg in participants not using antihypertensives and in participants using antihypertensives), diastolic blood pressure (DBP) in three groups (≥85, 75-84 and <75 mmHg). Smoking status was dichotomized in current smoking vs. former or never smoking and total cholesterol/high-density lipoprotein cholesterol (TC/HDL) ratio in ≥5 vs <5. For most predictors, the percentage of individuals with missing data was acceptable (<12%), except for measured DBP (31.8%) and waist circumference (WC) (34.9%) (Table S1). Missing data were multiply imputed using chained equations by creating 20 datasets with 200 iterations.[16] TC/HDL-ratio was calculated before imputation.[17] Post-imputation rounding was applied for limited-range variables (body mass index (BMI), WC, SBP, DBP, and TC/HDL-ratio), if needed.[18] Analyses were performed in the resulting 20 imputed datasets and results were pooled using Rubin's rules.[19,20]

Multivariable logistic regression was performed to determine the relationships between predictors and the presence of ≥50% and ≥70% ACS. We performed re-estimation of the intercept and predictor weights (beta-coefficients) of the predictors included in the risk score developed by de Weerd et al.[14] These predictors included age groups, sex, current smoking, diabetes mellitus, history of stroke or myocardial infarction, SBP groups, DBP groups, TC/HDL ratio groups. We also performed model extension with forward stepwise selection with predictors selected using Akaike Information Criterion (AIC).[21] For this, we tested whether adding PAD, BMI, and WC improved prediction, as well whether an additional risk group for SBP and SBP by use of antihypertensives improved prediction.

We examined the discrimination and calibration indices of the updated prediction models. Discrimination is the ability of the prediction model to distinguish between participants with and without ACS and is assessed with the area under receiver operating characteristic curve (AUROC).

Calibration is the agreement between predicted and observed risk of ACS and was assessed using calibration plots.

Internal validation and score chart

Internal validation of the predictive performance of the updated model was performed to correct for overfitting, since the predictive performance using the data to develop the model might overestimate the predictive performance in independent populations. We performed internal validation with bootstrapping techniques by creating 1000 bootstrap replications per imputed dataset.[22] We calculated the mean calibration slope, a measure that reflects the extent of overfitting, of the 1000 bootstrap replications in each imputed dataset used that as a uniform shrinkage factor to adjust the regression coefficients for risk of potential overfitting.[23] We used the shrunken beta-coefficients to calculate the adjusted intercept by fitting a logistic model with the shrunken beta-coefficients as dependent variables in the original dataset. We calculated overoptimism-corrected AUROC for each imputed dataset and combined the results with Rubin's rules.[19,20]

Regression coefficients for the predictors were converted into points on a score chart to enable use of such risks using one score chart for each predicted outcome. We calculated the risk of ≥50% and ≥70% ACS for the total points (sum scores). For conversion from regression coefficient to a score chart, we multiplied the beta-coefficients by three (the smallest number while maintaining accurate prediction) and then rounded to the closed integer. If the scores for ≥50% and ≥70% were conflicting, we used the score for ≥50%.

Clinical application and reclassification measures

Test characteristics (prevalence, NNS, sensitivity, specificity, positive and negative predictive values) of a targeted screening using the risk score were calculated for the highest decile and highest two deciles of predicted risk, respectively. We used the highest decile and highest deciles to enable comparison with established and previously validated models.[15]

We calculated reclassification measures to assess the ability of our PACAS risk score to correctly identify cases with and without ACS compared with the established risk score of de Weerd et al 2014 (called the 'original model').[14] We calculated integrated discrimination improvement (IDI), relative IDI (rIDI), and category-based net reclassification improvement (NRI).[24,25] IDI is the

absolute difference in discrimination slopes of the updated and original model. rIDI is the ratio of absolute difference in discrimination slopes of the updated and original model over the discrimination slope of the original model. Category-based NRI is the proportion of individuals correctly reclassified with the updated risk score across risk categories (in this study, the highest decile and highest two deciles of predicted risk) minus the proportion of individuals incorrectly reclassified. Positive values correspond to improved classification.

The reclassification measures were estimated for all 1000 bootstrap replications in each imputed dataset and the median value across the combined 20 datasets is reported (with the 95% confidence interval obtained from the 2.5th and 97.5th percentiles). *P* values <0.05 were considered significant.

Our study adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement (Table S2).[26] STATA version 15.1 was used for all statistical analyses and R version 3.5.1 was used for constructing the figures.

Sensitivity analyses

We performed a sensitivity analysis by omitting blood cholesterol measurements as a predictor in the prediction models.

Ethical approval

The University of Oxford Medical Sciences Inter-Divisional Research Ethics Committee approved the study. All individuals consented for the data collected at the screening to be used for research purposes.

Data availability statement

Data from large population-based studies conducted by the Nuffield Department of Population Health can be shared with bona fide researchers on application to the principal investigators of this study. Details of the departmental data access policy can be found at https://www.ndph.ox.ac.uk/data-access.

RESULTS

Study Population

The mean age in the derivation cohort was 62.2 ± 10.1 years and 35.7% were men. Overall, 12.17% of participants were current smokers and 28.2% was former smokers, and 8.4% reported a history of diabetes. For prior vascular disease, 5.3% reported prior CHD, 3.4% stroke or TIA, and 2.3% PAD. The mean levels and proportions of cardiovascular risk factors and vascular disease were higher in participants with ACS versus without ACS. The overall prevalence of ≥50% ACS was 1.87% and ≥70% ACS 0.34%. Baseline characteristics are shown in Table 1.

Table 1. Selected characteristics of participants at baseline

	All participants N = 596,469)	Participants with <50% ACS (N = 585,291)	Participants with 50-69% ACS (N = 9145)	Participants with ≥70% ACS (N = 2033)†
Age (y), mean ± SD	62.2 ± 10.1	62.0 ± 10.0	68.7 ± 8.9	68.3 ± 8.8
Sex (male)	212,736 (35.7)	208,285 (35.6)	3442 (37.6)	1009 (49.6)
Current smoker	64,318 (12.2)	62,032 (12.0)	1768 (22.2)	518 (28.8)
Ex-smoker	149,121 (28.2)	145,297 (28.0)	3097 (38.8)	727 (40.4)
Never smoked	314,859 (59.6)	311,192 (60.0)	3112 (39.0)	555 (30.8)
Diabetes mellitus	46,875 (8.4)	44,986 (8.2)	1577 (18.3)	312 (16.4)
Stroke or TIA	18,186 (3.4)	17,154 (3.3)	758 (9.0)	274 (15.0)
Coronary heart disease*	28,603 (5.3)	26,997 (5.1)	1262 (14.9)	344 (18.6)
Peripheral arterial disease	17,978 (3.1)	16,370 (2.8)	1184 (13.4)	424 (21.8)
SBP, mean ± SD	131.8 ± 19.6	131.6 ± 19.5	142.1 ± 21.9	145.8 ± 23.5
DBP, mean ± SD	78.3 ± 9.8	78.3 ± 9.8	76.2 ± 10.2	78.3 ± 11.5
TC/HDL-C ratio, mean ± SD	4.0 ± 1.6	4.0 ± 1.6	4.2 ± 1.7	4.4 ± 2.0
BMI, mean ± SD	28.1 ± 5.4	28.1 ± 5.4	28.0 ± 5.3	27.9 ± 5.1
WC, mean ± SD	94.5 ± 15.5	94.4 ± 15.5	96.2 ± 14.9	97.9 ± 15.3
Aspirin	170,272 (33.5)	165,200 (33.1)	4170 (52.4)	902 (52.8)
Lipid-lowering therapy	151,831 (27.1)	146,845 (26.7)	4065 (47.1)	921 (48.6)
Antihypertensives	197,396 (35.2)	191,112 (34.7)	5115 (59.0)	1169 (61.4)

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack; WC, waist circumference.
* Coronary heart disease is defined as previous myocardial infarction or a coronary intervention (bypass, angioplasty, or stenting). † In this group, 500 patients had a presumed occlusion.

Risk score update and internal validation

Multivariable analyses demonstrated that all predictors used in the risk prediction model of de Weerd et al were still significantly associated with the presence of ≥50% and ≥70% ACS, except for the association between diabetes and ≥70% ACS.[14] PAD demonstrated a significant association with both outcomes and was included in the final risk score. SBP risk groups also demonstrated significant associations with both outcomes. Risks were higher in participants using

antihypertensives compared not using antihypertensives in the same SBP risk groups (Table 2). In contrast, BMI and WC showed no improvement of risk prediction and were omitted in the final score.

The following predictors were included in the final risk score: age, sex, current smoking, diabetes mellitus, history of stroke/TIA, history of CHD, PAD, SBP (by use of antihypertensives), DBP, and TC-HDL ratio. The AUROC was 0.78 (95% CI 0.77-0.78) for ≥50% ACS and 0.82 (95% CI 0.81-0.83) for ≥70% ACS. Internal validation with bootstrapping techniques indicated that no correction for overoptimism of the beta-coefficients was needed. Calibration plots showed a very good concordance between predicted and observed risk of both ≥50% and ≥70% ACS, indicating that groups of patients at both low and high risk can reliably be predicted by the risk score (Figure 1).

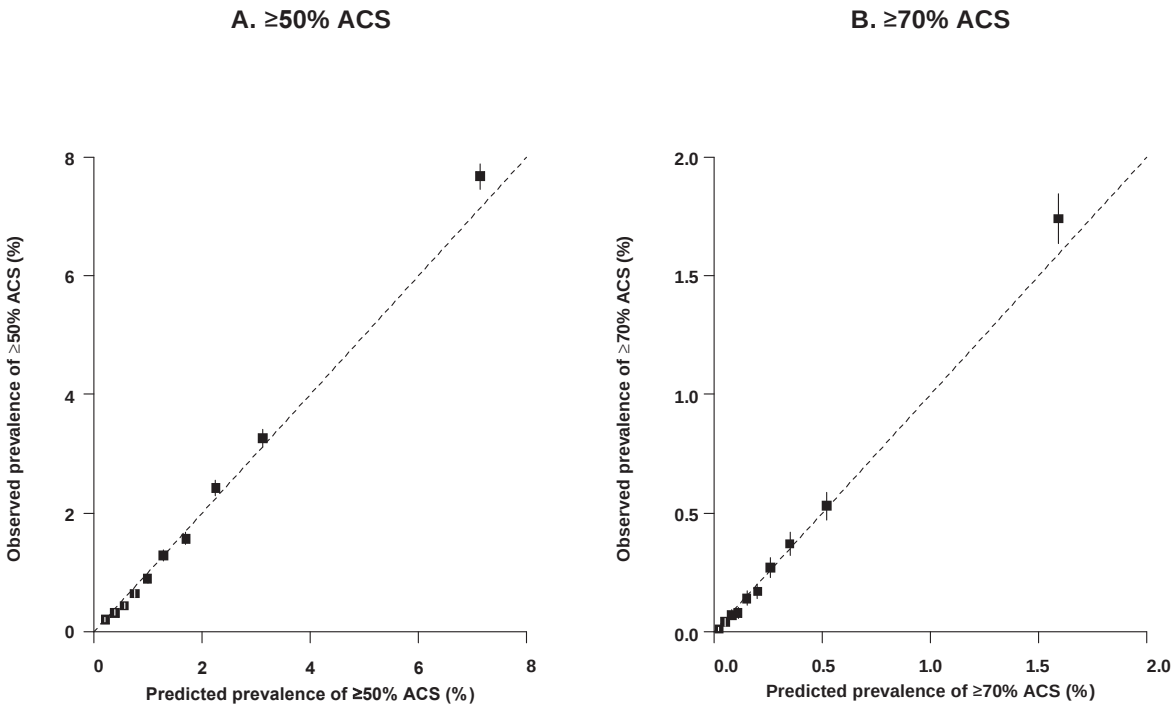
Table 2. Multivariable predictors of moderate and severe ACS

	Odds ratio (95% confidence intervals)			
	≥50% ACS		≥70% ACS	
Predictors*				
Age *(ref: <50 years)*				
50-59 years	2.11 (1.80-2.48)		2.77 (1.84-4.18)	
60-69 years	4.09 (3.50-4.77)		5.18 (3.46-7.74)	
≥70 years	5.87 (5.02-6.86)		6.25 (4.16-9.39)	
Male sex	1.32 (1.27-1.37)		1.93 (1.76-2.11)	
Current smoking	2.69 (2.56-2.84)		3.07 (2.75-3.42)	
Diabetes mellitus	1.37 (1.30-1.44)		1.07 (0.94-1.22)	
Stroke or TIA	1.69 (1.57-1.82)		2.47 (2.14-2.84)	
Coronary heart disease	1.78 (1.68-1.89)		1.85 (1.63-2.10)	
Peripheral arterial disease	2.85 (2.68-3.02)		3.90 (3.46-4.40)	
Systolic blood pressure	*Not using antihypertensives*	*Using antihypertensives*	*Not using antihypertensives*	*Using antihypertensives*
<125 mmHg	Reference	2.51 (2.31-2.74)	Reference	3.26 (2.62-4.05)
125-139 mmHg	1.69 (1.56-1.84)	2.91 (2.68-3.15)	1.90 (1.52-2.36)	3.19 (2.58-3.95)
140-159 mmHg	2.60 (2.39-2.83)	3.98 (3.67-4.32)	3.23 (2.60-4.01)	4.86 (3.95-5.96)
≥160 mmHg	4.41 (3.99-4.87)	5.81 (5.31-6.36)	6.30 (4.96-8.01)	8.46 (6.77-10.57)
Diastolic blood pressure *(ref: ≥85 mmHg)*				
75-84 mmHg	1.31 (1.23-1.39)		1.19 (1.04-1.35)	
<75 mmHg	1.98 (1.86-2.12)		1.63 (1.41-1.88)	
TC/HDL-C ratio of ≥5 *(ref: <5)*	1.32 (1.26-1.38)		1.45 (1.31-1.60)	
Intercept†	-7.08		-9.38	
Discrimination				
AUROC (after internal validation)‡ (95% CI)	0.78 (0.77-0.78)		0.82 (0.81-0.83)	
Reclassification measures				
IDI (95% CI; p-value)	0.0096 (0.0088-0.0105; P < 0.0001)		0.0052 (0.0042-0.0064; P < 0.0001)	
rIDI (95% CI)	0.431 (0.395-0.468)		0.636 (0.501-0.778)	
NRI highest decile of predicted risk (95% CI; p-value)	0.3255 (0.2752-0.3766; P < 0.0001)		0.4837 (0.3776-0.5974; P < 0.0001)	
NRI highest two deciles of predicted risk (95% CI; p-value)	0.3567 (0.2961-0.4153; P < 0.0001)		0.4600 (0.3325-0.5908; P < 0.0001)	

ACS, asymptomatic carotid stenosis; AUROC, area under receiver operating characteristic curve; HDL-C=high-density lipoprotein cholesterol; IDI, integrated discrimination improvement; NRI, net reclassification improvement; rIDI, relative integrated discrimination improvement; TC, total cholesterol; TIA, transient ischemic attack.
The original regression formula can be derived from the odds ratios and the intercept. The beta-coefficients of the linear predictor can be calculated by taking the natural logarithm of the odds ratios. The linear predictor function can be calculated with the following formula: $LP = \text{Intercept} + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \ldots \beta_n x_n$, where the β's are the beta-coefficients or weights of the predictors and the x's are the predictors. The predicted probability can be calculated by: $\frac{e^{LP}}{1+e^{LP}}$.

* Corrected for overoptimism with bootstrapping techniques (shrinkage of regression coefficients was not necessary with calibration slope of 1.00). † Bootstrap-adjusted intercepts are reported. The intercept before internal validation was -7.08 for ≥50% ACS and -9.38 for ≥70% ACS. ‡ The AUROC before internal validation were 0.78 (95% CI 0.77-0.78) for ≥50% ACS and 0.82 (95% CI 0.81-0.83) for ≥70% ACS.

Figure 1. Calibration plots (after internal validation)



Calibration plot shows the mean predicted risk against the observed risk of ≥50% (Figure 1A) and ≥70% ACS (Figure 1B) across deciles of predicted risk after internal validation. The boxes represent the mean predicted risk for each decile and the vertical lines represent the 95% confidence intervals. The dotted diagonal line indicates perfect calibration. Boxes above the diagonal line indicate underestimation of risk and below the diagonal line overestimation of risk. The prevalences and number of cases per decile are provided in Table S3.

Clinical application and reclassification measures

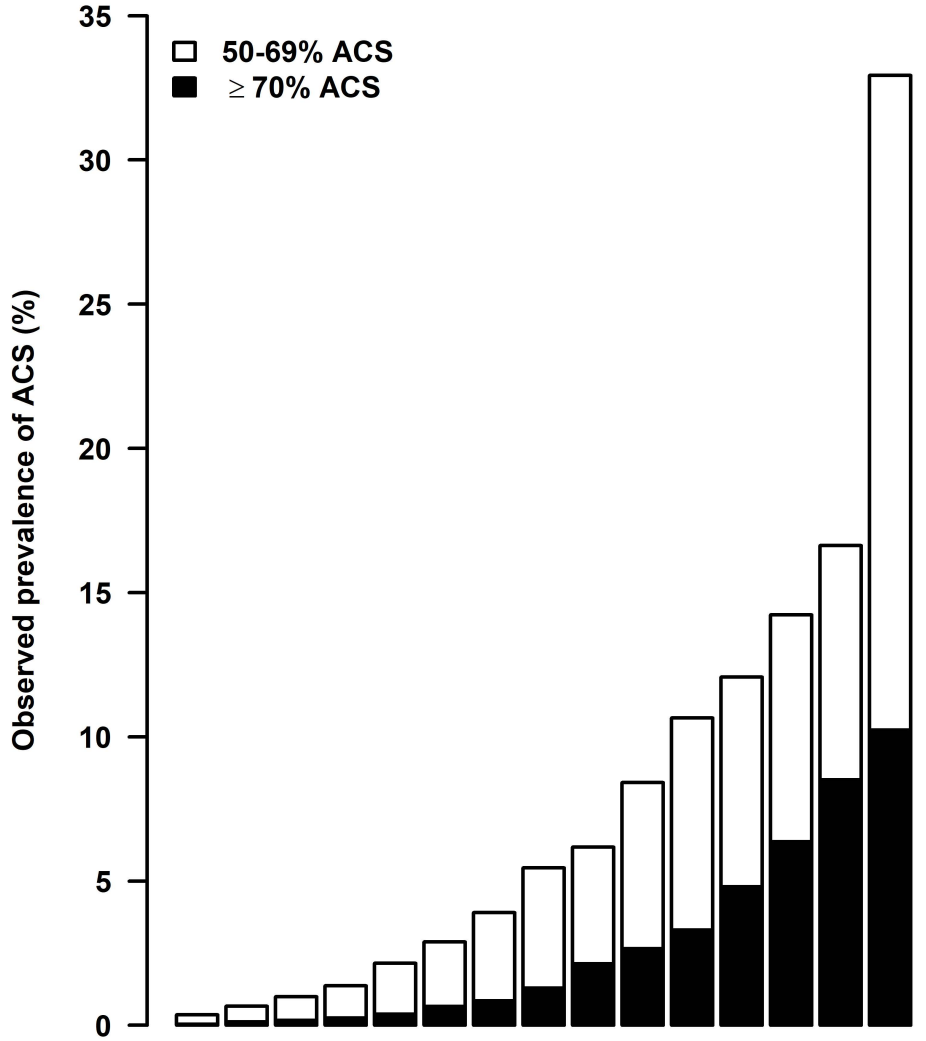
The variables included in the risk score (PACAS score chart) are shown in Table 3. The values of score ranged from 0 to 25. The risks of ≥50% and ≥70% ACS for each sum score are provided in Figure 2. The calculation of the risk of ≥50% and ≥70% ACS for an example patient is provided in Figure 3. The distribution of sum scores is provided in Figure S1.

Table 3. Predictors and associated scores

Predictors	Risk scores	
Age, years		
<50	0	
50-59	2	
60-69	4	
≥70	5	
Male sex	1	
Current smoking	3	
Diabetes mellitus	1	
History of stroke or TIA	2	
Coronary heart disease	2	
Peripheral arterial disease	3	
Systolic blood pressure, mmHg	*Not using antihypertensives*	*Using antihypertensives*
<125	0	3
125-139	2	3
140-159	3	4
≥160	4	5
Diastolic blood pressure, mmHg		
≥85	0	
75-84	1	
<75	2	
TC/HDL-C ratio		
<5	0	
≥5	1	

ACS, asymptomatic carotid artery stenosis; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TIA, transient ischemic attack.
The PACAS score ranges from 0 to 25. The risks of ≥50% and ≥70% ACS for each sum score are provided in Figure 2.

Figure 2. Observed prevalence of ACS by sum score



Bar chart showing the observed prevalence of ACS for each sum score. The black parts of the bars represent the prevalence of ≥70% ACS and the white parts the prevalence of 50-69% ACS. The prevalence of ≥50% ACS is calculated by taking the sum of the prevalences of 50-69% and ≥70% ACS.

Figure 3. Calculating the risk of ≥50% and ≥70% ACS using the PACAS risk score.

As an example, consider a male case, aged 65, current smoker, using antihypertensives, no diabetes, no stroke or TIA and no coronary heart disease, with peripheral arterial disease, with an SBP of 160 and DBP of 100 and TC-HDL-C ratio of 5.6.

Step 1: Calculate the sum score using the scores provided in Table 3

The sum score of this case is 17.

Step 2: Find the prevalence corresponding to the sum score in Figure 2

The corresponding prevalence of ≥50% ACS is 12% and ≥70% is 4.8%.

Step 3: Calculate the NNS

The NNS can be calculated as follows: $\frac{1}{\text{prevalence}} * 100$.

For this patient, the NNS to detect one patient with ≥50% ACS is 8 and ≥70% ACS is 21.

The prevalence of ≥50% ACS when screening the 10% highest risk participants was 7.7%. Hence, the NNS to detect one participant with ≥50% ACS of 13. A targeted screening of the 10% highest risk participants could identify 40.9% of cases with ≥50% ACS. The prevalence of ≥50% ACS when screening the 20% highest risk participants was 5.5%. Hence, the NNS to detect one participant with ≥50% ACS of 18. A targeted screening of the 20% highest risk participants could identify 58.4% of cases with ≥50% ACS (Table 4). The 10% highest risk corresponds approximately to targeted screening of participants with a sum score of 12 or more and the 20% highest risk corresponds approximately to targeted screening of participants with a sum score of 10 or more.

Table 4. Performance of the PACAS risk score to detect ACS

	Number of individuals	Number of cases with ACS	Sensitivity	Specificity	NPV	PPV / Observed prevalence	NNS
Targeted screening programme of the 10% highest risk participants							
≥50% ACS	59,647	4575	40.9%	90.6%	98.8%	7.7%	13
≥70% ACS	59,706	1036	51.0%	90.1%	99.8%	1.7%	57
Targeted screening programme of the 20% highest risk participants							
≥50% ACS	119,438	6524	58.4%	80.7%	99.0%	5.5%	18
≥70% ACS	121,213	1362	67.0%	79.8%	99.9%	1.1%	89

ACS, asymptomatic carotid stenosis; NNS, number needed to screen; NPV, negative predictive value; PPV, positive predictive value.
The number of false negatives and true negatives were 6603 and 530,219, and 4654 and 472,377 for the highest decile and highest two deciles of predicted risk of ≥50% ACS, respectively, and, 997 and 535,766 and, 671 and 474,585 for the highest decile and highest two decile of predicted risk of ≥70% ACS, respectively.

Reclassification measures demonstrated a significant improvement of the PACAS risk score compared to the established risk score of de Weerd et al.[14]

For the outcome ≥50% ACS, the IDI was 0.0102 (95% CI 0.0088-0.0115; P < 0.00001) and the rIDI was 0.455, corresponding to an 46% improved classification. The NRI with the highest decile as threshold was 0.3489 (95% CI 0.3019-0.3958; *P* < 0.00001) and the NRI with the two highest deciles as threshold was 0.3152 (95% CI 0.2780-0.3524; *P* < 0.00001).

For the outcome ≥70% ACS, the IDI was 0.0053 (95% CI 0.0039-0.0068; P < 0.00001) and the rIDI was 0.654, corresponding with an 65% improved classification. The NRI with the highest decile as threshold was 0.4320 (95% CI 0.3416-0.5224; *P* < 0.00001) and the NRI with the two highest deciles as threshold was 0.4162 (95% CI 0.3025-0.5299; *P* < 0.00001) (Table 2).

Sensitivity analysis

The discrimination of the internally validated PACAS risk score without inclusion of blood cholesterol measurements as predictors was 0.78 (95% CI 0.77-0.78) for ≥50% ACS and 0.82 (95% CI 0.81-0.82) for ≥70% ACS, respectively.

Discussion

This risk score was developed to identify individuals at high-risk of clinically significant ACS, which we define as a stenosis that might alter clinical management. Predictors for moderate and severe ACS included age, sex and vascular risk factors. Discrimination analyses was good for ≥50% ACS and even better for stenosis ≥70% ACS. Calibration plots showed reliable prediction of the prevalence of ≥50% and ≥70% ACS. The observed prevalence of ≥50% in the highest decile of predicted risk was 7.7% with an NNS of 13 and the observed prevalence of ≥70% in this decile was 1.7% with an NNS of 57. This new risk score outperformed existing risk scores by including additional predictors of ACS.

This risk scores may contribute to a clinically and cost-effective targeted screening protocol. Individuals in whom significant ACS is detected should receive intensive cardiovascular risk management that include life-style interventions and antihypertensive, antithrombotic, and lipid-lowering drug therapy.[8] Medical management not only aims to reduce the risk of stroke, but also reduce risks of other vascular disease, since ACS is also a risk factor for myocardial infarction and premature vascular death.[3]

Previous randomized trials that included a subset of ACS individuals taking low-dose aspirin reported an annual risk of ipsilateral stroke between 1.4% and 2.4%.[27-29] More recent studies reported annual risk of ipsilateral ischemic stroke of 0.34% in a cohort of individuals on intensive medical therapy after a TIA or minor stroke.[30] Risks in asymptomatic individuals without a history of contralateral ischemic cerebrovascular disease might be lower, but the intensity of medical prophylaxis is also often lower in such individuals. Our study showed considerable scope for further optimizing medical therapy with around half of cases with ACS reporting use of lipid-lowering therapy and aspirin. While this was higher in patients in the highest decile of ≥50 ACS risk with 76.4% reporting use of antihypertensives, 51.9% lipid-lowering therapy, and 56.4% aspirin, only 30.2% used triple medical therapy. In the highest two deciles, 73.1% reported use of antihypertensives, 47.4% lipid-lowering therapy, and 52.6% aspirin, and only 25.7% used triple medical therapy.

A cost-effectiveness analysis of this Swedish screening programme, where duplex ultrasound screening for abdominal aortic aneurysm was supplemented by ACS screening, estimated that the stroke risk could be reduced by 50% from antiplatelet and lipid-lowering therapy combined, but with a wide margin of variation due to the absence of comparative studies.[31,32]

Predictors of increased risk of stroke in individuals with ACS have been identified and carotid interventions might be considered in cases in whom the absolute gain of reducing the risk of stroke by carotid revascularisation are found to be worthwhile.[8] Use of imaging characteristics and risk stratification tools for individualized prediction of stroke based on multiple predictors have been proposed, but these have not been validated in independent contemporary populations.[8,33,34]

The PACAS risk score can both be applied to cases with and without overt cardiovascular disease and could be used for targeted screening. Such risk prediction can be performed easily by general practitioners and specialists with the aim to initiate or intensify cardiovascular risk management. Different imaging modalities and criteria for measuring stenosis of the carotid arteries are available. The validity of duplex ultrasound is good if performed by experienced sonographers.[35] PSV as a single measure may be useful as a screening tool to identify cases for more detailed evaluation.

The derivation cohort used in the present study has several limitations, including the fact that participants were self-referred and self-funded, which might influence the generalizability to other populations. Although we found a large number of participants with lower scores in our population, the magnitude of multivariable predictors of ACS were similar to previous population-based studies.[14] Duplex ultrasounds were not performed in validated ultrasound laboratories by qualified sonographers, but simplified screening methods showed reasonable interobserver reliability and validity.[36,37] Recall bias cannot be fully excluded for predictors that were self-reported. Blood pressure and cholesterol were measured once and might not reflect 'usual' values. Indications for duplex ultrasound were not available and recommended treatment for patients in whom carotid artery occlusion is found might differ from patients with carotid

stenosis. Clinical staging of PAD was not available. These limitations indicate the need for validation of our risk score in an external population. Even though the NNS was greatly reduced in high-risk cases compared with systematic screening, the positive predictive value (PPV) indicates that many cases considered high-risk will turn out to have no ACS. Past medication use and potential reasons for quitting were not recorded.

However, the present study has some important strengths, including use of a relatively contemporary derivation cohort of 0.6M participants for the development of the PACAS risk score and internal validation showed no evidence for overfitting. Our sensitivity analysis showed that risk prediction based on patient characteristics and measured blood pressure is equally reliable and excluding blood cholesterol measurement does not affect adequate risk predictions. Application of the PACAS risk score and calculation of individualized risks can be done quite easily.

Future research will establish the optimal threshold for targeted screening by determining the risks of stroke and other cardiovascular diseases in ACS cases and how many such cardiovascular events could be prevented by improved cardiovascular risk management in cases in whom ACS is detected using a cost-effective targeted screening programme. Whether screening for ACS can be combined with screening for other risk factors for stroke, such as atrial fibrillation, possibly further reducing stroke incidence should be determined.

Conclusions

The novel PACAS risk score including age, sex, current smoking, DM, history of stroke/TIA, CHD and PAD, SBP (by use of antihypertensives), DBP, and TC/HDL-ratio can predict the risk of ≥50% and ≥70% ACS reliably and classified better who has and who does not have ACS compared with established risk scores. The prevalence in the decile at highest predicted risk of ≥50% ACS was 7.7%. Targeted screening of this high-risk group identified around 40% of cases with ≥50% ACS, with an NNS of 13.

Contributors

SL, RB, and AH obtained the data from Life Line Screening. MHFP designed the study. MHFP and PS cleaned the data. MHFP performed the statistical analyses. The manuscript was drafted by MHFP. All authors interpreted the data, contributed to revisions of the manuscript and approved the final version for submission for publication.

Declaration of interest

The authors declare no conflicts of interest. This study was designed, conducted and reported independently of Life Line Screening who provided their data at no cost and all sources of support.

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SUPPLEMENTARY MATERIAL

Table S1: Missing data per variable

Table S2: TRIPOD Checklist

Table S3. Predicted and observed prevalence of ACS across deciles of predicted risk

Figure S1. Distribution of sum scores

Supplementary material is attached to this dissertation and can be found here

4

Detection of Asymptomatic Carotid Stenosis in Patients with Lower Extremity Arterial Disease: development and external validations of a risk score

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Abstract

Objective: We aim to identify established risk prediction models for asymptomatic carotid stenosis (ACS) in patients with lower extremity arterial disease (LEAD), then develop a new risk prediction model and, finally, validate this model in two independent populations.

Background: Recommendations for screening patients with LEAD to detect ACS and subsequently improve preventive therapy and compliance are conflicting. Prediction models might identify patients at high risk of ACS, possibly allowing targeted screening.

Methods: We conducted a systematic search for prediction models for ≥50% ACS in patients with LEAD. We subsequently developed a prediction model in screened patients from the United States with ankle-brachial index (ABI) of ≤0.9. We assessed discrimination and calibration. Finally, external validations in two independent cohorts, comprising 5400 patients from the United Kingdom and 1536 patients from The Netherlands.

Results After screening 4721 studies, no previously published prediction models were found. For development of our new model, we used data of 112,117 patients, of whom 6354 (5.7%) had ≥50% and 2801 (2.5%) had ≥70% ACS. Age, sex, smoking status, history of hypercholesterolemia, stroke/TIA, CHD and measured SBP were predictors of ACS. The model discriminated well, with an AUROC curve of 0.71 (95%CI, 0.71-0.72) for ≥50% and 0.73 (95%CI, 0.72-0.74) for ≥70% ACS. Screening the 20% patients at highest risk detected 13.1% with ≥50% ACS (NNS of 8), and 5.8% with ≥70% ACS (NNS of 17). This yielded 44.2% and 46.9% of patients with ≥50% and ≥70% ACS, respectively. External validations showed reliable discrimination and adequate calibration.

Conclusion The presence of significant ACS in patients with LEAD can be predicted reliably using our prediction model that is based on routinely collected clinical characteristics and simple physical measurements, and this prediction model identifies patients for targeted screening.

Introduction

Carotid stenosis is a cause of cerebral infarction in around 15% of ischaemic strokes.[1] Significant asymptomatic carotid stenosis (ACS) is also a predictor for coronary events and vascular death,[2] and both risks of strokes and heart attacks can be reduced with adequate medical therapy. Using duplex ultrasound, the prevalence of moderate or severe (≥50%) and severe (≥70%) ACS in the general population has been estimated to be 2.0% and 0.5%, respectively.[3] The prevalence is higher in patients with lower extremity arterial disease (LEAD),[4,5] but guideline recommendations for screening for significant ACS in patients with LEAD vary.[6-9] The Society for Vascular Surgery (SVS) advise targeted screening in patients with multiple risk factors, including LEAD, age >65 years with a history of one or more of coronary heart disease (CHD), smoking or hypercholesterolemia.[9] The "14 Society" guidelines recommends that targeted screening in patients with symptomatic LEAD, CHD or atherosclerotic aortic aneurysm may be considered.[6] The European Society for Vascular Surgery (ESVS) advise targeted screening in patients with multiple vascular risk factors.[8] In contrast, the American Heart Association (AHA) recommends against screening.[7] Arguments for screening include initiation or improvement of preventive therapies, but also closer follow-up to maintain compliance and decrease the risk of subsequent vascular events.[10,11] Arguments against screening include the low prevalence of significant ACS, even among patients with LEAD.

Risk prediction models allow targeted screening among patients with LEAD at particularly high risk of significant ACS based on multiple risk factors. Detection of ACS in patients with LEAD enables to initiate or improve medical therapy and its compliance. We conducted a systematic review for published risk prediction models, developed a new risk prediction model, (the Prevalence of Asymptomatic Carotid Artery Stenosis in patients with Lower Extremity Arterial Disease [PACAS-LEAD] risk score) in a large contemporary screened population and, finally, externally validated this model in two independent populations.

METHODS

Systematic review

We performed a systematic review to identify established risk prediction models for prediction of ≥50% ACS in patients with LEAD. This was conducted according to a predefined protocol that was registered prospectively in the international prospective registry for systematic reviews (PROSPERO): CRD42019155482. Details are provided in Appendix S1-S2.

Derivation cohort

Data of 3,050,448 self-referred and self-funded individuals who attended commercial vascular screening clinics between 2008 and 2013 in the USA were used to develop a risk prediction model.[12] All individuals completed a standardized questionnaire including questions about their age, sex, height and weight, smoking history, history of hypertension, hypercholesterolemia, diabetes mellitus and vascular disease (transient ischemic attack [TIA], stroke and coronary artery disease [CHD]), and use of antiplatelet, antihypertensive, and lipid-lowering medication. Blood pressure was measured as part of the ankle-brachial pressure index assessment. Standard blood pressure cuffs and sphygmomanometers were used, and systolic blood pressure (SBP) was measured using a Doppler probe.

Most participants underwent carotid duplex screening (conducted by trained staff using dedicated vascular ultrasound instruments [GE LOGIQ e®]). The highest peak systolic velocity (PSV) and end diastolic velocities (EDV) of both common and internal carotid arteries were measured.

We defined LEAD as ABI < 0.9 at either side, and such patients were included in these analyses. We excluded participants who did not undergo ABI measurement or in whom ABI was not possible because the arteries could not be compressed (N = 175,517) or with ABI > 0.9 at both sides (N = 2,759,591), who did not undergo duplex ultrasound (N = 2759) or with inconsistent values (N = 464).

External validation cohort

For the first external validation of our risk prediction model, we used data from 225,691 self-referred and self-funded individuals who attended commercial vascular screening clinics between 2008 and 2013 in the UK. As in the derivation cohort, we excluded participants who did not

undergo ABI measurement or in whom ABI was not possible because the arteries could not be compressed (N = 10,774) or with ABI > 0.9 at both sides (N = 209,276), who did not undergo duplex ultrasound (N = 106), or with inconsistent values (N = 135).

For the second external validation, we used data from the Second Manifestation of ARTerial disease (SMART) study. This is an ongoing prospective cohort at the University Medical Center Utrecht, The Netherlands. Rationale and design of the SMART study have been published previously.[13] Between September 1996 and October 2019, 13,799 patients with recent (one year prior to baseline) diagnosis of a first manifestation of arterial disease, including cerebrovascular disease, coronary artery disease, peripheral arterial disease or aneurysm of the abdominal aorta, were included. After inclusion, patients completed a questionnaire with questions about medical health and lifestyle, and underwent standardized vascular screening. Office blood pressure was measured with a non-random sphygmomanometer and the average of multiple measurements was taken. Use of anti-thrombotic, blood pressure lowering, and cholesterol-lowering medication was recorded. For external validation, we used baseline characteristics of patients who underwent ABI and duplex ultrasound of the carotid arteries. We excluded patients with ABI > 0.9 at both sides (N = 11,371), in whom no duplex ultrasound was performed (N = 35), or with recent (< 12 months) cerebrovascular symptoms (N = 220).

Predicted outcomes

We used two outcomes:

1) Moderate or severe ACS. This was defined as ≥50%; based on PSV ≥150 cm/s at either side or 0 cm/s for occluded arteries.

2) Severe ACS. This was defined as ≥70%; based on PSV ≥210 cm/s at either side or 0 cm/s for occluded arteries.

Model derivation

The development of our prediction model adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement (Table S1).[14] Baseline characteristics are presented as means and standard deviations (SD) for continuous variables and as absolute numbers and percentages for categorical variables. Age was categorized

in four groups (<50, 50-59, 60-69, and ≥70 years), SBP in three groups (<140, 140-159, and ≥160 mmHg), ABI in three group (>0.8-≤0.9, >0.4-≥0.8, ≤0.4), and we dichotomized smoking status in ever smoking vs. never smoking. For most predictors, the percentage of patients with missing data was acceptable (<10%), except for smoking status (10.5%) reported history of CHD (13.8%) and stroke/TIA (15.2%) (Table S2). Missing data were multiple imputed using chained equations and we created 20 datasets with 200 iterations. Results were combined with Rubin's rules.[15,16] The relationship between predictors and the presence of ≥50% and ≥70% ACS in patients with LEAD was determined with multivariable logistic regression. Predictors were selected based on established risk prediction models for significant ACS,[17] and forward stepwise selection with predictors selected using Akaike Information Criterion (AIC).[18] We examined discrimination and calibration of the developed risk prediction model. Discrimination is the ability of the prediction model to distinguish between patients with and without the disease outcomes, assessed using the area under receiver operating characteristic (AUROC) curve. Calibration is the agreement between predicted risk and observed risk and was assessed with calibration plots.

Internal validation and score chart

The risk prediction model was internally validated to control for potential overfitting, since the apparent predictive performance, i.e. the performance in the data used to develop the model, might overestimate the predictive performance in similar future patients. We performed internal validation with bootstrapping by creating 1000 bootstrap replications per imputed dataset.[19] We calculated the mean calibration slope of the 1000 bootstrap replications in each imputed dataset used that as a uniform shrinkage factor to adjust the regression coefficients for risk of potential overfitting. We used the shrunken beta-coefficients to calculate the adjusted intercept by fitting a logistic model with the shrunken beta-coefficients as dependent variables in the original dataset. We also calculated over-optimism-corrected AUROC curve for each imputed dataset and combined the results with Rubin's rules.[15,16]

Regression coefficients of the predictors were converted into points on a score chart to facilitate clinical use of the risk prediction model. We made one score chart for both ≥50% and ≥70% ACS. For this, we multiplied the beta-coefficients by four and then rounded to the closed integer. If the

scores for ≥50% and ≥70% were conflicting, we used the score for ≥50%. We calculated the risk of ≥50% and ≥70% ACS for the total points (sum scores).

External validation

We assessed the predictive performance in patients who attended commercial vascular screening clinics in the UK and in patients from the SMART cohort.[13] We applied the same methods for reporting baseline characteristics and handling missing data as in the derivation cohort. The original regression formula (after internal validation) was used to calculate the risk of ≥50% and ≥70% ACS. We assessed discrimination, using the area under receiver operating characteristic (AUROC) curve, and calibration with calibration plots. We were able to match all predictors in the validation cohorts, but we used a proxy for history of hypercholesterolemia in one external validation cohort. It was based on self report in the derivation cohort and blood measurement in the SMART cohort. Differences between the prevalence of the predicted outcome in the development cohort and the validation cohorts are known to influence calibration. For this reason, we recalibrated the PACAS-LEAD to the prevalence of the predicted outcome in the external validation cohorts by adjusting the original intercept. This type of recalibration is referred to as 'update intercept' or 'calibration-in-the-large'.[20]

STATA version 15.1 was used for all statistical analyses and R version 3.5.1 was used for constructing figures.

RESULTS

Systematic review of the literature

We screened 4907 unique reports identified by literature searching, assessed the full-texts of 43 reports for eligibility, and no study was found that met our inclusion criteria (Figure S1 & Table S3). No external validation of established risk prediction models could be performed.

Derivation cohort

In total, 112,117 patients with LEAD were used for development. The mean age in the derivation cohort was 70.5 ± 10.7 years and 27.7% were men. Around 50% of patients reported use of aspirin and lipid-lowering therapy and around 60% reported use of antihypertensive therapy. In patients with significant ACS, around 60% reported use of aspirin and lipid-lowering therapy and almost 75% reported use of antihypertensive therapy. The overall prevalence of ≥50% ACS in patients with LEAD was 5.7% and ≥70% ACS was 2.5%. Baseline characteristics are provided in Table 1.

Risk prediction model development and internal validation

The following predictors were included: age, sex, ever smoking vs never smoking, a history of hypercholesterolemia, stroke/TIA, CHD, measured SBP, and ABI. The AUROC curve adjusted for over-optimism was 0.714 (95% CI 0.707-0.720) for ≥50% ACS and 0.725 (95% CI 0.715-0.734) for ≥70% ACS (Table 2). Internal validation with bootstrapping techniques indicated that no shrinkage of the beta-coefficients was needed. Calibration plots showed good concordance between predicted and observed risk of both ≥50% and ≥70% ACS, indicating that groups of patients at both low and high risk can reliably predicted by the PACAS-LEAD risk score (Figure 1).

Table 1. Baseline characteristics

	Derivation cohort Life Line Screening (US patients)			
Baseline characterisics[1]	**All patients (N = 112,117)**	**Patients with <50% ACS (N = 105,763)**	**Patients with 50-69% ACS (N = 3553)**	**Patients with ≥70% ACS (N = 2801)[4]**
Age (y)	70.5 ± 10.7	70.3 ± 10.8	74.1 ± 8.8	72.4 ± 9.1
Sex (male)	31,004 (27.7)	28,505 (27)	1265 (35.6)	1234 (44.1)
Current smoker	19,706 (19.6)	18,089 (19.1)	814 (25.8)	803 (32)
Former smoker	38,851 (38.7)	36,231 (38.3)	1479 (46.9)	1141 (45.5)
Never smoked	41,819 (41.7)	40,397 (42.7)	858 (27.2)	564 (22.5)
Diabetes mellitus	21,549 (21.1)	19,951 (20.7)	951 (29.2)	647 (25.4)
Hypercholesterolemia	54,271 (51.4)	50,671 (50.8)	2048 (61.6)	1552 (59.2)
CHD[2]	15,099 (15.6)	13,587 (14.9)	844 (26.8)	668 (27.4)
Stroke or TIA	9103 (9.6)	8217 (9.2)	446 (14.6)	440 (18.4)
SBP (mmHg)	144.8 ± 23.9	144.4 ± 23.7	151.7 ± 24.8	152.3 ± 25.6
ABI[3]	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.2	0.7 ± 0.2
Aspirin	43,316 (50.2)	40,256 (49.5)	1715 (61.8)	1345 (62.5)
Lipid-lowering therapy	48,224 (46.6)	44,766 (45.8)	1958 (59.5)	1500 (58.0)
Antihypertensive therapy	65,323 (62.5)	60,855 (61.7)	2556 (76.2)	1912 (73.5)
	Validation cohort Life Line Screening (UK patients)			
	All patients (N = 5400)	**Patients with <50% ACS (N = 4909)**	**Patients with 50-69% ACS (N = 230)**	**Patients with ≥70% ACS (N = 261)[5]**
Age (y)	70.3 ± 9.5	70.0 ± 9.6	73.2 ± 8.4	73.2 ± 7.7
Sex (male)	2007 (37.2)	1775 (36.2)	101 (43.9)	131 (50.2)
Current smoker	1497 (32.2)	1333 (31.6)	79 (39.1)	85 (39.2)
Former smoker	1675 (36.1)	1509 (35.7)	79 (39.1)	87 (40.1)
Never smoked	1471 (31.7)	1382 (32.7)	44 (21.8)	45 (20.7)
Diabetes mellitus	711 (16.7)	637 (16.4)	34 (18.6)	40 (21.2)
Hypercholesterolemia	1899 (44.8)	1696 (43.7)	92 (52.9)	111 (62.4)
CHD[2]	655 (15.7)	559 (14.6)	37 (20.7)	59 (32.6)
Stroke or TIA	377 (9.3)	321 (8.6)	24 (14.4)	32 (18.8)
SBP (mmHg)	149.8 ± 24.6	149.0 ± 24.4	155.7 ± 24.0	158.9 ± 25.6
ABI[3]	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.7 ± 0.2
Aspirin	952 (38.4)	832 (36.9)	51 (52.0)	952 (38.4)
Lipid-lowering therapy	1849 (43.8)	1636 (42.2)	102 (59.3)	69 (55.2)
Antihypertensive therapy	2205 (51.3)	1963 (49.9)	116 (64.8)	126 (69.2)
	Validation cohort SMART			
	All patients (N = 1536)	**Patients with <50% ACS (N = 1278)**	**Patients with 50-69% ACS (N = 67)**	**Patients with ≥70% ACS (N = 191)[6]**
Age (y)	61.6 ± 10.3	60.7 ± 10.5	65.7 ± 6.9	65.8 ± 7.9
Sex (male)	1021 (66.5)	838 (65.6)	45 (67.2)	138 (72.3)
Current smoker	755 (50.9)	648 (51.2)	33 (49.3)	94 (49.7)
Former smoker	601 (39.5)	490 (38.7)	25 (37.3)	86 (45.5)
Never smoked	146 (9.6)	128 (10.1)	9 (13.4)	9 (4.8)
Diabetes mellitus	354 (23.0)	279 (21.8)	19 (28.4)	56 (29.3)
Hypercholesterolemia	852 (56.8)	706 (56.6)	35 (53.8)	111 (59.7)
CHD[2]	339 (22.1)	264 (20.7)	20 (29.9)	55 (28.8)
Stroke or TIA	110 (7.2)	71 (5.6)	4 (6)	35 (18.3)
SBP (mmHg)	147 ± 22.9	146 ± 22.8	148 ± 23.6	153 ± 22.8
ABI[3]	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
Antiplatelet therapy	721 (53.2)	617 (53.7)	26 (46.4)	78 (52)
Anticoagulant	136 (9.2)	112 (9)	5 (7.8)	19 (10.9)
Lipid-lowering therapy	866 (56.4)	700 (54.8)	40 (59.7)	126 (66)

Antihypertensive therapy	993 (64.6)	799 (62.5)	50 (74.6)	144 (75.4)

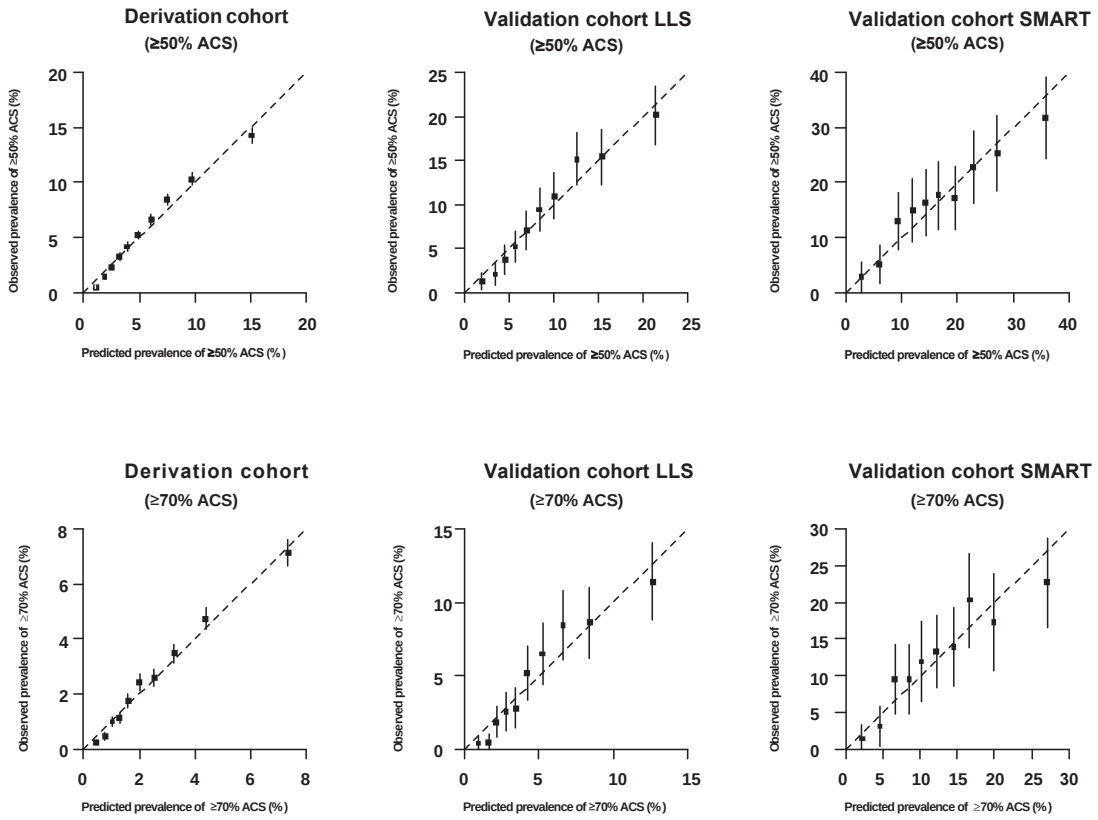
ABI, Ankle-brachial pressure index; CHD, coronary heart disease; SBP, systolic blood pressure; SD, standard deviation; SMART, Second Manifestation of ARTerial disease; TIA, transient ischemic attack.
[1] Baseline characteristics are presented as means and standard deviations (SD) for continuous variables and as absolute numbers and percentages for categorical variables. [2] Coronary heart disease is defined as previous myocardial infarction or a coronary intervention (bypass, angioplasty, or stenting). [3] The lowest ABI value of both lower extremities was included. [4] In this group, 629 patients of the derivation cohort had a presumed occlusion. [5] In this group, 41 patients of the validation cohort had a presumed occlusion.[6] In this group, 67 patients of the validation cohort had a presumed occlusion.

Table 2. Predictors of moderate and severe ACS in patients with LEAD

	Odds ratio (95% confidence intervals)	
	≥50% ACS	≥70% ACS
Predictors [1]		
Age *(ref: <50 years)*		
50-59 years	3.27 (2.11-5.09)	3.26 (1.78-5.99)
60-69 years	5.15 (3.34-7.95)	4.41 (2.42-8.01)
≥70 years	5.76 (3.74-8.87)	4.16 (2.29-7.55)
Male sex	1.35 (1.27-1.42)	1.60 (1.48-1.73)
Ever smoking	1.94 (1.82-2.07)	2.07 (1.88-2.28)
Hypercholesterolemia	1.35 (1.28-1.42)	1.27 (1.17-1.38)
Stroke or TIA	1.42 (1.31-1.54)	1.63 (1.46-1.82)
CHD	1.52 (1.42-1.62)	1.44 (1.31-1.58)
SBP *(ref: <140 mmHg)*		
140-159 mmHg	1.24 (1.16-1.32)	1.26 (1.14-1.38)
≥160 mmHg	1.73 (1.63-1.85)	1.80 (1.63-1.98)
ABI *(ref: 0.8-0.9)*		
0.4-0.8	2.08 (1.97-2.20)	2.15 (1.98-2.34)
<0.4	3.62 (3.18-4.12)	3.69 (3.08-4.43)
Intercept [2]	-5.93	-6.69
Discrimination derivation cohort [3]		
AUROC curve after internal validation (95% CI)	0.714 (0.707-0.720)	0.725 (0.715-0.734)
Discrimination validation cohorts		
AUROC curve in LLS - UK patients (95% CI)	0.703 (0.680-0.726)	0.716 (0.693-0.740)
AUROC curve in SMART study (95% CI)	0.667 (0.633-0.700)	0.671 (0.637-0.705)

ABI, ankle-brachial index; ACS, asymptomatic carotid stenosis; AUROC curve, area under receiver operating characteristics curve; CHD, coronary heart disease; LLS, Life Line Screening; SMART, Second Manifestation of ARTerial disease; TIA, transient ischemic attack.
The original regression formula can be derived from the odds ratios and the intercept. The beta-coefficients for the linear predictor can be calculated by taking the natural logarithm of the odds ratios. The linear predictor can be calculated with the following formula: $LP = \text{Intercept} + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \ldots \beta_n x_n$,where the β's are the beta-coefficients or weights of the predictors and the x's are the predictors. The predicted probability can be calculated by: $\frac{e^{LP}}{1+e^{LP}}$.
[1] Beta-coefficients and intercept corrected for overoptimism with bootstrapping techniques (shrinkage of regression coefficients was not indicated with calibration slope of 1.00). [2] Bootstrap-adjusted intercepts were the same the intercept before internal validation. [3] AUROC curves before internal validation were 0.714 (95% CI 0.708-0.720) for ≥50% ACS and 0.725 (95% CI 0.716-0.734) for ≥70% ACS.

Figure 1. Calibration plots of PACAS-LEAD in derivation and validation cohorts



Calibration plots of PACAS-LEAD showing the predicted risk against the observed risk of ≥50% *(top row)* and ≥70% ACS *(bottom row)* across deciles of predicted risk in the derivation cohort after internal validation *(left column)*, in the validation cohorts LLS – UK patients *(middle column)* and SMART after recalibration *(right column)*. The boxes represent the mean predicted risk for each decile and the vertical lines represent the 95% confidence intervals. The dotted diagonal line indicates perfect calibration. Boxes above the diagonal line indicate underestimation of risk and below the diagonal line overestimation of risk. The calibration plots of PACAS-LEAD in the validation cohorts before recalibration are provided as Figure S3. The prevalences and number of cases per decile are provided in Table S4.

Clinical application

The PACAS-LEAD score chart is provided in Table 3. The sum scores ranged from 0 to 22. The prevalence of ≥50% ACS ranged from 0.5% for sum scores ≤7 to 14% for sum scores ≥16. The prevalence of ≥70% ACS ranged from 0.2% for sum scores ≤7 to 6.6% for sum scores ≥16. The prevalence of ≥50% and ≥70% ACS by each sum score is provided in Figure 2. The distribution of sum scores is shown in Figure S2.

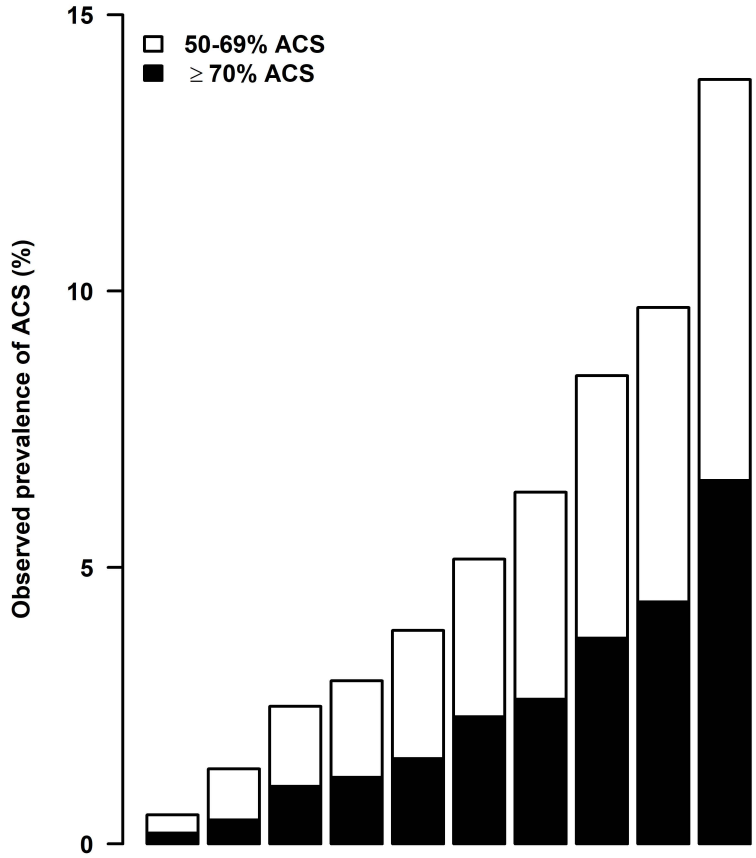
We introduced four thresholds of sum scores allowing targeted screening of a group of patients with LEAD at high risk of significant ACS. The observed prevalence of ≥50% ACS increased from 5.7% by screening all patients to 13.1% by targeted screening of the 20% patients at very high risk. The corresponding NNS decreased from 18 to 8. The observed prevalence of ≥70% ACS increased from 2.5% by screening all patients to 5.8% by targeted screening of the 20% patients at very high risk. The corresponding NNS decreased from 40 to 17 (Table 4).

Table 3. PACAS-LEAD score chart

Predictor	Score
Age, years	
<50	0
50-59	5
60+	7
Male sex	1
Ever smoking	3
Hypercholesterolemia	1
Stroke or TIA	1
CHD	2
SBP, mmHg	
<140	0
140-159	1
160+	2
ABI	
0.8-0.9	0
0.4-0.8	3
<0.4	5

ABI, ankle-brachial index; CHD, coronary heart disease; SBP, systolic blood pressure; TIA, transient ischemic attack.
The PACAS-LEAD score ranges from 0 to 22. The risks of ≥50% and ≥70% ACS for each sum score are provided in Figure 2.

Figure 2. Observed prevalence of ACS by sum score



Bar chart showing the predicted prevalence of ACS in the derivation cohort for each sum score. The black parts of the bars represent the prevalence of ≥70% ACS and the white parts the prevalence of 50-69% ACS. The prevalence of ≥50% ACS is calculated by taking the sum of the prevalences of 50-69% and ≥70% ACS.

Table 4. Performance of the risk scores to detect asymptomatic carotid stenosis

	Sum score	Number of cases screened	Number of cases with ACS	Observed prevalence	Sensitivity	Specificity	PPV	NPV	NNS
Systematic screening of all patients									
≥50% ACS		112,117	6354	**5.7%**					18
≥70% ACS		112,117	2801	**2.5%**					40
Screening those at least low risk									
≥50% ACS	≥9	92,630	6193	**6.7%**	97.5%	18.3%	6.7%	99.2%	15
≥70% ACS	≥9	92,630	2747	**3.0%**	98.1%	17.8%	3.0%	99.7%	33
Screening those at least intermediate risk									
≥50% ACS	≥11	71,521	5639	**7.9%**	88.8%	37.7%	7.9%	98.2%	13
≥70% ACS	≥11	71,521	2521	**3.5%**	90.0%	36.9%	3.5%	99.3%	29
Screening those at least high risk									
≥50% ACS	≥13	44,713	4435	**9.9%**	69.8%	61.9%	9.9%	97.2%	10
≥70% ACS	≥13	44,713	2010	**4.5%**	71.8%	60.9%	4.5%	98.8%	22
Screening those at least very high risk									
≥50% ACS	≥15	22,704	2809	**12.4%**	44.2%	81.2%	12.4%	96.0%	8
≥70% ACS	≥15	22,704	1313	**5.8%**	46.9%	80.4%	5.8%	98.3%	17

ACS, asymptomatic carotid stenosis; NNS, number needed to screen; NPV, negative predictive value; PPV, positive predictive value.
The number of false negatives and true negatives were 161 and 19,326; 715 and 39,881; 1919 and 65,485; 3545 and 85,868 for sum scores for ≥50% ACS of ≥9, ≥11, ≥13, and ≥15, respectively and, 54 and 19,433; 280 and 40,316; 791 and 66,613; 1488 and 87,925 for sum scores for ≥70% ACS of ≥9; ≥11; ≥13; and ≥15, respectively.

External validation populations

Baseline characteristics are provided in Table 1. In the first validation cohort (Life Line Screening; UK participants), more patients were men (37.2%) and current smoker (32.2%), and less patients had diabetes mellitus (16.7%) and hypercholesterolemia (44.8%) compared to the derivation cohort. The prevalence of ≥50% ACS was 9.1% and ≥70% ACS was 4.8%. In the second validation cohort (SMART), patients were younger (mean age 61.6 ± 10.3 years) and more patients were men (66.5%) compared to the derivation cohort. The prevalence of ≥50% ACS was 16.8% and ≥70% ACS was 12.4%.

External validation

The AUROC of PACAS-LEAD in the first external validation cohort was 0.703 (95% CI 0.680-0.726) for ≥50% ACS and 0.716 (95% CI 0.693-0.740) for ≥70% ACS, and in the second 0.667 (95% CI 0.633-0.700) for ≥50% ACS and 0.671 (95% CI 0.637-0.705) for ≥70% ACS (Table 2). The predicted and observed prevalences in the validation cohorts were higher compared with the derivation cohort, but calibration plots showed very good concordance between the predicted prevalence calculated with the PACAS-LEAD and the observed prevalence in the validation

cohorts (after adjusting the intercept) (Figure 1). This indicates that, after adjusting the average predicted risk to the observed risk in the validation cohorts, the PACAS-LEAD risk score could be applied to populations with LEAD with different overall prevalences of significant ACS.

Discussion

We developed and validated the first risk prediction model to identify groups of patients at high risk of significant ACS among patients with LEAD. Predictors for moderate and severe ACS used in the PACAS-LEAD risk score were age, sex, ever smoking, history of hypercholesterolemia, stroke/TIA, CHD and measured SBP and ABI. Discrimination was good and calibration plots showed good concordance of predicted and observed risks. The NNS to detect significant ACS in the high risk group that consisted of approximately 20% patients at highest risk was a more than halved compared with systematic screening of all LEAD patients. Application of PACAS-LEAD to the validation cohort showed reliable predictions (after adjusting for the difference in overall prevalence of significant ACS in the different cohorts).

The PACAS-LEAD risk score can be applied to patients with decreased ABI of 0.9 or below. These ABI values have been associated with cardiovascular morbidity and mortality and might also improve cardiovascular risk stratification.[21,22] The prevalence of significant ACS is higher in patients with LEAD and increases with severity of LEAD.[23] A meta-analysis including 13 prospective studies of patients with PAD showed a prevalence of ≥50% ACS of 25% and a prevalence of ≥70% ACS of 14%, but heterogeneity between studies was high, due to different selection criteria and application of different diagnostic criteria to determine the degree of carotid stenosis.[5] Our derivation cohort showed an overall prevalence of ≥50% ACS of 5.7% and of ≥70% ACS of 2.5%, but the prevalence in the validation cohorts was higher due to inclusion of patients with a first manifestation of arterial disease in the SMART cohort and possibly different reasons for undergoing vascular screening between the US and UK. Our risk prediction model enables clinicians to stratify the risk of ≥50% ACS in patients with LEAD from 0.5% to 14% based on risk predictors. This might contribute to a clinical and more cost-effective screening strategy.

Detection of significant ACS in patients with asymptomatic LEAD might lead to initiation or intensification of preventive therapy. In patients with symptomatic LEAD who are using optimal medical preventive therapy, detection might lead to closer follow-up to maintain compliance to decrease the risk of subsequent vascular events,[10,11] since significant ACS is associated with an

increased risk of stroke and has an incremental effect on risk of coronary events in patients with LEAD.[24] Compliance to medical therapy is challenging as recently shown in a study from Sweden on screening for ACS of males aged 65 years. In this study, statins and antiplatelet agents were prescribed if ACS was detected, but were used by 29% and 21% of patients after five years of detection compared with approximately 23% and 14% who used them at 65 years.[25]

Whilst the annual risk of ipsilateral stroke in patients with significant ACS using best medical therapy is low,[26,27] the 5-10 year risk is not negligible, and our study showed considerable scope for further optimizing medical therapy with around 60% of cases with ACS reporting use of aspirin and 60-70% reporting use of lipid-lowering therapy. Risk factors for increased risk of stroke have been identified and carotid interventions might be considered in selected cases to decrease the risk of stroke, but should, amongst other considerations, be weighed against the limited life expectancy in patients with LEAD.[8] Risk prediction models for individualized calculation of absolute stroke risks in medically treated patients with significant ACS have been developed, but these have not been validated in patients using current standards of medical preventive therapy or in patients with LEAD and significant ACS.[28-30] Imaging features of plaque vulnerability might help improving risk prediction in those patients with significant ACS.[8]

Participants of the derivation cohort and one of the validation cohorts were self-referred and self-funded, possibly influencing generalizability to other populations. Our derivation cohort was not primarily designed for research purposes, but participants were prospectively identified. ABI and PSV as single measurements for the diagnosing LEAD and ACS may be useful as screening tool to identify patients for more intensive diagnostic work-up. Different diagnostic criteria are proposed to determine degree of carotid stenosis based on duplex findings and different cut-offs leading to different prevalences of ACS might need adjustment of the risk equation for reliable risk prediction. Clinical staging of LEAD with the Fontaine or Rutherford classification was not performed and could have improved the predictive performance. Adjustment of the risk prediction model to populations with different severity of LEAD might be necessary. For predictors that were self-reported, recall bias should be taken into account. Blood pressure was

measured once in the derivation cohort and might not reflect 'usual' values. We used a proxy for history of hypercholesterolemia in the SMART cohort which might have influenced external validity. The prevalence of ACS in our derivation cohort was lower compared with other populations, possibly making targeted screening more worthwhile in different settings.[5]

Our study has several strengths. We developed and validated the first risk score to detect significant ACS in patients with LEAD. A large cohort of patients was used for development of the PACAS-LEAD risk score. Missing data was limited for most predictors in the derivation and validation cohorts and we used multiple imputation to handle missing data. Internal validation showed no evidence for overfitting and external validation showed reliable prediction after recalibration. ABI was measured bilaterally and patients with incompressible ankle arteries or ABI >1.4 were excluded. Patients underwent bilateral examination of the carotid arteries and the highest degree of stenosis of both sides was used as outcome.

Before targeted screening can be implemented in clinical practice, future research will determine risks of cardiovascular events in patients with LEAD and concomitant significant ACS under best medical therapy, will identify patients with significant ACS at increased risk of ischemic stroke who benefit from carotid interventions, and whether closer follow-up and better compliance after detecting significant ACS might improve cardiovascular risk management and prevent cardiovascular events. Differences in the overall prevalence of ACS between the derivation and validation cohorts indicates that updating the (intercept of the) risk prediction model to local settings is necessary before implementation in clinical practice.

Conclusions

The PACAS-LEAD risk score can predict the presence of moderate and severe ACS in patients with LEAD reliably, using the following predictors: age, sex, smoking status, history of hypercholesterolemia, stroke/TIA, CHD and measured SBP. Targeted screening of the 20% patients at highest risk yielded 44% of cases with ≥50% and 47% of cases with ≥70% ACS. The prevalence was a twofold higher in this high risk group compared with systematic screening of all LEAD patients, reducing the NNS substantially and help targeting screening to those in whom ACS is more often detected.

Contributors

MHFP designed the study. MHFP, PS and RaC cleaned the data. MHFP performed the statistical analyses. The manuscript was drafted by MHFP. All authors interpreted the data, contributed to revisions of the manuscript and approved the final version for submission for publication.

Declaration of interest

The authors declare no conflicts of interest. This study was designed, conducted and reported independently of Life Line Screening who provided their data at no cost and all sources of support.

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SUPPLEMENTARY MATERIAL

Appendix S1: Research protocol for a systematic review of the literature

Appendix S2: Search strategy

Table S1: TRIPOD Checklist

Table S2: Missing data per variable

Table S3: Full-text evaluation

Table S4: Predicted and observed prevalence of ACS across deciles of predicted risk

Figure S1: Flowchart

Figure S2: Distribution of sum scores in the derivation cohort

Figure S3: Calibration plots of the PACAS-LEAD in validation cohorts (before recalibration)

Supplementary material is attached to this dissertation and can be found here

Part II

Risk factors and Detection of Atrial Fibrillation

5

Joint Associations Between Body Mass Index and Waist Circumference with Atrial Fibrillation in Men and Women

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Abstract

Objectives: To determine precise estimates of the risk of atrial fibrillation (AF) by body mass index (BMI) and waist circumference (WC) in men and women.

Methods: Between 2008 and 2013, over 3.2 million adults attended commercial screening clinics. Participants completed health questionnaires and underwent physical examination along with cardiovascular investigations, including an electrocardiogram. We excluded those with cardiovascular and cardiac disease. We used multivariable logistic regression and determined joint associations of BMI and WC and the risk of AF in men and women by comparing likelihood ratio (LR) χ^2 statistics.

Results: Among 2.1 million included participants 12,067 (0.6%) had AF. A positive association between BMI per 5 kg/m^2 increment and AF was observed, with an odds ratio of 1.65 (95% CI 1.57-1.73) for men and 1.36 (95% CI 1.30-1.42) for women amongst those with a BMI above 20 kg/m^2. We found a positive association between AF and WC per 10 cm increment, with an odds ratio of 1.47 (95% CI 1.36-1.60) for men and 1.37 (95% CI 1.26-1.49) for women. Improvement of LR χ^2 was equal after adding BMI and WC to models with all participants. In men, WC showed stronger improvement of LR χ^2 than BMI (30% vs. 23%). In women, BMI showed stronger improvement of LR χ^2 than WC (23% vs. 12%).

Conclusions: We found a positive association between BMI and AF (above 20 kg/m^2), and between WC and AF in both men and women. BMI seems a more informative measure about risk of AF in women and WC seems more informative in men.

Introduction

The prevalence of obesity has increased over recent decades, affecting over 2.5 billion people (almost 40% of the global population).[1,2] Individuals who are overweight or obese are at higher risk of cardiovascular disease, type 2 diabetes mellitus, cancer, and premature death.[3,4]

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in clinical practice and its prevalance is increasing.[5] The estimated prevalence of AF in 2009 in the United States of America was 5.3 million of which 0.7 million were undiagnosed cases.[6] The increasing burden of disease has been attributed mainly to ageing populations but also to an increased AF incidence, related to the rise in prevalence of established AF risk factors such as hypertension and obesity.[7] AF is associated with higher cardiovascular and cerebrovascular morbidity and mortality, including a five-fold higher risk of ischemic stroke.[8] People with AF who are also overweight or obese are at even higher risk of ischemic stroke, thromboembolism or death, compared to people with AF and healthy weight.[9]

To date, most studies have used body mass index (BMI) to assess weight status in relation to AF. Waist circumference (WC), a measure of abdominal or central adiposity, has received less attention than BMI yet may provide additional information on the risk of AF.[10-14] Furthermore, whether the risk of AF varies across different measures of adiposity and between sexes remains uncertain. For example, the association between WC and AF might differ across sexes as a result of differences in the distribution of adipose tissue. In this study, we used a large screened population to determine whether either BMI or WC alone, or in combination, better estimated the risk of AF risk in men and women.

METHODS

This study adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (Table S1).

Study participants

This cross-sectional study consisted of self-referred and self-funded individuals who attended a commercial vascular screening clinic between 2008 and 2013 in the United States of America and the United Kingdom.[15] All individuals completed an extensive questionnaire with information on their age, sex, height and weight, smoking status, alcohol use, history of diabetes, hypertension, vascular disease (coronary artery disease (CAD), stroke, transient ischemic attack (TIA) and peripheral arterial disease (PAD)), congestive heart failure, valvular heart disease, left ventricular hypertrophy, and medication use (antiplatelet, antihypertensive, and lipid-lowering medication). BMI was calculated from self-reported height and weight. Self-reported anthropometric data showed to be suitable for use in analyses.[16] We found a high correlation between reported height and measured height in a subset of 295,282 participants with a Spearman's rho of 0.9461 ($p<0.0001$). We also found a high correlation between reported weight and reported weight in a subset of 292,176 participants with a Spearman's rho of 0.9675 ($p<0.0001$). WC was measured by trained personnel using an inelastic tape measure. WC was defined as the smallest perimeter located between the last rib and the iliac crest, rounded to the nearest inch. Abdominal obesity was defined as WC of >102 cm in men or >88 cm in women.

In this study, we included 2,137,557 participants in whom BMI or WC was recorded and with ECG measurement, without a history of vascular disease (reported history of stroke, TIA, CAD or PAD), history of congestive heart failure, valvular heart disease, left ventricular hypertrophy, chronic obstructive pulmonary disease, or missing values for sex or smoking status from the dataset (Tables S2-S3). Those with a history of vascular and cardiac disease were excluded to minimise reverse causation. BMI was available in 2,127,173 (99.5%) individuals and WC in 307,254 (14.4%) individuals. Resurvey measurements for BMI were available for 8626 individuals re-screened at median 2.3 (interquartile range 1.2-2.4) years later. Resurvey measurements for WC were available for 184 individuals re-screened at median 1.2 (interquartile range 1.2-1.5) years later.

Outcome and its ascertainment

The primary outcome was the prevalence of AF, measured with a single 12-lead ECG. All ECGs were evaluated by physicians who received in-house training.

Statistical analyses

BMI was categorized into: <20 kg/m^2; 20-<25 kg/m^2; 25-<30 kg/m^2; 30-<35 kg/m^2; 35-<40 kg/m^2, and ≥40 kg/m^2. WC was converted from inch to cm and categorized into quintiles. We calculated quintiles for men and women separately.

Baseline characteristics are presented as means and standard deviations (SD) for continuous variables and as absolute numbers and percentages for categorical variables. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) for AF. Models were adjusted for age at screening (with 5-year intervals), sex, and country ("basic adjustment"), and additionally for smoking status (never, ever), alcohol use (never, 1-7, 8+ units weekly), history of diabetes, history of hypertension, history of hypercholesterolemia, use of anti-hypertensive medication, and lipid-lowering medication ("full adjustment").

For comparison of BMI and WC categories, the variance of the log odds in each group was calculated from the variances and covariances of the log ORs. This provides group-specific confidence intervals, which allow comparison between the BMI and WC categories without the choice of a reference group.[17,18] We also calculated ORs per 5 kg/m^2 increment in BMI where the association was log-linear (excluding the lowest BMI group). The ORs for WC were calculated for an equivalent multiple of the SD of BMI to facilitate the comparison between BMI and WC.

ORs were corrected for regression dilution using resurvey measurements for BMI and WC.[19,20] This correction accounts for measurement error and changes in BMI and WC between baseline and resurvey measures. ORs for each risk factor group were plotted against the mean of the resurvey values (ie, estimated 'usual value'), and summary log ORs (and their standard errors) were divided by the regression dilution ratio.[19] The regression dilution ratios were calculated as Spearman self-correlation regression dilution ratios (Table S4).

We compared the likelihood ratio (LR) χ^2 statistics to directly compare the associations between both BMI and WC and the risk of AF. These analyses were performed using the participants in

whom both BMI and WC were recorded. The LR χ^2 statistics was calculated as twice the increase in the log-likelihood on the addition of extra terms of the logistic models after adding BMI and WC to the fully adjusted logistic model (without adiposity measures). With this we quantified the extent to which BMI and WC improve prediction of the prevalence of AF. We also compared the LR χ^2 statistics of the logistic models after adding BMI to the fully adjusted logistic model with WC, and after adding WC to the logistic model with BMI to quantify the extent to which BMI and WC provide additional useful information.[21] We performed these comparisons in all participants and in men and women separately.

We performed subgroup analyses by age, smoking status, alcohol use, history of diabetes, history of hypertension or use of anti-hypertensive medication in participants in whom both BMI and WC were recorded.

STATA version 15.1 was used for statistical analyses and R version 3.5.1 was used for plotting figures.

Patient involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethical approval

The University of Oxford Medical Sciences Inter-Divisional Research Ethics Committee approved the study. All individuals consented for the data collected at the screening to be used for research purposes.

RESULTS

Baseline characteristics of 2,088,728 individuals are shown in Table 1. The mean age was 63.6 (SD: 10.1), 65% were female, and ever smoking prevalence was 44% in men and 35% in women. A history of hypertension or use of antihypertensives was reported in 63% of the participants with AF and 46% of the participants without AF. A history of diabetes was reported in 17% of the participants with AF and 11% of the participants without AF. Mean BMI was 27.8 (SD: 5.3) kg/m^2 in 2,078,630 participants with BMI recorded and 28.7 (SD: 5.7) kg/m^2 in 11,976 participants with AF. Mean WC was 94 (SD: 15.3) cm in 299,479 participants with WC recorded and 103 (SD: 16.4) cm in 1521 participants with AF (Table 1). Mean BMI in 299,479 participants in whom both BMI and WC was recorded was 28.2 (SD: 5.4) kg/m^2. Baseline characteristics of participants with both BMI and WC recorded are provided in Table S5.

Table 1. Baseline characteristics

	Participants with AF (n = 12,067)	Participants without AF (n = 2,076,661)	All Participants (n = 2,088,728)
Age (y)	72.7 ± 9.4	63.6 ± 10.1	63.6 ± 10.1
Female sex	4957 (41.1)	1,348,707 (64.9)	1,353,664 (64.8)
Height in men (m)	1.79 ± 0.1	1.78 ± 0.1	1.78 ± 0.1
Height in women (m)	1.63 ± 0.1	1.63 ± 0.1	1.63 ± 0.1
BMI (kg/m^2)[1]	28.7 ± 5.7	27.8 ± 5.3	27.8 ± 5.3
WC (cm)[2,3]	102.6 ± 16.4	94.1 ± 15.3	94.1 ± 15.3
Male ever smoker[4]	3598 (50.6)	320,997 (44.1)	324,595 (44.2)
Female ever smoker[4]	1635 (33)	474,811 (35.2)	476,446 (35.2)
Current alcohol use	2660 (44.8)	403,545 (43.2)	406,205 (43.2)
Hypertension or antihypertensive therapy	7070 (63)	877,658 (45.7)	884,728 (45.8)
Diabetes mellitus	1826 (16.6)	200,901 (10.5)	202,727 (10.6)
Hypercholesterolemia or lipid-lowering therapy	5588 (51)	971,451 (50.7)	977,039 (50.7)

Values are mean ± SD for continuous variables and n (%) for categorical variables.
AF indicates atrial fibrillation; BMI, body mass index; SD, standard deviation; WC, waist circumference.
[1] Mean BMI was 28.3 ± 4.6 kg/m^2 in all men, 29.0 ± 5.2 kg/m^2 in men with AF, and 28.3 ± 4.6 kg/m^2 in men without AF. Mean BMI was 27.6 ± 5.6 kg/m^2 in all women, 28.4 ± 6.3 kg/m^2 in women with AF, and 27.6 ± 5.6 kg/m^2 in women without AF.
[2] Mean WC was 100.9 ± 13.2 cm in all men, 105.9 ± 14.9 cm in men with AF, and 100.8 ± 13.1 cm in men without AF. Mean WC was 90.3 ± 15.1 cm in all women, 96.9 ± 17.2 cm in women with AF, and 90.3 ± 15.1 cm in women without AF.
[3] Waist circumference was measured in a subset of 299,479 participants. [4] Ever smoker was defined as current or former smoker.

Overall, 0.6% of the participants had AF (n = 12,067). The prevalence rose steeply with age and was two to three times higher in men compared to women for each decade of age (Figure 1). Multivariable analyses showed a positive association between usual BMI per 5 kg/m^2 increment (excluding the lowest BMI group) and AF, with an odds ratio of 1.65 (95% CI 1.57-1.73) for men and 1.36 (95% CI 1.30-1.42) for women (p_{trend}<0.0001). Absolute risks were higher in men compared to women and the relationship was stronger in men (Figure 2 & Table S6). We found a significantly higher risk of AF with higher usual WC, with an odds ratio of 1.74 (95% CI 1.55-1.95) for men per 14 cm increase and 1.52 (95% CI 1.36-1.71) per 13 cm increase (p_{trend}<0.0001) (Figure 2). Abdominal obesity was also associated with a higher risk of AF, with an OR of 1.83 (95% CI 1.56-2.15) for men and 1.84 (95% CI 1.46-2.32) for women when compared to no abdominal obesity (Table S7). We found similar results restricting these analyses to the 289,381 participants in whom both BMI and WC were recorded.

In the analyses of participants in whom both BMI and WC were recorded, there was a stronger improvement of LR χ^2 for WC than BMI (30% vs. 23%, respectively) in men. In contrast, for women BMI showed a stronger improvement of LR χ^2 than WC (23% vs. 12%).

Adding BMI to the fully adjusted models plus WC showed a marginal improvement of LR χ^2 in men (1%) and showed 9% improvement in women. Adding WC to the fully adjusted models plus BMI showed 6% improvement of LR χ^2 in men but no improvement in women (Table 2).

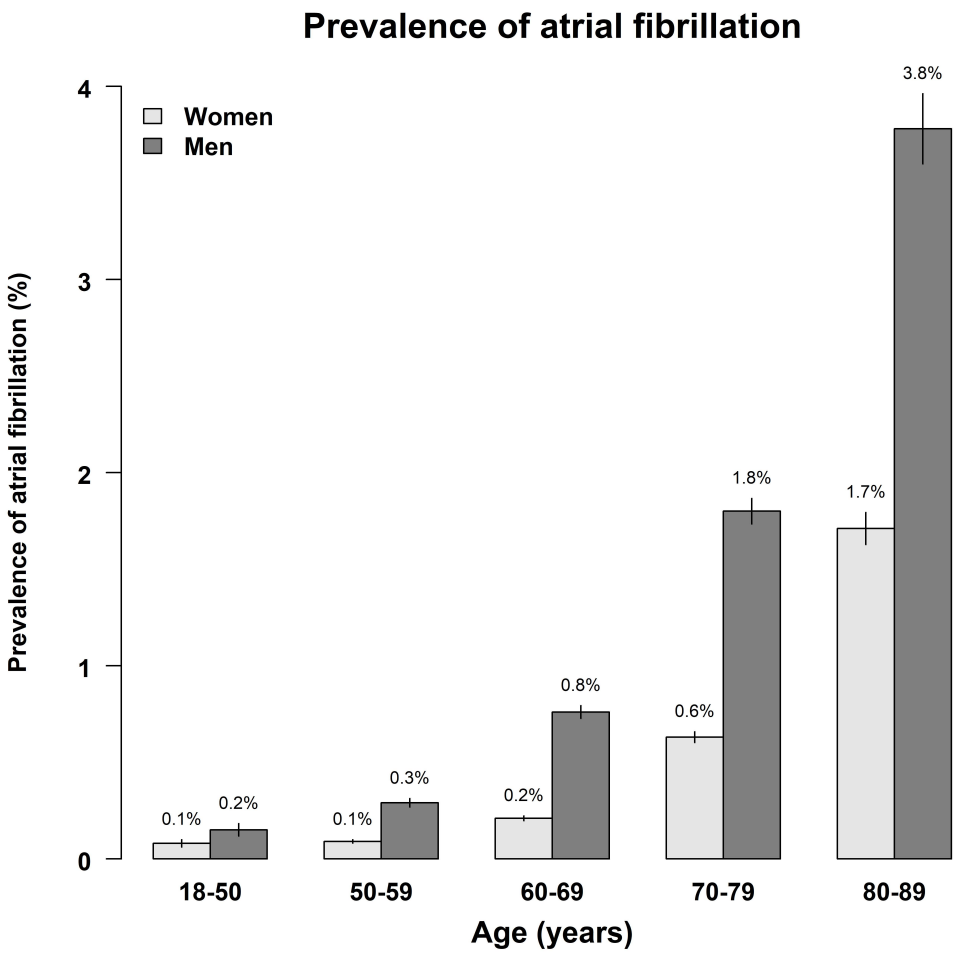
Subgroup analyses found consistent results across age, smoking status, alcohol use, and reported history of diabetes. The positive association of both BMI and WC with the risk of AF was higher in participants with reported hypertension or use of antihypertensive therapy compared to no reported hypertension / antihypertensive therapy (p_{het}=0.007 and p_{het}=0.01, respectively) (Figure 3).

Table 2. Comparison of predictive strengths for atrial fibrillation odds ratios of adding adiposity measures

	All participants[a] (N = 193,140)		Men[a] (N = 69,404)		Women[a] (N = 123,736)	
Model (+ Added adiposity measure)	**LR χ^2**	**Improvement of LR χ^2 (%)**	**LR χ^2**	**Improvement of LR χ^2 (%)**	**LR χ^2**	**Improvement of LR χ^2 (%)**
Fully adjusted model without adiposity measures[b]	843.9	-	359.4	-	228.8	-
+ BMI	982.8	139 (16)	443.6	84 (23)	280.5	52 (23)
+ WC	976.3	132 (16)	467.1	108 (30)	256.4	28 (12)
Fully adjusted model with WC[c]	976.3	-	467.1	-	256.4	-
+ BMI	997.1	21 (2)	469.7	3 (1)	280.6	24 (9)
Fully adjusted model with BMI[d]	982.8	-	443.6	-	280.5	-
+ WC	997.1	14 (1)	469.7	26 (6)	280.6	0 (0)

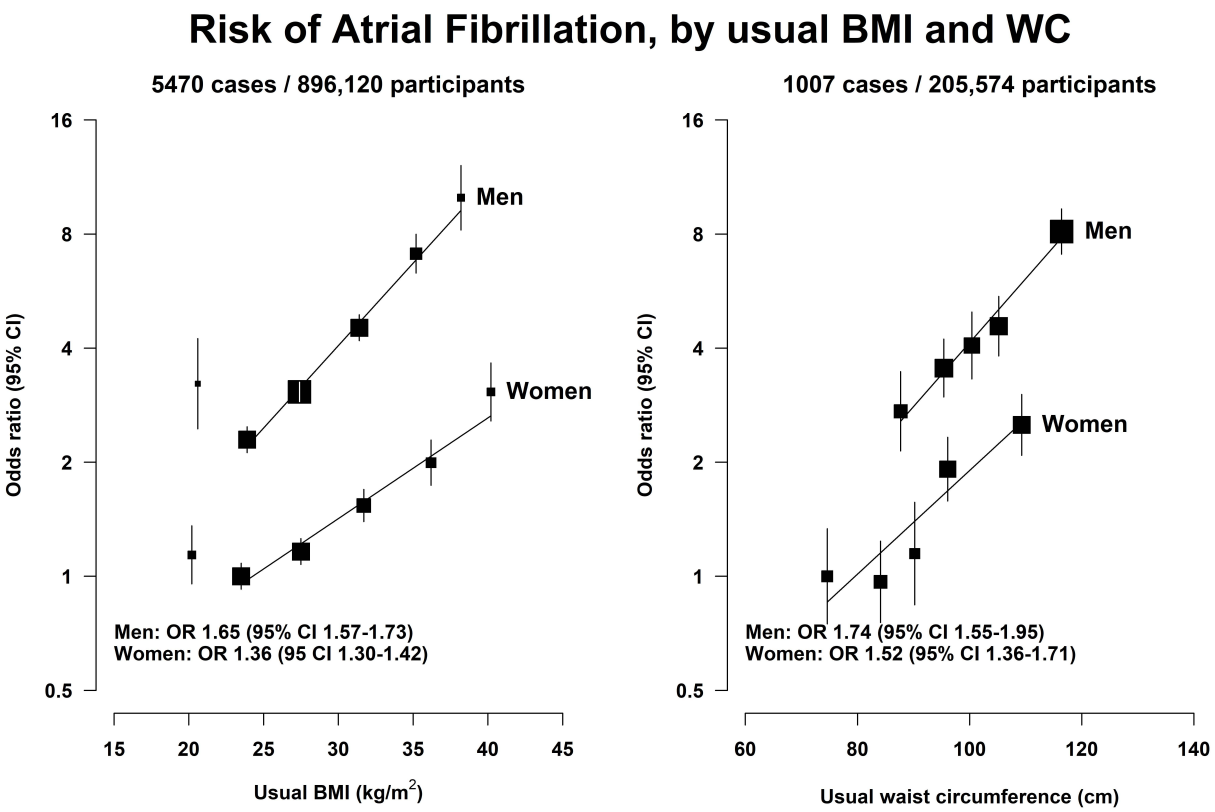
BMI indicates body mass index; LR, Likelihood Ratio; WC, waist circumference.
The χ^2 value is twice the improvement in the log-likelihood on addition of extra variables, with df as the number of extra variables. Models with an added adiposity measure had 1 degree of freedom.
[a] Analyses were restricted to participants in complete cases in whom both BMI and WC were recorded and with BMI ≥20 kg/m^2.
[b] Improvement in LR χ^2 by the addition of the adiposity measures (either BMI continuous or WC continuous) to the model with full adjustment in which the odds ratio depends on sex (in the analysis of all participants), age groups, country, history of hypertension, diabetes, smoking status, alcohol use, hypercholesterolemia, use of anti-hypertensive medication and lipid-lowering medication.
[c] Improvement in LR χ^2 by the addition of BMI continuous to the model with WC continuous in which the odds ratio depends on WC, sex (in the analysis of all participants), age groups, country, history of hypertension, diabetes, smoking status, alcohol use, hypercholesterolemia, use of anti-hypertensive medication and lipid-lowering medication.
[d] Improvement in LR χ^2 by the addition of WC continuous to the model with BMI continuous in which the odds ratio depends on BMI, sex (in the analysis of all participants), age groups, country, history of hypertension, diabetes, smoking status, alcohol use, hypercholesterolemia, use of anti-hypertensive medication and lipid-lowering medication.

Figure 1. Prevalence of atrial fibrillation



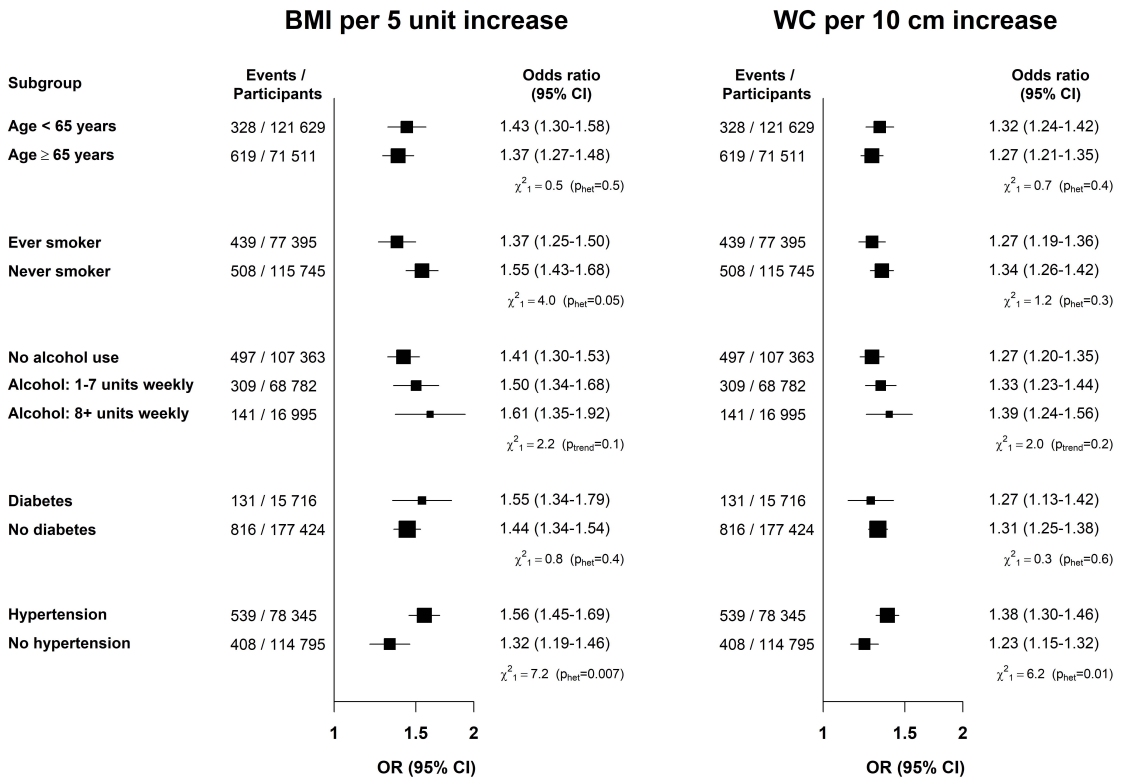
Prevalence of atrial fibrillation in men and women, by age. The vertical lines on the top of the bars represent the 95% confidence interval.

Figure 2. Risk of Atrial Fibrillation, by usual BMI and WC



Risk of Atrial Fibrillation by usual BMI and WC for men and women, using the fully adjusted model. For BMI, women with BMI 20-25 kg/m² were used as reference group. For WC, we used the first quintile of WC in women as reference group. ORs of each BMI and WC category were plotted against the mean of the resurvey values (ie estimated 'usual value'). We used group-specific confidence intervals.
The size of the boxes is relative to the total number of participants in each category. The ORs for usual BMI are provided per 5 units increment in participants with BMI ≥20 kg/m². The ORs for usual WC are provided per 14 cm increment for men and 13 cm for women, being the equivalent multiple of the standard deviation of BMI.
The number of AF cases and total number of participants per category, the risk estimates and 95% CI are provided in Table S6 for BMI and Table S7 for WC.

Figure 3. Subgroup analyses



Forest plot showing the risk of atrial fibrillation in subgroups, by BMI and WC. Analyses were restricted to 193,140 complete cases in whom both BMI and WC were recorded and with BMI ≥20 kg/m² and without missing values of covariates included in the multivariable model with full adjustment (nested sample). The ORs for BMI are shown per 5 units increment and the ORs for WC are shown for an increase of 10 cm. Ever smoker was defined as either current or former smoker. Hypertension was defined as either a reported history of hypertension or use of antihypertensive therapy.

Discussion

In this large cross-sectional study, including over 2 million screened participants, we found a positive log-linear association between BMI (except for the lowest BMI group) and WC and the risk of AF. We found higher risks of AF in men than women. BMI seems more informative about risk of AF in women whereas WC seems more informative in men.

The risk of AF is higher in men compared to women, but the difference in AF incidence attenuates in older patients aged 80 and above.[22] Reasons for these differences include sex-specific atrial electrophysiologic properties, atrial remodeling, and mechanisms of atrial fibrosis. BMI has been identified as a risk factor for AF. A recent meta-analysis including 25 studies found a non-linear relationship between BMI and AF risk, with higher BMI values associated with a steeper increase in risk.[23] In their meta-analysis, a 5-unit increment in BMI was associated with a 28% increased relative risk of AF (RR 1.28, 95% CI 1.20-1.38).[23] Their subgroup analysis showed a stronger association in men compared to women, with an RR of 1.39 (95% CI 1.30-1.48) for men compared to 1.30 (95% CI 1.14-1.48) for women.

WC has previously been shown to provide additional predictive information on all-cause mortality beyond BMI.[24] Only a limited number of studies have looked at the association between WC and AF risk.[10-14] When pooled in a meta-analysis, these results appeared to show a roughly linear relationship with a summary risk ratio for a 10 cm increase in WC of 1.18 (95% CI 1.12-1.25).[23] Two studies that provided risk estimates by sex showed that the risk in men seems higher than women.[10,13] In addition, we found that BMI is more informative about risk of AF in women, whereas WC is more informative in men.

Strengths and limitations

Our study is one of the largest to date to assess the association between adiposity measures and AF. We were able to compare BMI, WC and their association with AF both individually and in combination and we determined sex-specific analyses. We adjusted for regression dilution bias and excluded participants with cardiovascular and cardiac disease to minimize the risk of reverse

causation. Standardized measurement of outcome was used, including a 12 lead ECG to confirm a diagnosis of AF, reviewed by physicians who received in-house training.

Using single time point ECG is likely to underestimate the true prevalence of AF in the population, as cases of paroxysmal and persistent AF may be missed. This might have contributed to a lower prevalence of AF compared to other populations. Other reasons might be the inclusion of relatively young and a high proportion of female participants in our study as well as the exclusion of participants with CVD. The prevalence was however comparable with the prevalence of 0.5% found in the STROKESTOP study that included participants aged 75 to 76 years.[25] Furthermore, there may also be participants included in the 'no AF' group who have either persistent or paroxysmal AF for the same reason. We were not able to validate the diagnosis of AF and reported comorbidities, for example via health records. Similarly, there may have been confounding factors missed that attribute to the observed relationship between underweight and increased AF risk, such as muscle wasting conditions or hyperthyroidism. Participants were self-referred and self-funded, which might influence generalizability. The type of anti-hypertensive agent was not recorded. BMI was based on self-reported weight and height, but reporting errors might not affect suitability for analyses.[16] However, others found that the accuracy of self-reported height and weight was different for men and women.[26] WC was available in a subset of participants but we performed comparative analyses in the subset of participants in whom both BMI and WC were recorded (Table 2) Relying on BMI and WC may not fully account for differences in proportion of muscle mass and adipose tissue. The number of participants with resurvey measurement was small and this might affect the preciseness of the correction for regression dilution, and this number was too small to perform analysis of change in measures of adiposity and risk of AF. The cross-sectional study design may underestimate the importance of previous weight change as obesity in early life appears to confer a long-term increase in risk of AF even after accounting for subsequent weight loss.[27]

Implications for practice

Our cross-sectional data highlights the important relationship between increasing weight and AF risk and the difference in informativeness of adiposity measures in men and women. When assessing adiposity measures in clinical practice, WC might be a more informative measure about risk of AF in men and BMI in women. This stresses the importance of sex-specific risk prediction of AF. Longitudinal data showed weight gain over time increases the risk of AF, irrespective of baseline weight status and sex.[28] Amongst 15,214 participants in the HUNT-study, overweight and obesity were associated with an increased risk of AF compared to healthy weight, but so too was both weight loss and weight gain over a median of 8 years follow-up when compared to people with stable weight.[27] Interventions to prevent weight gain and promote healthy weight might therefore help reduce the burden of AF in the population.

The LEGACY randomized controlled trial demonstrated that intentional weight loss through a goal-directed weight management program could help reduce AF symptom burden in people who were overweight at baseline.[29] However, as yet there is no consistent evidence that non-surgical weight loss leads to a reduction in AF incidence.[30] Although weight reduction in overweight or obese individuals is likely to have cardiovascular benefits beyond the risk of AF, the current evidence base supports public health strategies that promote maintenance of a healthy weight. Further research is needed to confirm the sex-specific associations between adiposity measures and AF risk so that interventions can be targeted at appropriate populations and risk prediction of AF should consider sex-specific differences.

Conclusions

Our study highlights the importance of overweight and obesity as potentially modifiable AF risk factors. BMI may be a more informative measure of AF risk in women and WC in men. This stresses the importance of sex-specific risk prediction of AF. Clinicians should consider measuring and addressing adiposity where possible. Interventional studies are required to demonstrate whether intentional weight loss can reduce the risk of AF. At present public health strategies and health promotion should advise individuals to maintain a healthy weight and avoid weight gain.

Contributors

MHFP, PS, AH, SL, RB designed the study. MHFP, PS, and RC cleaned the data. MHFP performed the statistical analyses, supervised by PS and SL. The manuscript was drafted by MHFP. All authors interpreted the data, contributed to revision and editing of the manuscript and approved the final version of the manuscript for submission for publication.

Declaration of interest

The study funders had no role in study design, data collection, analysis, or interpretation, drafting the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to publish the report. The views of the Life Line Screening are not necessarily those of the authors.

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SUPPLEMENTARY MATERIAL

Table S1: STROBE checklist for cross-sectional studies

Table S2: Number of excluded participants, with reasons for exclusion

Table S3: Missing data in our cohort

Table S4: Overview of regression dilution ratios

Table S5: Baseline characteristics in participants with both BMI and WC recorded

Table S6: Odds ratios of AF by BMI in men and women

Table S7: Odds ratios of AF by WC in men and women

Supplementary material is attached to this dissertation and can be found here

6

Utility of Risk Prediction Models to Detect Atrial Fibrillation in Screened Participants

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ABSTRACT

Aims: Atrial fibrillation (AF) is associated with higher risk of stroke. While the prevalence of AF is low in the general population, risk prediction models might identify individuals for selective screening of AF. We aimed to systematically identify and compare the utility of established models to predict prevalent AF.

Methods: Systematic search of PubMed and EMBASE for risk prediction models for AF. We adapted established risk prediction models and assessed their predictive performance using data from 2.5M individuals who attended vascular screening clinics in the United States and the United Kingdom and in the subset of 1.2M individuals with CHA_2DS_2-VASc ≥2. We assessed discrimination using area under the receiver operating characteristic (AUROC) curves and agreement between observed and predicted cases using calibration plots.

Results: After screening 6959 studies, 14 risk prediction models were identified. In our cohort, 10,464 (0.41%) participants had AF. For discrimination, six prediction model had AUROC curves of 0.70 or above in all individuals and those with CHA_2DS_2-VASc ≥2. In these models, calibration plots showed very good concordance between predicted and observed risks of AF. The two models with the highest observed prevalence in the highest decile of predicted risk, CHARGE-AF and MHS, showed an observed prevalence of AF of 1.6% with a number needed to screen of 63. Selective screening of the 10% highest risk identified 39% of cases with AF.

Conclusion: Prediction models can reliably identify individuals at high risk of AF. The best performing models showed an almost fourfold higher prevalence of AF by selective screening of individuals in the highest decile of risk compared with systematic screening of all cases.

Registration: This systematic review was registered (PROSPERO CRD42019123847).

Introduction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in clinical practice and its prevalance is increasing, due to ageing populations, altered lifestyle habits and increasing levels of adiposity. Over 33.5 million people worldwide are currently diagnosed with AF.[1] AF may be categorised in different ways, including by the frequency of the arrhythmia as either paroxysmal, persistent, permanent. However, all subtypes are associated with an increased risk of stroke and other cardiovascular disease outcomes, which include a 5-fold higher risk of cardioembolic stroke. Risk prediction scores such as CHA_2DS_2-VASc are recommended to help determine the stroke risk for people who are diagnosed with AF, categorised as low, medium or high.[2] Anticoagulation with either a vitamin K antagonist such as warfarin or a Direct Oral Anticoagulant (DOAC) in high-risk individuals can reduce their stroke risk by around 65%. Yet many people with AF currently go undetected, either because they are asymptomatic or have paroxysmal disease not detected at the time of assessment. A recent systematic review of single time-point screening reported a prevalence of undetected AF of 1.4% in adults aged ≥65 years old in the general population.[3] However, AF is typically found in up to 20% of cases with ischaemic stroke.[4,5] In at least half of such cases, AF is newly diagnosed at the time of the event.[6,7] This has prompted interest in implementing national screening programmes to detect people with AF, particularly in individuals who might benefit from anticoagulation.[2,8,9]

One argument against population level systematic screening is the low overall prevalence of AF in the general population. Accurate identification of individuals at higher risk of AF could help to target screening, reduce the number needed to screen. Most simply, this involves screening above a certain age threshold given the increased prevalence of AF in older people; over 80% of cases with AF occur in individuals aged over 65 years compared to 2.8% who are aged below 45 years.[10] Currently, international guidelines suggest either opportunistic screening in individuals aged 65 years or older, or systematic screening in those aged 75 years or older and individuals at high-risk of stroke since the latter approach has been shown to be particularly cost-effective.[11-13]

Risk prediction models have been developed to detect either incident or prevalent AF and may be able to more accurately identify populations at high-risk of AF to inform selective screening. These

have the additional benefit of identifying people who are also at higher risk of stroke and therefore likely to benefit from treatment. Assessing the predictive performance of such models is necessary before seeking to implement these approaches to determine their comparative accuracy and utility. We conducted a systematic review of established risk prediction models of AF and then evaluated the predictive performance of these models in a large contemporary screened population.

METHODS

We conducted a systematic review according to a predefined protocol to identify established prediction model to detect AF. This protocol has been registered prospectively in the international prospective registry for systematic reviews (PROSPERO): CRD42019123847. We report the results of our systematic review consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[14]

Search strategy and eligibility criteria

We searched Medline (via PubMed interface) and EMBASE (via OVID interface) from inception to March 1, 2019 using comprehensive electronic strategies, which incorporated a validated search filter (Table S1). We included articles that: (1) develop risk prediction models for the prevalence or incidence of AF based on multiple risk factors; (2) used general or screened population as domain, not diseased populations at higher risk of AF; (3) used a single time-point 12-lead electrocardiogram (ECG) for diagnosing AF; and (4) published in peer-reviewed journals without any language restrictions.

Screening process and data extraction

Two authors (MHFP & NRJ) independently screened all titles and abstract of the retrieved references and subsequently independently reviewed full-texts for final inclusion in this study. We performed backward citation searching using the bibliographies of included studies.

Two authors (MHFP & NRJ) independently extracted the following data from the included studies that report the development of a risk prediction model, based on the CHARMS checklist:[15] source of data, setting study, geographic area (country and continent), study years, sample size, modelling method (eg, logistic model), number of participants with missing data, handling of missing data, investigation of satisfaction of modelling assumptions, selection methods for predictor selection, shrinkage of predictor weights, number of outcome events, number of patients, ascertainment of outcome, number and type of predictors used in the final model, number of outcome events per variable, presentation of model, model performance (calibration and validation).

Validation cohort

A cohort of self-referred and self-funded individuals who attended commercial vascular screening clinics (Life Line Screening Inc.) between 2008 and 2013 in the United States of America (USA) and United Kingdom (UK) was used to assess the predictive performance. All individuals completed standardized questionnaires including questions about their age, sex, smoking status, alcohol use, height and weight, history of vascular disease (coronary artery disease, congestive heart failure, stroke, transient ischemic attack, and peripheral arterial disease), valvular disease, chronic obstructive pulmonary disease, hypertension and use of antihypertensive medication, and diabetes mellitus. Blood pressure was measured as part of the ankle-brachial pressure index assessment. Standard blood pressure cuffs and sphygmomanometers were used, systolic blood pressure (SBP) being measured using a Doppler probe.

Predicted outcome and its ascertainment

The predicted outcome was the prevalence of AF, measured with a single 12-lead ECG. All ECGs were evaluated by physicians who received in-house training.

Statistical analyses (external validation)

Characteristics of the predictor variables in the included models were summarized using standard methods. We excluded participants with an established history of AF prior to screening (N = 285,934), who did not undergo a single 12-lead ECG (N = 356,684), or with inconsistent values for sex (N = 14,287). We used the same population for all analyses to enable comparisons between different models. Some models applied age and body mass index (BMI) restrictions (Table S2). We therefore further excluded participants who were younger than 45 at screening (N = 59,357) or who had a BMI lower than 18 (N = 18,175).

Variables only relevant for predicting incident AF, such as ECG and echocardiographic characteristics, were not included in our assessment of the risk prediction models. Predictors involving biochemical or other blood measurements were not included, since their availability for inclusion in screening programmes or measurement before performing a single ECG might limit the clinical applicability (Table S3). We used proxies whenever possible and appropriate for any

predictors that were not available in our dataset. Predictors for which no proxy was found were considered missing (Table S3).

Missing data were imputed if data were missing in <30% (Table S4). We used chained equations and created 20 imputed datasets with 200 iterations.[16] BMI was calculated before imputation.[17] Post-imputation rounding was applied to limited-range variables (SBP, heart rate, BMI, height, and weight), if needed.[18] Analyses were performed in the resulting 20 imputed datasets.

We used the risk equations to calculate the probability of AF for each participant. We used the β-coefficients (predictor weights) of prediction models that were based on logistic regression and on time-dependent regression modelling, such as cox regression (Table S5). We also calculated a sum score (total points) for each participant by summing the points assigned to each predictor of the score chart.

We examined the discrimination and calibration indices of the prediction models, assessed using the area under receiver operating characteristic (AUROC) curve and calibration plots respectively. We calculated the AUROC curve per imputed dataset and results were pooled using Rubin's rules.[19,20] For models that reported the risk equation, we estimated the mean probability per participant across the 20 imputed datasets and subsequently we split the predicted risks in deciles and calculated observed probability with corresponding 95% confidence interval (CI) per decile. We recalibrated the prediction models to the prevalence of AF in our cohort by re-estimating the intercept. This type of recalibration is referred to as 'update intercept' or 'calibration-in-the-large'.[21] For this, we fitted a logistic model with a fixed calibration slope and the intercept as the only free parameter. In addition, for models that reported a score chart, we created bar charts with the observed prevalence of AF by sum score.

We performed additional assessments of discrimination and calibration using participants with CHA_2DS_2-VASc of two or more, since anticoagulation is recommended for these people if AF is found.[11]

Test characteristics and reclassification measures

We assessed two possible cutoffs for a selective screening. We assessed test characteristics, such as sensitivity, specificity, positive predictive value, negative predictive value, prevalence, and number

needed to screen (NNS), of selective screening of the 10% and 20% individuals at highest predicted risk of AF.

We calculated reclassification measures to assess the ability of the included risk prediction models to correctly identify cases with and without AF compared to the threshold of ≥65 years of age.[22] We calculated integrated discrimination improvement (IDI), relative IDI (rIDI), and continuous net reclassification improvement (NRI).[22,23] IDI is the absolute difference in discrimination slopes of the risk prediction models and the age threshold. rIDI is the ratio of absolute difference in discrimination slopes of the risk prediction models and the age threshold over the discrimination slope of the age threshold. Continuous NRI is the sum of the net percentages of participants with and without the AF correctly assigned a different predicted risk with the risk prediction models compared to the age threshold. Positive values correspond to improved classification. The reclassification measures were estimated for all 1000 bootstrap replications in each imputed dataset and the median value across the combined 20 datasets is reported (with the 95% CI obtained from the 2.5th and 97.5th percentiles). *P* values <0.05 were considered significant. STATA version 15.1 was used for all statistical analyses and R version 3.5.1 was used for constructing the figures.

Sensitivity analyses

We performed additional assessment of the prediction models in complete cases.

RESULTS

We screened 6961 unique reports identified by our literature search, assessed 249 full-texts, and included 14 studies (Figure 1 and Table S6).[2,9,24-35] Six studies used incident AF as predicted outcome,[27-32] three used incident AF or atrial flutter,[24,25,34] one used prevalent AF,[33] and one did not specify the type of AF.[26] HATCH was developed to predict progression to sustained AF and $CHADS_2$ and CHA_2DS_2-VASc were developed to predict the risk of stroke in cases with AF.[2,9,35] These three prediction models were included, although not originally designed for detecting AF, because they have been used in a number of subsequent studies for predicting AF and might be used for combined prediction of outcomes.[32,33,36,37] Characteristics of model development are provided in Table 1.

Figure 1. Flowchart

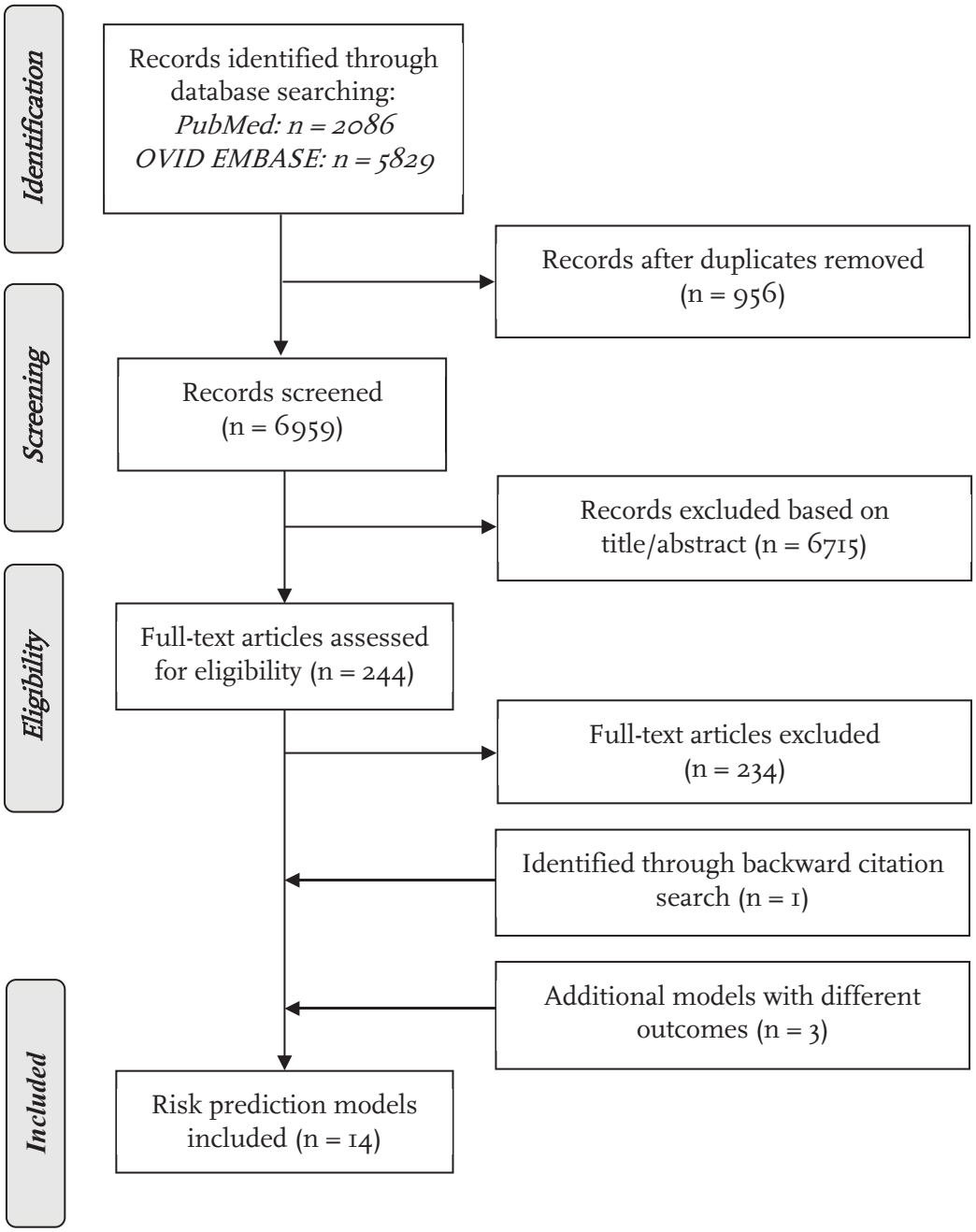


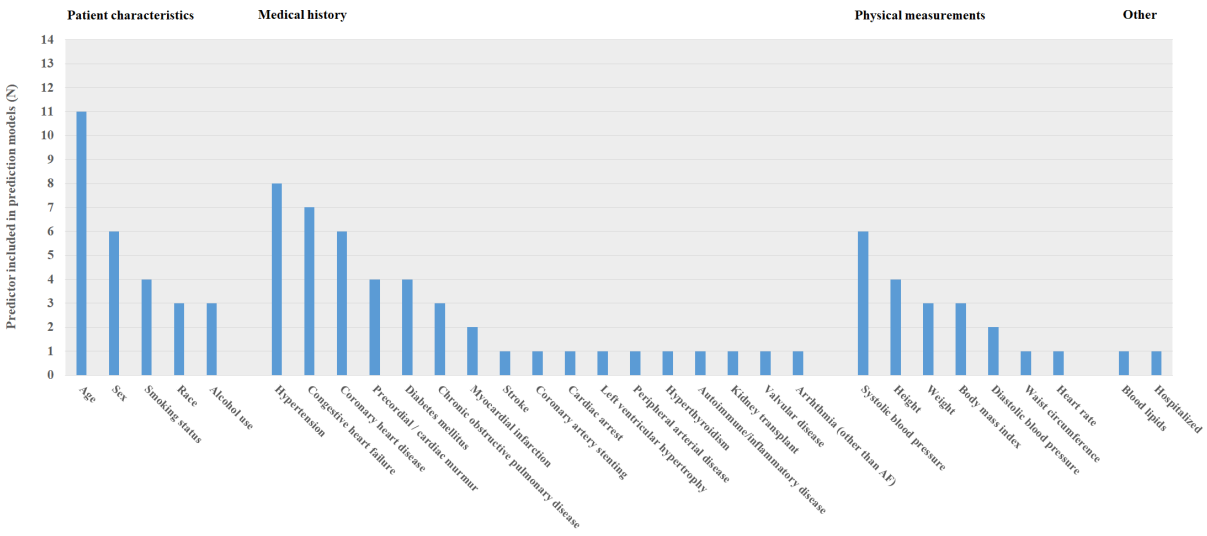
Table 1. Selected characteristics of studies assessing different risk prediction models for AF

Author, year, and study name	Predicted outcome	Country	Cases / participants in derivation cohort (%)	Number of predictors*
Alonso *et al*, 2013 (CHARGE-AF)[24]	Incident AF or atrial flutter	USA	1186 / 18,556 (6.39%)	11
Aronson *et al*, 2018 (MHS)[25]	Incident AF or atrial flutter	Israel	5660 / 96,778 (5.8%)	10
Brunner *et al*, 2014 (MAYO)[26]	AF	-	-	7
Chamberlain *et al*, 2011 (ARIC)[27]	Incident AF	USA	515 / 14,546 (3.54%)	12
Ding *et al*, 2017 (JINAN)[28]	Incident AF	China	134 / 33,186 (0.4%)	4
Everett *et al*, 2013 (WHS)[29]	Incident AF	USA	404 / 13,743 (2.9%)	6
Hamada *et al*, 2019 (SEIREI)[30]	Incident AF	Japan	349 / 65,984 (0.53%)	7
Kokubo *et al*, 2017 (SUITA)[31]	Incident AF	Japan	311 / 6864 (4.5%)	9
Li *et al*, 2018 (C_2HEST)[32]	Incident AF	China	921 / 471,446 (0.20%)	6
Linker *et al*, 2018 (SAAFE)[33]	Prevalent AF	USA	509 / 3790 (13.4%)	13
Schnabel *et al*, 2009 (FHS)[34]	Incident AF or atrial flutter	USA	457 / 4764 (9.6%)	7
de Vos *et al*, 2010 (HATCH)[35]	Progression to sustained AF	-	-	5
Gage *et al*, 2001 ($CHADS_2$)[9]	Stroke risk	-	-	5
Lip *et al*, 2010 (CHA_2DS_2-VASc)[2]	Stroke risk	-	-	7

* Number of predictors of the risk prediction models assessed in the present study are provided.
AF, atrial fibrillation; USA, United States of America.

The number of predictors in the models varied from four to thirteen. An overview of predictors of the included prediction models originally developed for detecting AF is provided in Figure 2. Age was used as predictor in all of the models. Other predictors frequently included were hypertension (n=8), heart failure (n=7), coronary heart disease (n=6), sex (n=6) and systolic blood pressure (n=6). Of the fourteen included prediction models, predictor weights of twelve models were reported and score charts of eleven models.

Figure 2. Included predictors



An overview of predictors used in the eleven risk prediction models that were developed to predict atrial fibrillation.

Validation cohort

The validation cohort consisted of 2,541,702 participants, of whom 10,464 (0.4%) had AF. In total, 1,153,878 (52.4%) participants had a CHA_2DS_2-VASc score of two or higher of which 5298 (0.5%) of the participants with AF. The mean CHA_2DS_2-VASc score was two in participants without AF and three in participants with AF. Characteristics of our cohort that were used as predictors in the included prediction models are provided in Table 2.

Table 2. Characteristics of variables used as predictors in the prediction cohort

	All participants (N = 2,541,702)	Participants with AF (N = 10,464)	Participants without AF (N = 2,531,238)
Age (y)	64.8 ± 9.6	72.9 ± 9.4	64.8 ± 9.6
Female sex	1,648,242 (64.8)	4315 (41.2)	1,643,927 (64.9)
Current smoker	219,444 (9.7)	751 (8.3)	218,693 (9.7)
Former smoker	693,974 (30.6)	3340 (36.7)	690,634 (30.5)
Never smoked	1,357,094 (59.8)	5012 (55.1)	1,352,082 (59.8)
Medical history			
Hypertension	1,015,663 (41.8)	5014 (51.9)	1,010,649 (41.8)
Antihypertensive medication	1,023,749 (43.4)	5317 (56.5)	1,018,432 (43.3)
DM	276,051 (11.9)	1622 (17.7)	274,429 (11.8)
CHD*	137,508 (6.2)	1156 (12.9)	136,352 (6.1)
Valvular disease	76,985 (4.0)	494 (6.9)	76,491 (4.0)
CHF	20,847 (0.9)	426 (4.8)	20,421 (0.9)
COPD	64,592 (3.4)	486 (6.8)	64,106 (3.4)
PAD	91,823 (3.7)	938 (9.5)	90,885 (3.6)
Stroke or TIA	78,048 (3.5)	819 (9.4)	77,229 (3.5)
Physical measurements			
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Weight (kg)	79.1 ± 18.2	86.5 ± 21.1	79.1 ± 18.2
BMI (kg/m^2)	27.9 ± 5.3	28.9 ± 5.7	27.9 ± 5.3
SBP (mmHg)	133 ± 19.7	139 ± 21.2	133 ± 19.7
Heart rate (beats/min)	66 ± 10.3	77 ± 16.7	66 ± 10.3
CHA_2DS_2-VASc of ≥2	1,153,878 (52.4)	5298 (60.9)	1,148,580 (52.4)
Mean CHA_2DS_2-VASc	2 ± 1.3	3 ± 1.6)	2 ± 1.3

Values are mean ± SD for continuous variables and n (%) for categorical variables.
* CHD is defined as previous myocardial infarction or a coronary intervention (bypass, angioplasty, or stenting).
AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PAD, peripheral arterial disease; SBP, systolic blood pressure; TIA, transient ischemic attack.

Predictive performance in validation cohort

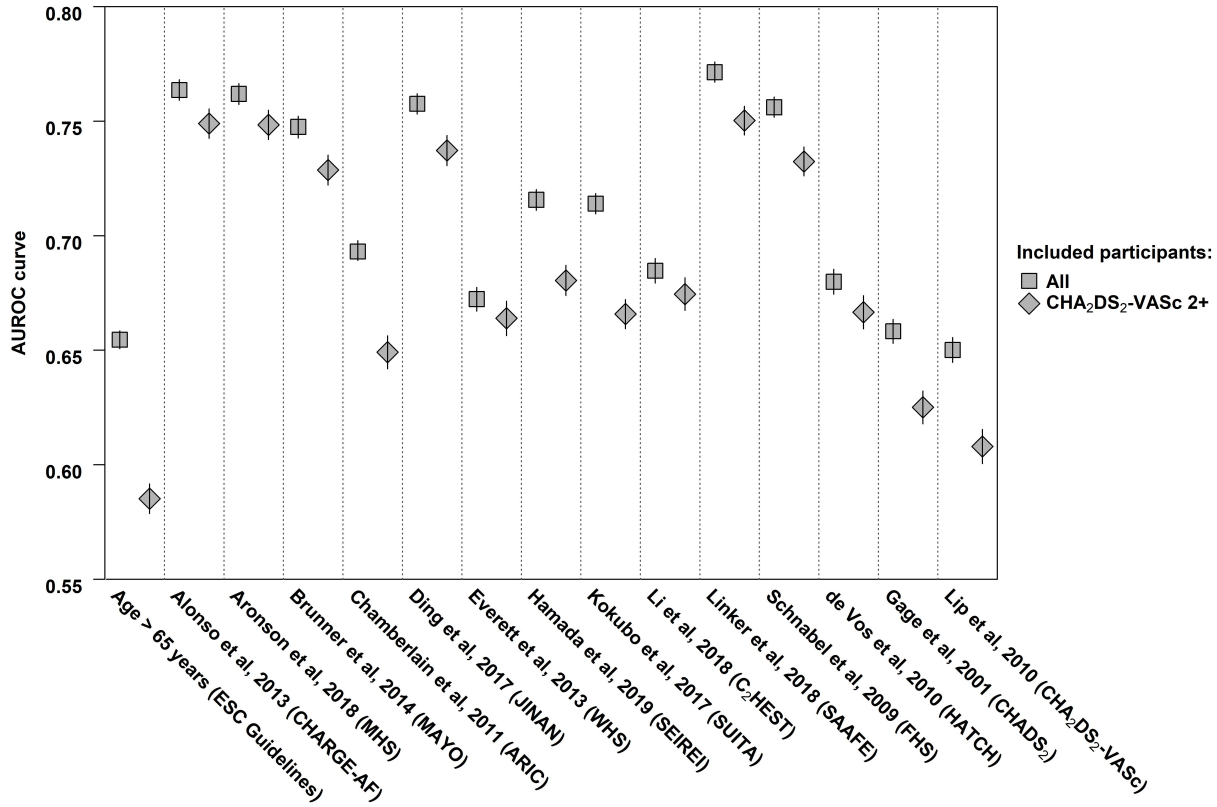
Discrimination

For discrimination in all participants, AUROC curves were between 0.71 and 0.77 in eight models,[24-26,28,30,31,33,34] and between 0.65 and 0.69 in six models.[2,9,27,29,32,35] (Figure 3 and Table S7) All models showed a statistically significant better discrimination compared with the age threshold of 65 years or older suggested for opportunistic screening in the current ESC guidelines.[38] All the models also had a statistically significant better discrimination than both $CHADS_2$ and CHA_2DS_2-VASc.[2,9]

In participants with CHA_2DS_2-VASc scores of two or higher, AUROC curves were between 0.73 and 0.75 in six studies,[24-26,28,33,34] and between 0.65 and 0.68 in six studies.[27,29-32,35] The AUROC

curve for the age threshold was 0.59.[38] (Figure 3 and Table S7) The difference in discrimination between age alone and all other models was also statistically significant.

Figure 3. Discriminative performance of risk prediction models

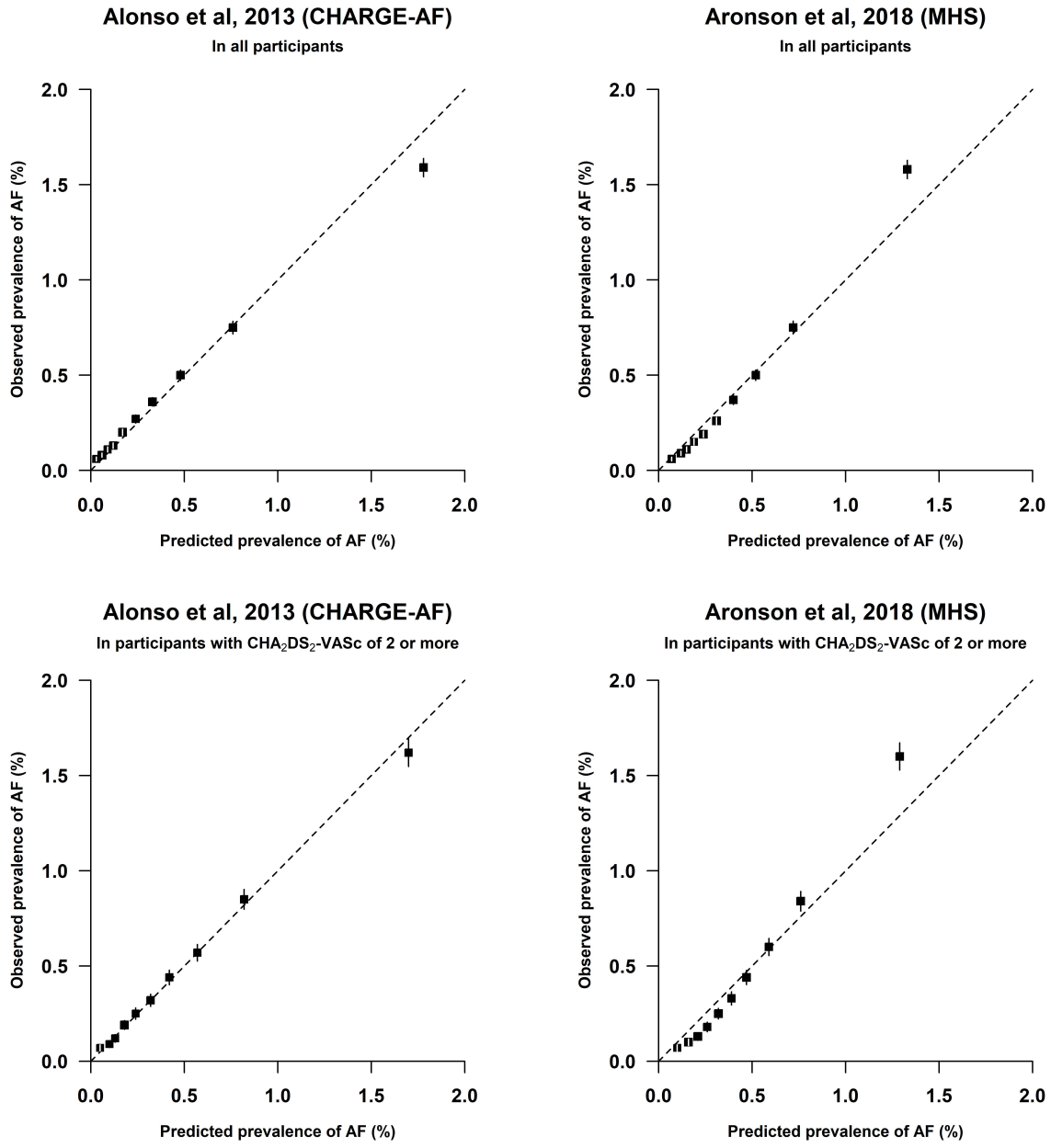


Squares represent the AUROC curves in the analysis of all participants and diamonds in participants with CHA2DS2-VASc of two or more.[2] The vertical bars represent the 95% CIs. The AUROC curves are based on the regression equation in twelve prediction models,[24-35] and on the point chart for two prediction models.[2, 9] The values are provided in eTable 7.

Calibration

Calibration showed good correspondence between predicted and observed risks of AF in six of the eight models with AUROC curves >0.70.[24-26,28-31,34] (Figure 4 & Figure S1) The two models with the highest observed prevalence in the highest decile of predicted risk were CHARGE-AF and MHS. An observed prevalence of AF of 1.6% was found in this decile (Figure 4).[24,25] Prevalences were predicted accurately across all deciles of predicted risk except for the highest decile, where CHARGE-AF overestimated the observed prevalence (1.8% vs. 1.6%) and MHS underestimated the observed prevalence of AF (1.3% vs. 1.6%). In participants with CHA_2DS_2-VASc scores of two or higher, calibration plots showed similar results (Figure 4).

Figure 4. Calibration plots



Calibration plots of the two risk prediction models with the highest observed prevalence of AF in the highest decile of predicted risk: CHARGE-AF and MHS.[24, 25] To construct the calibration plots, data of all 2.5M participants was *(top row)* and 1.2M participants with CHA2DS2-VASc of 2 or more *(bottom row)*. Mean predicted risk against the observed risk of AF across deciles of predicted risk (after recalibration with adjusting the intercept) is shown. The boxes represent the mean predicted risk for each decile and the vertical lines represent the 95% confidence intervals. The dotted diagonal line indicates perfect calibration. Boxes above the diagonal line indicate underestimation of risk and below the diagonal line overestimation of risk. The prevalences and number of cases of each decile are provided in eTable 9.

The predictors included in CHARGE-AF are age, ethnicity, height, weight, SBP, diastolic BP, smoking, antihypertensive medication use, diabetes, heart failure and myocardial infarction, of which ethnicity and diastolic BP were not included in the present analysis. The predictors included in MHS are age, sex, BMI, myocardial infarction, peripheral arterial disease, treated

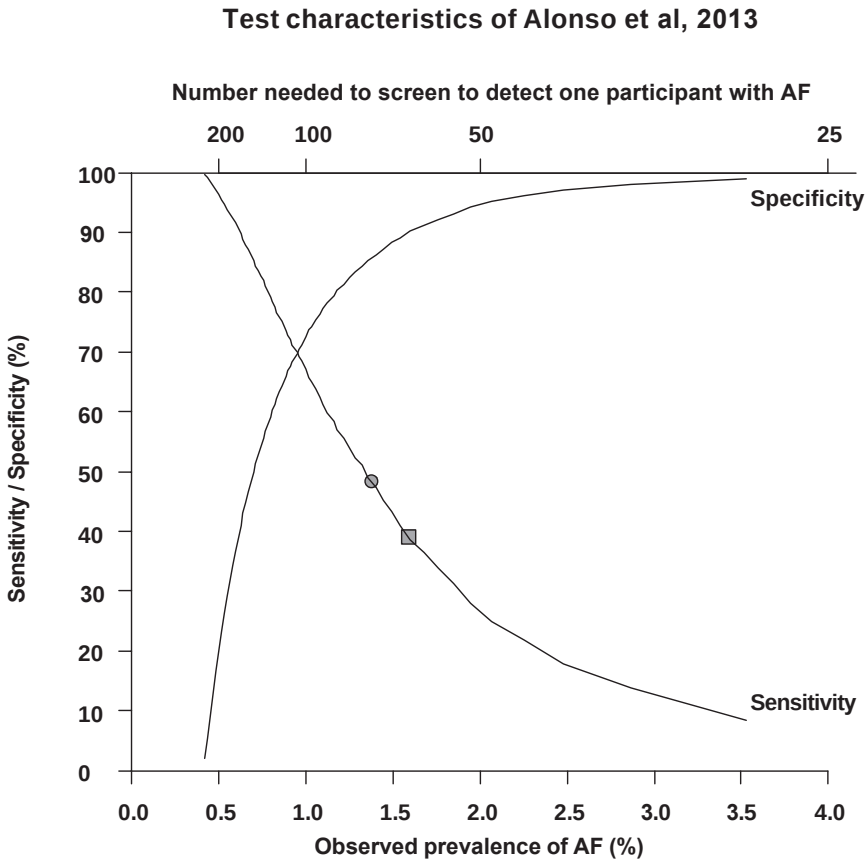
hypertension, SBP, chronic obstructive lung disease, female with autoimmune or inflammatory disease and heart failure by age group, of which female with autoimmune or inflammatory disease was not included in the present analysis. Other calibration plots are provided in Figure S1. The bar charts showed increasing observed prevalence with increasing sum scores (Figure S2).

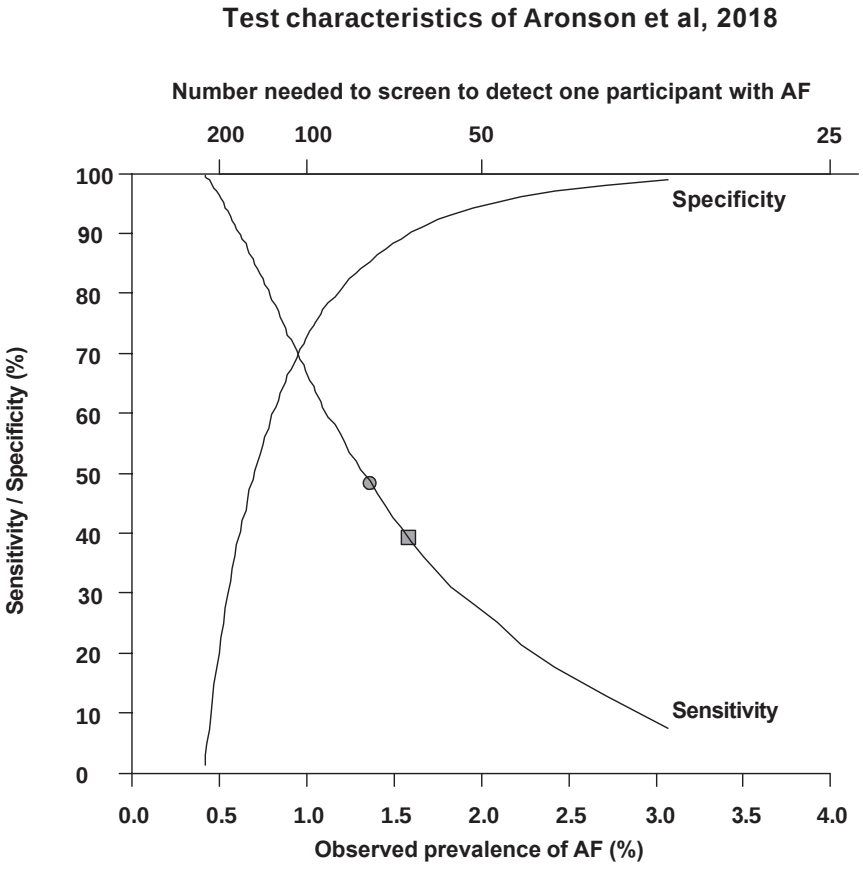
Test characteristics

We assessed selective screening of participants in the highest decile and highest two deciles of predicted risk. The prevalence of AF in the highest decile of predicted risk varied from 1.0% to 1.6% with corresponding NNS of 96 to 63 across the twelve prediction models (Table S10). CHARGE-AF and MHS showed the highest observed prevalence of 1.6% by selective screening of these 10% highest risk cases. This identified 39% of cases with prevalent AF with a specificity of 90%.

The prevalence of AF in the highest two deciles of predicted risk varied from 0.9% to 1.3% with corresponding NNS of 107 to 76 across the twelve prediction models. CHARGE-AF and MHS showed the highest observed prevalence of 1.3% by selective screening of these 20% highest risk cases. This identified 48% of cases with prevalent AF with a specificity of 85% (Table S10). Observed prevalence, NNS, sensitivity and specificity for other cutoffs of predicted risk using CHARGE-AF and MHS are shown in Figure 5.

Figure 5. Test characteristics





Graph showing the sensitivity and specificity and corresponding observed prevalence and number needed to screen to detect 1 participant with AF using the prediction model developed by Alonso et al 2013 *(Left)* and Aronson et al, 2018 *(Right)*. The squares and circles correspond to selective screening of participants in the highest decile and highest two decile of predicted risk, respectively.

Reclassification measures

Reclassification measures demonstrated a significant improvement of the CHARGE-AF and MHS prediction models compared to the age threshold of 65 years.[38] For the CHARGE-AF risk prediction model, the IDI was 0.0048 (95% CI 0.0046-0.0051; P < 0.00001), rIDI was 1.84 corresponding to an 184% improved classification, and the NRI was 0.6201 (95% CI 0.6011-0.6387; P < 0.00001). For the MHS risk prediction model, the IDI was 0.0021 (95% CI 0.0020-0.0022; P < 0.00001), rIDI was 0.80 corresponding to an 80% improved classification, and the NRI was 0.4447 (0.4258-0.4643; P < 0.00001)

Sensitivity analysis

Discrimination values were only marginally decreased in subsets with complete cases (Table S8).

Discussion

Our study is the first to compare the performance of all established risk prediction models for prevalent AF. We conducted an external validation in a large contemporary screened population who underwent a single time point 12-lead ECG to detect AF. Eight models showed AUROC curves of >0.70 and in seven of these there was good concordance of predicted and observed risks. Several common predictors were included in most models, such as age, hypertension and heart failure. The two models with the highest observed prevalence of AF in the highest decile of predicted risk were developed in the CHARGE-AF and MHS cohorts.[24,25] The observed prevalence of AF in the highest deciles across the two models was 1.6%, with a number needed to screen to detect one case with AF of 63. This was almost 4-fold higher than the overall prevalence and 25-fold higher than the lowest decile of predicted risk. These prediction models showed better discriminative performance compared to an age threshold of 65 years, $CHADS_2$ and CHA_2DS_2-VASc. Application of these risk models therefore may be able to inform more selective opportunistic or systematic screening.

Unselected population screening is likely to detect only small numbers of people with AF. For example, the recent Apple Heart Study screened nearly 420,000 people using smartwatch technology with an irregular pulse notification system.[39] Possible cases wore an ECG patch for seven days to confirm a diagnosis of AF. Irregular pulse notifications were received by 0.16% of people aged under 40 but 3.1% of those aged ≥65 years. Of those who received a notification, 18% of people under 40 years were diagnosed with AF but 35% of those aged ≥65 years. If screening is to be both cost effective and clinically relevant, it must be targeted at high-risk groups.

Different types of screening for AF in the population have been suggested, including systematic screening where participants are invited to have an ECG and opportunistic screening where pulse palpation is performed followed by an ECG if an irregular pulse is found.[40-43] These strategies were informed by randomised trials which used an age threshold for case selection rather than a prediction model with multiple predictors. Our results show that age alone is not the best discriminator of AF risk. Two previous studies also compared risk prediction models to the age

criterion of 65 years of age and over and found better discrimination when prediction models were used.[29,33]

A previous external validation compared nine prediction models to age for predicting the 3-year risk of incident AF using data from the ARIC study. Five models were significantly better than age alone but the $CHADS_2$ and CHA_2DS_2-VASc scores were not.[33] We found comparable results of discriminative indices for predicting prevalent AF, indicating that predictors for prevalent and incident AF overlap and the same models might be used for selection of high risk cases in both situations.

Strengths and Limitations

We conducted a comprehensive literature search to identify all established prediction models, according to a prespecified protocol. We are the first external validation using the outcome prevalent AF, an outcome relevant for a selective screening protocol with a single ECG. A large contemporary screened population of 2.5M participants was used for validation of included models. Included models were validated in the same participants enabling direct comparison of predictive performance. Missing data were handled with multiple imputation and did not affect our findings. Both risk equations and point charts were used for validation if reported. Point charts are easier to apply but contemporary presentation formats, such as webtools and smartphone apps, might use more complicated equations to estimate risks more precisely. We recalibrated risks to update the risk prediction models to the setting of our cohort, with its prevalence of AF.

Most included models were not developed to predict prevalent AF, and this might have influenced predictive performance. Some predictors were not available and for some we used proxies if a direct match was not available which might also have influenced predictive performance. Participants in our cohort were self-referred and self-funded, which might influence generalizability of our findings and might indicate the need to update (the intercept of) the models to new settings before implementation.[21] Participants were also relatively young and healthy compared to most people who develop AF, which may impact on the external validity of these results to the wider public.

Nonetheless, we include data on over 10,000 cases of AF within the population. It is also important to note that studies such as AppleWatch demonstrate a trend to increased screening in younger participants.[39] Recall bias cannot be excluded for predictors that were self-reported. Symptoms of AF were not recorded. ECG was performed only once in the screened participants, therefore cases of paroxysmal AF are likely to have been missed.[41] However, given stroke risk increases with frequency of AF, people detected on single-timepoint ECG are more likely to benefit from anticoagulation compared to people with brief episodes of paroxysmal AF, who are most likely to be missed by this approach to screening. Data on use of anticoagulant drugs were not available, but participants with a reported history of AF were excluded from the analyses. The prevalence of AF in our population was lower compared with other populations, possibly making targeted screening more worthwhile in different settings.[3]

Implications for practice and future research

The relatively poor performance of CHA_2DS_2-VASc for predicting either AF prevalence or incidence hampers the possibility of using a single score for prediction of AF diagnosis and risk stratification of outcomes, such as stroke or systemic thromboembolism. Using CHA_2DS_2-VASc for selection of cases was recently applied by the REHEARSE-AF trial, a RCT of AF screening using the AliveCor Kardia smart phone device in people with a CHA_2DS_2-VASc score ≥2. Among 1001 participants, 19 were diagnosed with AF in the AliveCor Kardia arm compared to 5 in the control arm at a cost per AF diagnosis of $10,780 in the intervention arm.[44] Our findings suggest that future research should consider using alternative prediction models, such as CHARGE-AF or MHS to limit screening to high-risk populations and reduce the number needed to screen. Future research will determine how many strokes could be prevented by improved cardiovascular risk management in cases in whom AF is detected by a selective screening programme and whether that leads to a cost-effective screening programme for AF. This might also help determining a threshold probability for selective screening.

Primary care computer software systems currently use electronic alerts based on CHA_2DS_2-VASc to help healthcare professionals identify people to consider for opportunistic screening. Such

software providers may wish to consider updating their diagnostic algorithms to use a more accurate risk score, such as CHARGE-AF or MHS.

Conclusions

We identified 14 potential models for predicting prevalent AF, all of which outperformed an age threshold of 65 years, $CHADS_2$ and CHA_2DS_2-VASc. The CHARGE-AF and MHS risk scores had the highest observed prevalence of AF in the highest decile of predicted risk (1.6%). Using these prediction models could reduce the number needed to screen to detect one case with AF using single time point ECG. Our study showed that established prediction models are able to identify reliably individuals at higher risk of AF. Application of these risk models therefore may be able to inform more selective opportunistic or systematic screening.

Contributors

AH, RB and SL obtained the data from Life Line Screening. MHFP designed the study. MHF, PS and RaC cleaned the data. MHFP designed the search strategy, performed literature searches and removed duplicates. MHFP and NJ screened titles and abstracts and assessed full-text articles and reference lists of included studies. MHFP performed the statistical analyses. The manuscript was drafted by MHFP. All authors interpreted the data, contributed to revision and editing of the manuscript and approved the final version of the manuscript for submission for publication.

Declaration of interest

The authors declare no conflicts of interest. This study was designed, conducted and reported independently of Life Line Screening and all funding sources. Life Line Screening provided data at no cost.

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SUPPLEMENTARY MATERIAL

Supplementary material can be found at the journal website:

https://academic.oup.com/eurjpc/advance-article/doi/10.1093/eurjpc/zwaa082/6067152?searchresult=1#supplementary-data

Supplementary material is also attached to this dissertation and can be found here

Part III

Combined Prediction of Major Causes of Ischaemic Stroke

7

Yield and Accuracy of Targeted Screening for Atrial Fibrillation and Carotid Stenosis in a Population at Increased Cardiovascular Risk

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Submitted

ABSTRACT

Background: Primary prevention strategies are important for individuals at higher risk of cardiovascular disease (CVD). Those with atrial fibrillation (AF) and significant asymptomatic carotid stenosis (ACS) can benefit from specific interventions to prevent heart attack and stroke. However, because AF and ACS are often clinically 'silent', this group may only be detected after stroke or other thrombo-embolic events. We aim to determine yield and accuracy of screening for AF and ACS targeted to a population at increased cardiovascular risk.

Methods: In this risk prediction modelling study, we used data of adults who attended voluntary and self-funded commercial screening clinics in the United States of America or the United Kingdom between 2008 and 2013. Attendees completed health questionnaires and underwent physical examinations along with cardiovascular investigations, including an electrocardiogram and duplex ultrasound of the carotid arteries. We applied the established Atherosclerotic CVD (ASCVD) risk equation to predict the 10-year risk of a first CVD event for each participant in order to assess yield and accuracy of targeted screening for AF and ≥50% ACS when offered to those at highest risk of CVD. Finally, we assessed whether additional measurement of height and weight improved screening for AF.

Results: Among 0.4 million individuals between 40 and 80 years, without known CVD, 1026 (0.3%) had AF and 6191 (1.6%) had ACS. ASCVD discriminated well between cases with and without AF and ACS [c-statistic 0.68 (95%CI 0.66-0.69) and 0.70 (95%CI 0.70-0.71) respectively]. Targeted screening of participants with a predicted 10-year CVD risk ≥20% identified 39% of cases with AF, a prevalence of 0.6%, a number needed to screen (NNS) of 175, as well as 41% of cases with ACS, a prevalence of 3.7% and an NNS of 27. Addition of height and weight improved discrimination of ASCVD [c-statistic 0.72 (95%CI 0.71-0.74)] and groups of participants at higher risk of AF were identified.

Conclusions: ASCVD risk assessment enables those at highest risk to have AF and ACS screening, greatly reducing NNS when compared with population-level screening. Detection of

AF and ACS could enable intervention to prevent serious CVD outcomes in appropriate high-risk cases.

Introduction

CVD remains a leading cause of morbidity and mortality despite improvements in treatment and prevention over recent decades. Most cardiovascular events occur in those without prior known disease.[1] The aim of primary prevention of cardiovascular disease (CVD) to reduce the incidence of CVD in asymptomatic individuals by optimizing modifiable risk factors. Several validated risk prediction models estimate CVD risk based on multiple risk factors.[2] Current guidelines use these to individualized risk prediction and tailor primary prevention strategies.[3-3] Current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines advise use of ASCVD risk equations to estimate 10-year risk of a first CVD event.[4] However, many strokes and myocardial infarctions still occur in patients at average risk.

Atrial fibrillation (AF) and asymptomatic carotid stenosis (ACS) are particularly high vascular risk factors, and strokes associated with these conditions are commonly disabling or fatal.[5,6] Both conditions are usually clinically silent until occurrence of the thrombo-embolic event. Anti-thrombotic therapy and carotid intervention should be considered in selected cases,[7,8] but are commonly delayed until after stroke or transient ischemic events. Whilst secondary prevention is effective,[9-14] it may be too late (especially where disabling or fatal stroke has occurred). Screening programmes for both AF and ACS can improve detection rates and prevent avoidable disability and premature deaths, but systematic population-level screening has a low yield, a high number needed to screen (NNS) and is not thought cost-effective.[15-20] High risk patients could be identified and, using risk stratification, this might impact on future clinical practice and prevention.[21]

We investigated the yield and accuracy of targeted screening for AF and ACS using the ASCVD cardiovascular risk assessment.

Methods

Study participants

Individuals in this cross-sectional dataset attended commercial vascular screening clinics in the United States of America and the United Kingdom between 2008 and 2013. They were self-referred and self-funded. An extensive questionnaire was completed by individuals with questions about their age, sex, height and weight, smoking status (never, former, or current), history of hypertension, diabetes mellitus, and vascular disease (coronary heart disease [CHD], stroke or transient ischemic attack [TIA], peripheral arterial disease [PAD]), and use of antiplatelet, antihypertensive, and lipid-lowering medication.

Blood pressure was measured as part of the ankle-brachial pressure index assessment. Standard blood pressure cuffs and sphygmomanometers were used, with systolic pressure (SBP) measured using a Doppler probe. Carotid duplex screening was performed with dedicated vascular ultrasound instruments (GE LOGIQ e®) and conducted by trained staff. The highest peak systolic velocity (PSV) and end diastolic velocities (EDV) of each common carotid artery and internal carotid artery were measured. A blood sample was provided by a subgroup of the participants to measure total cholesterol and high-density lipoprotein-cholesterol (HDL-C) by enzymatic methods using point-of-care testing methods (Alere Cholestech LDX® system, Alere Inc, Waltham MA, USA).

Participants with a reported history of AF or CVD (CHD, stroke, TIA or PAD) were excluded. Participants aged between 40 and 80 years who underwent screening in the United States of America including a single 12-lead ECG or duplex ultrasound of the carotid arteries, and who provided a blood sample were included.

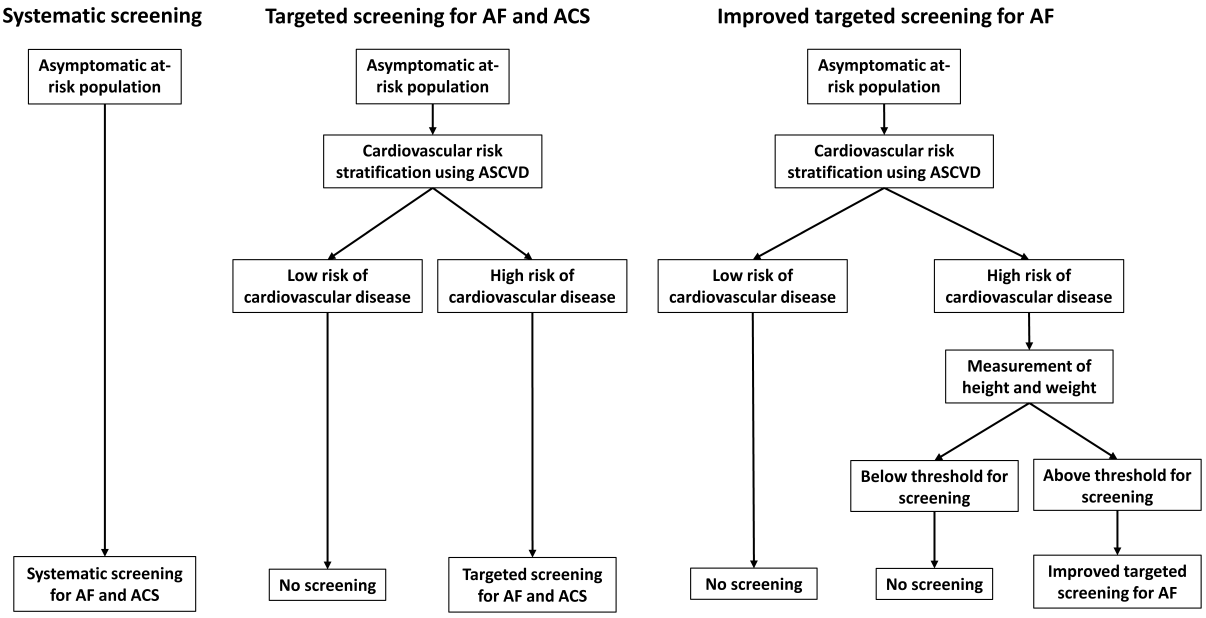
Outcomes and their ascertainment

The primary outcomes were AF and significant ACS. AF was measured with a single 12-lead ECG and evaluated by physicians who received in-house training. Significant ACS is the estimated diameter reduction of ≥50% based on PSV of ≥140 cm/s at either side or 0 cm/s for occluded arteries as measured with duplex ultrasound.

Statistical analyses

Baseline characteristics were summarized using standard methods. Missing data (Table S1) were imputed with chained equations.[22] We created 20 imputed datasets with 200 iterations. We applied the original risk equation of the new pooled cohort atherosclerotic CVD risk equations (ASCVD) to calculate the predicted 10-year risks of non-fatal myocardial infarction or CHD death, or fatal or nonfatal stroke for each individual.[4] We used the seven risk groups as defined in the original study (ranging from <2.5% to ≥20% predicted 10-year CVD risk; Figure 1).[4]

Figure 1. Different types of screening



Flow chart showing different types of screening: systematic screening of the population *(Left)*, targeted screening for atrial fibrillation and asymptomatic carotid stenosis implemented in cardiovascular risk assessment *(Middle)*, and targeted screening for atrial fibrillation implemented in cardiovascular risk assessment with additional measurement of height and weight *(Right)*.

Discrimination of ASCVD to detect AF and ACS

We assessed the discrimination of ASCVD, using concordance-statistic (c-statistic). Calculation of discrimination was performed in the 20 imputed datasets and results were pooled using Rubin's rules.[23,24]

Test characteristics of targeted screening for AF and ACS

We assessed the yield and accuracy of targeted screening for AF and ACS by calculating the prevalence of AF and ACS, the NNS, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each of the seven thresholds of predicted CVD risk. For this, we used the mean predicted probabilities across the 20 imputed datasets.

Test characteristics of targeted screening for AF and ACS in subgroups

Discrimination, yield, and accuracy of targeted screening were also calculated in men with CHA_2DS_2-VASc score of two and more and women with three or more, for AF, and in participants who reported no use of aspirin, for the outcome ACS, these being indications to initiate anticoagulation and antiplatelet therapy.[6,15,18]

Improvement of AF prediction by adding height and weight to ASCVD

We assessed whether adding height and weight as predictors improved prediction of AF,[25] since these are known risk factors for AF but are not included in the ASCVD risk model.[26] This was assessed for men and women separately. For this, we categorized weight in four groups (<60; 60-69; 70-79; ≥80kg in women; <80; 80-89; 90-99; ≥100kg in men) and height in three groups (<160; 160-199; ≥170 cm in women; <170; 170-179; ≥180 cm in men). We calculated discrimination and prevalence of AF across the seven ASCVD risk groups for each of the weight and height groups, and for men and women separately.

Risk of ischemic stroke and systemic embolism

We calculated mean predicted risk of ischemic stroke by ASCVD risk group, using the CHA_2DS_2-VASc. The risks of the Swedish Atrial Fibrillation cohort study (that were adjusted for use of aspirin) were used.[6,27] We performed similar analyses for the composite outcome of stroke, TIA and peripheral emboli. These analyses were performed for men and women separately.

Sensitivity analysis

We performed sensitivity analyses in complete cases.

STATA version 15.1 was used for statistical analyses and R version 3.5.1 was used for constructing figures.

RESULTS

In total, 3,276,139 individuals underwent screening. After exclusion of participants with reported vascular disease or AF, those aged younger than 40 or aged 80 and older, or without blood measurement, 396,869 individuals were eligible for our study (Table S2). Their mean age was 61.4 (SD: 8.7) years, 65% women, 95% identified themselves as Caucasian and 5% African American, and 12% were current smokers, 28% were former smokers, and 60% were never smokers (Table 1). A history of hypertension was reported in 34% of the participants and a history of diabetes in 7%. Mean SBP was 131 (SD: 19) mmHg and mean total cholesterol 199 (SD: 42) mg/dL. The prevalence of cardiovascular risk factors was higher in participants with AF and ACS, compared with participants without AF and ACS.

Table 1. Selected characteristics

	Participants with AF (N = 1026)	Participants without AF (N = 395,843)	Participants with ACS (N = 6191)*	Participants without ACS (N = 390,678)	All participants (N = 396,869)
Age (y)	66.3 ± 8.7	61.4 ± 8.7	66.3 ± 7.6	61.3 ± 8.7	61.4 ± 8.7
Women	418 (41)	256,852 (65)	3863 (63)	253,407 (65)	257,270 (65)
Caucasian	978 (98)	370,772 (95)	5910 (97)	365,840 (95)	371,750 (95)
African American	24 (2)	17,584 (5)	178 (3)	17,430 (5)	17,608 (5)
Current smoker	86 (10)	42,049 (12)	1382 (25)	40,753 (12)	42,135 (12)
Former smoker	307 (34)	97,614 (28)	2041 (37)	95,880 (28)	97,921 (28)
Never smoker	508 (56)	212,327 (60)	2047 (37)	210,788 (61)	212,835 (60)
Hypertension	424 (43)	132,249 (34)	3320 (55)	129,353 (34)	132,673 (34)
Diabetes mellitus	121 (13)	26,940 (7)	901 (15)	26,160 (7)	27,061 (7)
SBP (mmHg)	136 ± 22	131 ± 19	141 ± 22	131 ± 19	131 ± 19
Total cholesterol (mg/dL)	183 ± 41	199 ± 42	199 ± 47	199.0 ± 42	199 ± 42
HDL-C (mg/dL)	51 ± 18	55 ± 19	52 ± 18	55 ± 19	55 ± 19
Aspirin	373 (41)	109,624 (32)	2520 (46)	107,477 (32)	109,997 (32)
Lipid-lowering therapy	276 (29)	93,359 (25)	2407 (41)	91,228 (25)	122,148 (32)
Antihypertensive therapy	404 (42)	121,744 (32)	3178 (53)	118,970 (32)	93,635 (25)
CHA_2DS_2-VASc ≥2 in men or ≥3 in women	368 (44)	80,154 (24)	-	-	80,522 (24)

Values are mean ± SD for continuous variables and n (%) for categorical variables.
ACS, asymptomatic carotid stenosis; AF, atrial fibrillation; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure.
* In this group, 250 participants had a presumed occlusion.

Overall, 7200 (1.8%) participants had either AF or ACS, of whom 1009 (0.3%) participants had AF, 6174 (1.6%) had ACS, and 17 had both. In those in whom ACS was detected, 2520 (46.0%) reported aspirin use and 1060 (18.6%) reported use of triple medical therapy. This was 1185 (53.0%) and 584 (25.1%) in participants with predicted 10-year CVD risk of ≥20%, and 1562 (52.1%) and 742 (23.8%) in participants with predicted 10-year CVD risk of ≥15%, respectively.

Discrimination of ASCVD to predict AF and ACS

The ability of ASCVD to distinguish between participants with and without AF was 0.68 (95% CI 0.66-0.69) in all participants and 0.59 (95% CI 0.57-0.61) in analyzing men with CHA_2DS_2-VASc of two or higher and women with a score of three or higher.

The discriminative performance for ACS was 0.70 (95% CI 0.70-0.71) and 0.70 (95% CI 0.69-0.71) in participants reporting no use of aspirin.

Test characteristics of combined targeted screening for AF and ACS

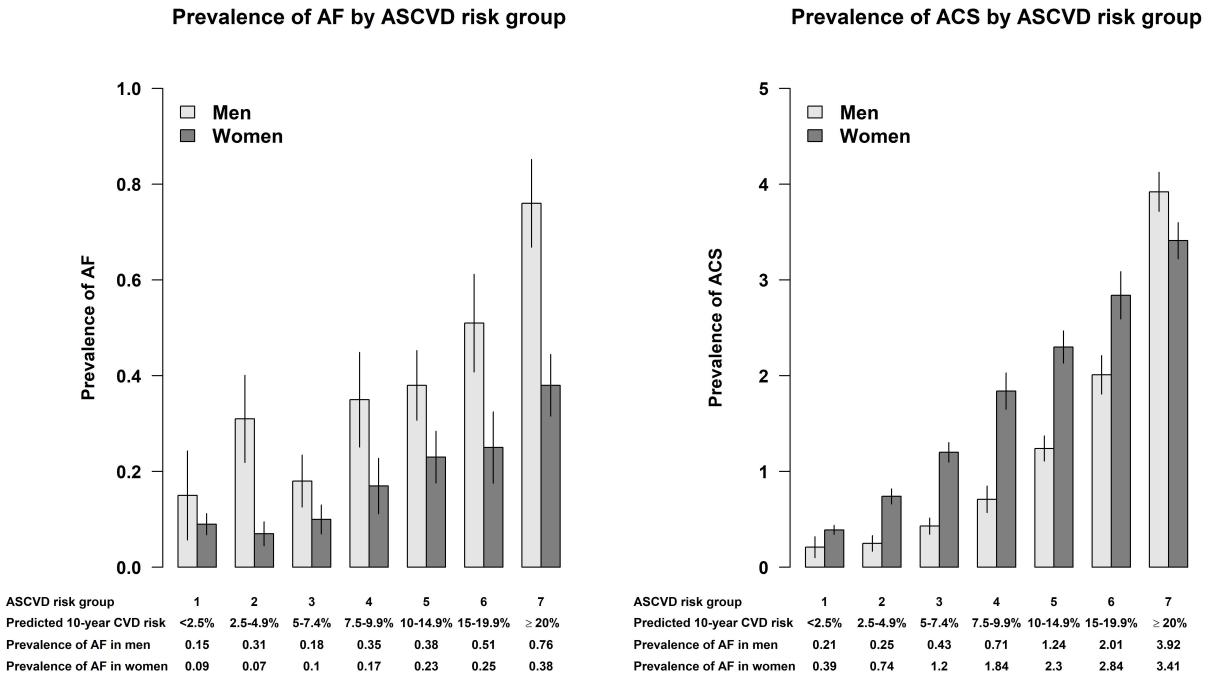
Combined targeted screening of the 70,059 participants with predicted 10-year CVD risk of ≥20%, yielded 2948 (4.2%) participants with either AF or ACS, corresponding to an NNS of 24. This identified 40.9% of cases with AF or ACS.

Combined targeted screening of the 106,175 participants with predicted 10-year CVD risk of ≥15% yielded 3953 (3.7%) participants with either AF or ACS, corresponding to an NNS of 27. This identified 54.9% of cases with AF or ACS.

Test characteristics of targeted screening for ACS

The prevalence of ACS increased with increasing ASCVD risk group for both women and men. The prevalence of ACS was higher in women for most risk groups, but in the highest risk group, the prevalence of ACS was higher in men than in women (Figure 2).

Figure 2. Prevalence of AF and ACS by ASCVD risk group



Bar chart showing the prevalence of AF and ACS across the seven ASCVD risk groups in men and women. The overall prevalence of AF in men and women was 0.4% and 0.2%, respectively. Significant ACS was found in 1.7% of men and 1.5% of women. The vertical lines on the top of the bars represent the 95% confidence intervals.
ASCVD, atherosclerotic cardiovascular disease; ACS, asymptomatic carotid stenosis; AF, atrial fibrillation.

Targeted screening for ACS of participants with predicted 10-year CVD risk of ≥20% showed a prevalence of 3.7% with corresponding NNS of 27 (compared with an NNS of 64 if all participants had been screened). This yielded 41.4% of ACS cases by screening 18% of all participants.

Targeted screening for ACS of participants with predicted 10-year CVD risk of ≥15% showed a prevalence of 3.2% with corresponding NNS of 31. This yielded 55.4% of ACS cases by screening of 27% of all participants (Table 2). The observed prevalence, NNS, sensitivity and specificity for each ASCVD risk group are shown in Figure S1.

In participants reporting no use of aspirin, results were comparable but prevalences and sensitivity were lower and NNS was higher (Table 2).

Table 2. Yield of targeted screening for AF and ACS according to ASCVD risk group

ASCVD risk groups[4]	No. individuals	No. outcomes	Sensitivity (%)	Specificity (%)	NPV (%)	PPV/ Prevalence (%)	NNS
AF							
Very high risk (≥20%)	70,059	400	39.0	82.4	99.8	0.6	175
High risk (15-19.9%)	36,116	138	52.4	73.3	99.8	0.5	197
Intermediate risk (10-14.9%)	58,122	178	69.8	58.7	99.9	0.4	229
Low risk (7.5-9.9%)	33,145	81	77.7	50.3	99.9	0.4	248
Low risk (5.0-7.4%)	66,408	85	86.0	33.6	99.9	0.3	299
Very low risk (2.5-4.9%)	58,902	76	93.4	18.7	99.9	0.3	337
AF in men with CHA_2DS_2-VASc of two or more and women with three or more							
Very high risk (≥20%)	42,268	249	66.9	48.6	99.7	0.6	170
High risk (15-19.9%)	13,973	50	80.4	31.6	99.7	0.5	188
Intermediate risk (10-14.9%)	13,264	50	93.8	15.5	99.8	0.5	199
Low risk (7.5-9.9%)	4444	11	96.8	10.1	99.9	0.5	205
Low risk (5.0-7.4%)	3934	7	98.7	5.3	99.9	0.5	212
Very low risk (2.5-4.9%)	1057	1	98.9	4.0	99.9	0.5	215
ACS							
Very high risk (≥20%)	70,059	2560	41.4	82.7	98.9	3.7	27
High risk (15-19.9%)	36,116	869	55.4	73.7	99.0	3.2	31
Intermediate risk (10-14.9%)	58,122	1048	72.3	59.1	99.3	2.7	37
Low risk (7.5-9.9%)	33,145	452	79.6	50.7	99.4	2.5	40
Low risk (5.0-7.4%)	66,408	619	89.6	33.9	99.5	2.1	48
Very low risk (2.5-4.9%)	58,902	364	95.5	18.9	99.6	1.8	55
ACS in participants reporting no use of aspirin							
Very high risk (≥20%)	33,594	1049	35.5	85.9	99.0	3.1	32
High risk (15-19.9%)	18,135	386	48.6	78.2	99.2	2.8	36
Intermediate risk (10-14.9%)	31,498	536	66.7	64.8	99.3	2.4	42
Low risk (7.5-9.9%)	19,048	252	75.3	56.7	99.4	2.2	46
Low risk (5.0-7.4%)	40,335	344	86.9	39.4	99.6	1.8	56
Very low risk (2.5-4.9%)	38,871	217	94.2	22.6	99.7	1.5	65

ACS, asymptomatic carotid stenosis; AF, atrial fibrillation; NNS, number needed to screen; NPV, negative predictive value; PPV, positive predictive value.

Test characteristics of targeted screening for AF

Increasing ASCVD risk group showed increased AF prevalences in both women and men (Figure 2). Screening for AF targeted to participants with predicted 10-year CVD risk of ≥20% showed a prevalence of 0.6% with corresponding NNS of 175 (compared with an NNS of 387 if all participants had been screened). Screening 18% of all participants yielded 39.0% of AF cases. In participants with predicted 10-year CVD risk of ≥15%, the prevalence of targeted screening was 0.5% with corresponding NNS of 197. This yielded 52.4% of AF cases by screening 27% of all participants (Table 2). The observed prevalence, NNS, sensitivity and specificity for each ASCVD risk group are shown in Figure S1.

We found similar results in participants with CHA_2DS_2-VASc of two or more, but the sensitivity was higher with yield of 66.9% of all participants with AF by targeted screening of participants

with predicted 10-year CVD risk of ≥20%, and 80.4% of all participants with AF by targeted screening of participants with predicted 10-year CVD risk of ≥15% (Table 2).

Improvement of AF prediction by adding height and weight

Addition of height and weight improved prediction of AF significantly with c-statistic of 0.72 (95% CI 0.71-0.74). The prevalence of AF in women was higher for those whose height was ≥180 cm and weighing between 70-79 kg, and those weighing ≥80 kg regardless of their height compared with women in the same ASCVD risk group.

The prevalence of AF in men was higher for those whose length was ≥180 cm weighting between 90-99 kg, and those weighing ≥100 kg regardless of their height compared with men in the same ASCVD risk group (Figure 3).

Figure 3. Prevalence of AF by height and weight, by ASCVD risk groups

Men

ASCVD risk group	1	2	3	4	5	6	7
Predicted 10-year risk of CVD (%)	<2.5	2.5-4.9	5.0-7.4	7.5-9.9	10-14.9	15-19.9	≥20
Prevalence of AF in our cohort (%)	0.15	0.31	0.18	0.35	0.38	0.51	0.76

Height								Weight
<170 cm	0.08	0.16	0.09	0.19	0.20	0.28	0.42	
170-179 cm	0.08	0.16	0.09	0.19	0.20	0.28	0.42	*<80 kg*
≥180 cm	0.12	0.24	0.13	0.28	0.30	0.41	0.61	
<170 cm	0.10	0.20	0.11	0.23	0.24	0.34	0.50	
170-179 cm	0.10	0.20	0.11	0.23	0.25	0.34	0.50	*80-89 kg*
≥180 cm	0.15	0.29	0.16	0.34	0.36	0.49	0.73	
<170 cm	0.12	0.23	0.13	0.27	0.29	0.40	0.59	
170-179 cm	0.12	0.23	0.13	0.27	0.29	0.40	0.60	*90-99 kg*
≥180 cm	0.18	0.34	0.19	0.40	0.43	0.58	0.87	
<170 cm	0.19	0.36	0.20	0.42	0.45	0.61	0.91	
170-179 cm	0.19	0.36	0.20	0.42	0.45	0.62	0.92	*≥100 kg*
≥180 cm	0.27	0.52	0.30	0.61	0.66	0.90	1.33	

Women

ASCVD risk group	1	2	3	4	5	6	7
Predicted 10-year risk of CVD (%)	<2.5	2.5-4.9	5.0-7.4	7.5-9.9	10-14.9	15-19.9	≥20
Prevalence of AF in our cohort (%)	0.09	0.07	0.10	0.17	0.23	0.25	0.38

Height								Weight
<160 cm	0.06	0.05	0.07	0.11	0.16	0.16	0.26	
160-169 cm	0.06	0.05	0.07	0.12	0.16	0.17	0.27	*<60 kg*
≥170 cm	0.08	0.07	0.10	0.16	0.22	0.23	0.37	
<160 cm	0.06	0.04	0.07	0.11	0.15	0.16	0.25	
160-169 cm	0.06	0.05	0.07	0.11	0.16	0.16	0.26	*60-69 kg*
≥170 cm	0.08	0.06	0.09	0.15	0.21	0.22	0.36	
<160 cm	0.08	0.06	0.09	0.15	0.20	0.22	0.34	
160-169 cm	0.08	0.06	0.09	0.15	0.21	0.22	0.36	*70-79 kg*
≥170 cm	0.11	0.09	0.13	0.21	0.29	0.31	0.49	
<160 cm	0.11	0.09	0.14	0.22	0.30	0.32	0.51	
160-169 cm	0.12	0.09	0.14	0.23	0.32	0.33	0.53	*≥80 kg*
≥170 cm	0.16	0.13	0.19	0.31	0.43	0.46	0.72	

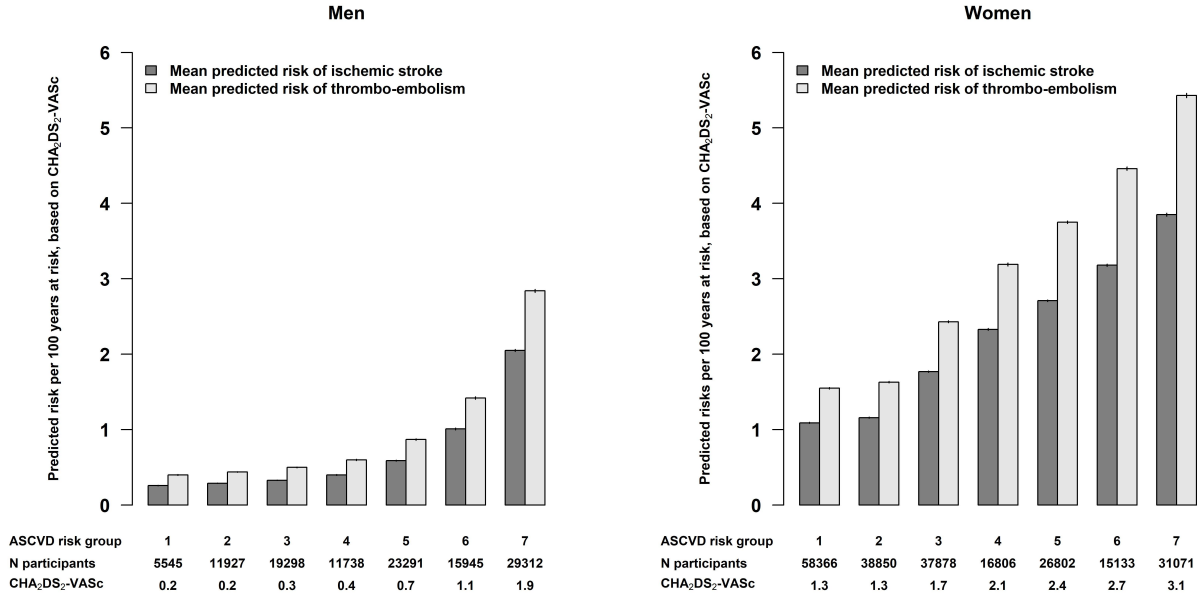
Chart showing the prevalence of AF by height and weight categories, for men *(top)* and women *(bottom)*. Green highlight indicates a lower prevalence of AF in an ASCVD risk group with specific height and weight groups compared with participants in the same ASCVD risk group, yellow indicates the same prevalence, and red indicates a higher prevalence.
For example: the prevalence of AF in a woman who is 165 cm with a weight of 84 kg and a predicted 10-year CVD risk of 12% is 0.32%. That is higher compared with the prevalence of 0.23% for all women in the same ASCVD risk group.

Predicted risk of ischemic stroke and systemic embolism

The predicted risk of ischemic stroke was increased with increasing cardiovascular risk. The predicted risk of ischemic stroke was 1.0 per 100 person-years (PY) in the lowest ASCVD risk group and rose to 3.0 per 100 PY in the highest ASCVD risk group. The predicted risk of systemic embolism increased from 1.5 to 4.2 per 100 PY.

In men, the predicted risk of ischemic stroke increased from 0.3 to 2.1 per 100 PY and the predicted risk of systemic embolism increased from 0.4 to 2.8 per 100 PY. In women, risks were higher with predicted risks of ischemic stroke that increased from 1.1 to 3.9 per 100 PY and risks of systemic embolism that increased from 1.6 to 5.4 per 100 PY (Figure 4).

Figure 4. Predicted risks of AF-related complications, by ASCVD risk group



Bar charts showing the predicted risk of ischaemic stroke and systemic embolism per 100 years at risk based on the CHA_2DS_2-VASc risk score in men *(left)* and women *(right)* across the seven ASCVD risk groups. The predicted risks are based on the Swedish Atrial Fibrillation cohort study and were adjusted for use of aspirin.[27] The vertical lines on the top of the bars represent the 95% confidence intervals.

Sensitivity analysis

Analyses in complete cases showed similar discrimination and test characteristics (Tables S3-S4).

Discussion

Our study shows that the commonly used ASCVD risk assessment has fair discrimination to distinguish between cases with and without AF and ACS. AF and ACS were commoner in people at higher predicted CVD risk. Targeted screening will substantially reduce the number needed to screen compared to population-level screening. Adding simple measurements of height and weight could further improve AF detection. High risk CVD and AF individuals were high risk for AF-related complications, such as ischemic stroke and systemic embolism and could benefit from preventive strategies.

Screening for AF and ACS meets many of Wilson and Junger's criteria for a successful screening program.[28] Early identification of cases with AF and ACS enables antithrombotic therapy and other primary preventive strategies, such as lifestyle interventions, lipid-lowering and antihypertensive therapy, to be used. Our study shows that screening can be targeted to those at highest predicted CVD risk, improving its yield and accuracy. Close follow-up to maintain compliance is facilitated by embedding this screening into cardiovascular risk management. Current approaches to target screening for AF in at-risk populations has mainly been limited to selection based on age,[29-31] while risk prediction models using multiple predictors have been developed that showed better discriminative ability than an age threshold.[32,33] Screening for ACS is recommended in populations at-high risk, but selection criteria vary between guidelines.[16-19]

Different types of AF screening have been proposed, including systematic screening and opportunistic screening where pulse palpation is performed followed by an ECG if an irregular pulse if found.[34] The use of a single ECG might not detect all AF cases, since many AF cases have paroxysmal disease.[35] Modern technology, for example Smartwatches using photoplethysmography, or other wearable devices, will enable continuous self-monitoring for AF detection. What is a significant burden of screen detected AF in terms of stroke risk has yet to be determined.[36]

Recommendations for antithrombotic therapy are based on weighing the risk of stroke and thromboembolism against the risk of bleeding. Antiplatelet therapy for primary prevention is currently not recommended.[37] A risk reduction of serious vascular events from 0.57% to 0.51% per year was found, but major gastrointestinal and extracranial bleeds were increased by 0.03% per year.[37] In contrast, oral anticoagulants might reduce ischemic strokes rates by 65% and premature death by 25% in patients with non-valvular AF.[7] The estimated annual reduction in absolute stroke risk was 2.7%, with a number need to treat for 1 year to prevent 1 stroke was 37 for primary prevention.[7] The decision to initiate oral anticoagulants in patients with AF is based on the CHA_2DS_2-VASc risk score and should be weighed against the risk of major bleeding calculated with the HAS-BLED risk score.[6,38]

In patients with significant ACS, triple medical therapy consisting of lipid-lowering, antihypertensive, and anti-thrombotic therapy, is currently recommended.[18] A recent cost-effectiveness analysis of a screening program to detect ACS in Sweden estimated that the stroke risk reduction from antiplatelet and lipid-lowering therapy combined was 50%.[39] While preventive effects of lipid-lowering therapy and antihypertensives are derived from primary prevention trials,[9,40,41] anti-thrombotic therapy has also been assessed specifically in patients with ACS. The preventive effective of aspirin was seen in the observational Asymptomatic Carotid Emboli Study (ACES) that included patients with 70-99% ACS,[42] but this was not seen in the Asymptomatic Carotid Bruit trial that randomized 372 patients with 50-99% ACS between 325 mg enteric-coated aspirin daily versus placebo.[43] Antiplatelet therapy in patients with ACS therefore provokes conflicting opinions and the optimal antithrombotic therapy in these patients and possibly among subgroups of patients with ACS need to be established.[44]

The COMPASS trial raised the possibility of long-term prevention by dual pathway inhibition in patients with stable atherosclerotic vascular disease by comparing low-dose rivaroxaban twice a day plus aspirin with aspirin alone.[45] The point estimate of the subgroup of patients with previous stable carotid disease was comparable to the main analysis and showed that major adverse cardiovascular events were reduced. The effect in this subgroup was however not

statistically significant, possibly due to the relative low number of patients with carotid disease and presumably needs additional confirmation in these patients.[46]

Strengths and limitations

The present study has several strengths. We used a large contemporary cohort to determine the yield and accuracy of screening targeted to participants at heightened risk of CVD. We also assessed the improvement of AF prediction by using additional measurement of height and weight. Bilateral examination of the carotid arteries was performed, and the highest degree of stenosis was used as outcome. We performed analyses restricted to participants with CHA_2DS_2-VASc score or 2 or more (for AF) and to participants not using aspirin (for ACS), since screening those will have clinical implications for anti-thrombotic therapy. We calculated predicted risk of ischemic stroke and systemic embolism using CHA_2DS_2-VASc, and showed that those at highest CVD risk were also at highest risk of developing AF-related complications, such as ischemic stroke and systemic embolism.

There are also limitations to consider. Participants were self-referred and self-funded for screening which might influence generalizability. Recall bias might have influenced predictors that were self-reported. We excluded a substantial number of cases without blood measurement. Blood pressure values were based on a single measurement and might not reflect 'usual' values. Degree of stenosis was based on PSV as single measure. Cases with paroxysmal and persistent AF might have been missed with a single time point ECG, likely underestimating the true prevalence of AF. It does show, however, the screening prevalence of AF using a single ECG measurement. Use of anticoagulants was not collected, but the proportion of participants is presumably low after exclusion of reported AF and prior vascular disease. The generalizability of CHA_2DS_2-VASc to populations with screen detected AF is unclear. The HAS-BLED score could not be calculated due to missing laboratory measures.[38]

Implications for practice and future research

Screening for AF and ACS implemented in ASCVD cardiovascular risk assessment might be performed by general practitioners and specialists concerned with primary prevention of CVD. Screening should be applied to cases where primary preventive therapy can be improved, for example in those not on anti-thrombotic therapy, and those eligible for anti-coagulation. It has yet to be determined what might be an appropriate threshold for targeted screening for AF and ACS; useful improvement of primary prevention needs to be achieved by balancing cost and benefit for NNS, yield and absolute reduction of stroke and other CVD events. A large scale (cluster) randomized clinical trial to randomize patients between targeted screening and routine care and powered to detect differences in stroke risk is needed to determine the benefit of screening targeted to high cardiovascular risk patients.

Conclusions

The present study showed that the ASCVD prediction model, originally developed to predict 10-year CVD risk, has fair discrimination to distinguish between cases with and without AF and ACS. Targeted screening of AF and ACS implemented in cardiovascular risk assessment using the ASCVD risk groups showed a higher prevalence of AF and ACS in those at higher risk of CVD. Addition of height and weight measurement might further refine screening to increase detection rates of AF. The calculated risk of AF-related complications, such as ischemic stroke and systemic embolism, was higher in cases at high risk of CVD, suggesting that those in whom AF is detected by targeted screening might achieve the highest reduction in absolute CVD risk by improving primary prevention strategies.

Contributors

AH, RB and SL obtained the data from Life Line Screening. MHFP designed the study. MHFP, PS and RaC cleaned the data. MHFP performed the statistical analyses. The manuscript was drafted by MHFP. All authors interpreted the data, contributed to revision and editing of the manuscript and approved the final version of the manuscript for submission for publication.

Declaration of interest

The authors declare no conflicts of interest. This study was designed, conducted and reported independently of Life Line Screening and all funding sources.

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SUPPLEMENTARY MATERIAL

Table S1: Number of excluded participants, with reasons for exclusion

Table S2: Missing data per variable

Table S3: Discrimination in complete cases

Table S4: Yield of targeted screening for AF and ACS according to ASCVD risk groups, in complete cases

Figure S1: Test characteristics of ASCVD to detect AF and ACS

Supplementary material is attached to this dissertation and can be found here

Part IV

Risk factors and Prediction of Outcomes After Carotid Revascularization

8

High Operator and Hospital Volume Are Associated with a Decreased Risk of Death and Stroke After Carotid Revascularization

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Abstract

Objective To examine the association between operator or hospital volume and procedural outcomes of carotid revascularization.

Background Operator and hospital volume have been proposed as determinants of outcome after carotid endarterectomy (CEA) or carotid artery stenting (CAS). The magnitude and clinical relevance of this relationship are debated.

Methods We systematically searched PubMed and EMBASE until August 21, 2017. The primary outcome was procedural (30 days, in-hospital, or perioperative) death or stroke. Obtained or estimated risk estimates were pooled with a generic inverse variance random-effects model.

Results We included 87 studies. A decreased risk of death or stroke following CEA was found for high compared to low operator volume with a pooled adjusted odds ratio (OR) of 0.50 (95% confidence interval [CI] 0.28-0.87; 3 cohorts), and a pooled unadjusted relative risk (RR) of 0.59 (95% CI 0.42-0.83; 9 cohorts); for high compared to low hospital volume with a pooled adjusted OR of 0.62 (95% CI 0.42-0.90; 5 cohorts), and a pooled unadjusted RR of 0.68 (95% CI 0.51-0.92; 9 cohorts). A decreased risk of death or stroke after CAS was found for high compared to low operator volume with an adjusted OR of 0.43 (95% CI 0.20-0.95; 1 cohort), and an unadjusted RR of 0.50 (95% CI 0.32-0.79; 1 cohort); for high compared to low hospital volume with an adjusted OR of 0.46 (95% CI 0.26-0.80; 1 cohort), and no significant decreased risk in a pooled unadjusted RR of 0.72 (95% CI 0.49-1.06; 2 cohorts).

Conclusions We found a decreased risk of procedural death and stroke after CEA and CAS for high operator and high hospital volume, indicating that aiming for a high volume may help to reduce procedural complications.

Registration This systematic review has been registered in the international prospective registry of systematic reviews (PROSPERO): CRD42017051491.

Introduction

Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are the mainstay surgical procedure as prophylaxis for future (recurrent) stroke, and hundreds of thousands of both procedures are performed worldwide each year. A low procedural mortality and stroke rate are necessary to guarantee net clinical benefit of intervention.[1] Hemodynamic disturbance and procedural thromboembolism have been identified as important underlying mechanisms of stroke after both CEA and CAS although the mechanisms differ between the two treatment modalities.[2-5] Procedural factors associated with adverse events are timing of surgery after presenting symptom,[6] patch-use during CEA,[7] and possibly the use of embolic protection devices during CAS.[8] General versus local anesthesia[9] and shunt use during CEA[10] do not seem to influence the rate of adverse events.

Volume is sometimes used as a surrogate measurement of quality of care.[11] As a consequence, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[12,13], the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S)[14], the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE)[15], and the International Carotid Stenting Study (ICSS) used volume thresholds for their credentialing process.[16] The reported associations between operator or hospital volume and outcomes following carotid revascularization are, however, inconsistent.[17]

We therefore systematically reviewed the literature on the relationship between operator or hospital volume and outcomes following carotid revascularization and meta-analyzed the published data to determine the magnitude and clinical relevance.

METHODS

This systematic review and meta-analysis was conducted according to a predefined protocol (Appendix S1) that has been registered prospectively in the international prospective registry for systematic reviews (PROSPERO): CRD42017051491. Our study adhered to The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Appendix S2).[18,19]

Search strategy

We used comprehensive electronic strategies (Appendix S3) to search PubMed and EMBASE from inception until August 21, 2017 for observational studies and subgroup analyses of randomized clinical trials meeting our predefined eligibility criteria. Grey literature was not included in the search strategy, because these data may not have been subject to peer-reviewed evaluation.

Eligibility criteria

Articles were included based on the following eligibility criteria: 1) full-text articles published in peer-reviewed journals; 2) written in: English, German, French, Spanish, or Dutch; 3) presenting original procedural outcome data about patients undergoing either CEA or CAS for asymptomatic or symptomatic carotid stenosis; 4) reporting: hospital volume, defined as the number of carotid procedures performed per hospital within a certain timeframe; or operator volume, defined as the number of carotid procedures performed per operator within a certain timeframe. Since in-trial volume can differ largely from annual volume results, we discarded in-trial volume from this review[20]; and 5) presenting effect estimates or providing raw data to calculate effect estimates for our predefined outcomes. Data on learning curve, defined as the effect on the outcomes of the early procedures performed by an individual operator, were not included in this systematic review.

Study selection

All titles and abstracts were independently screened for eligibility by two authors (MHFP and ECB) and full-text copies were independently assessed for final inclusion in this review. Subsequently, we cross-checked reference lists of included articles and identified reviews for further relevant

studies until no further publications were found. In case of disagreement, discrepancies were resolved in consensus meetings by MHFP, ECB and GJdB.

Data extraction

Two authors (MHFP and ECB) independently extracted the following study characteristics from the included studies: 1) Methods: study design, design of data-collection, data source, setting study, number of study centers, number of operators, geographic area (country and continent) of study, study years, sample size (patients/procedures); 2) Patient characteristics: A) Baseline characteristics: sex, age, and cardiovascular risk factors (adhering to the definitions of the individual studies) B) Disease characteristics: clinical presentation (symptomatic or asymptomatic status), degree of stenosis revealed by duplex ultrasound (<70%, 70-99%, occlusion), duration of hospital stay; 3) Determinant: total number of operators; total number of hospitals, thresholds of operator and hospital categories, number of patients/procedures per category, number of events per category; 4) Outcome: definition of the outcome as used by the authors, specification of the timeframe of outcome measurement, unadjusted RRs or ORs, adjusted RRs, ORs or HRs, and the adjustment factors if applicable.

Results from studies that only reported a *P* – value for an association, only textually mentioned an association without providing data with which risk estimates could be calculated, or assessed operator or hospital volume as a continuous variable are provided in Table S1. These results were not used in the quantitative analysis.

Outcome measures

PRIMARY

The primary end-point comprises procedural death or stroke, defined as within 30-days, unless stated otherwise (e.g. in-hospital). Although a composite endpoint might be difficult to interpret, because relative risks for the separate outcomes might be the opposite of each other, we expected studies commonly report the combination of these two postoperative outcomes, which are both important to patients.

Secondary

Procedural: 1) death; 2) stroke; 3) MI; 4) death, stroke or MI; 5) following CEA: cranial nerve injury, defined as any temporary palsy of a cranial nerve at the operative side without an underlying stroke or transient ischemic attack.

Risk of bias assessment

To assess the risk of bias, we developed an adapted version of the Newcastle-Ottawa Scale for non-experimental studies with three domains: Selection, comparability, and outcome. To address the domain selection, we assessed three domains: 1) Study design: population based study, multi-centered, data-collection (prospective, retrospective); 2) Representativeness of study cohort: low risk of bias if no selection in patients was applied. High risk of bias if risk factors that influence outcome were used for selection; 3) Ascertainment of intervention: low risk of bias if ascertainment was from medical records or registry. High risk of bias if ascertainment was from administrative sources. To address the domain comparability, we assessed: Comparability of case-mix between volume categories: low risk of bias if adjustment for case-mix differences in statistical analysis; high risk of bias if significant differences in case-mix were reported or no adjustment for case-mix differences. To address the domain outcome, we assessed two domains: 1) Assessment of outcomes: low risk of bias if independent blind assessment of outcomes was performed or outcomes were assessed using record linkage. High risk of bias if self-reporting of outcomes was used; 2) Addressing incomplete data: low risk of bias if loss of outcome data for participants or participants lost to follow-up was unlikely to introduce bias (non-differential lost to follow-up and <20%); high risk of bias if outcome data missing for participants or participants lost to follow-up was likely to introduce bias (differential loss to follow-up and/or >20%).

Statistical analyses

From the included articles, we obtained or calculated the relative risks (RRs), odds ratios (ORs) and hazard ratios (HRs) with corresponding 95% confidence intervals (CI) stratified per determinant. For calculation, we used the number of patients. If the absolute number of patients was not provided, we contacted authors for additional data. Otherwise, we used the absolute number of

procedures instead. If the absolute number of procedures was not provided and could not be obtained, the total number of patients in the meta-analysis was reported preceded by ">". If articles reported data on different cohorts, we meta-analyzed the cohorts as separate studies. We calculate the inversed risk estimate and 95% CI, if the highest volume group was used as reference group in the original articles. Risk estimates less than 1 indicate decreased risk of the defined outcome in high volume operators or hospitals, and risk estimates greater than 1 indicate an increased risk of the defined outcome in high volume operators or hospitals. If the 95% CI of the pooled risk estimate did not include 1 the association was considered statistically significant. Only risk estimates with a 95% CI were used for pooled analyses. Associations for which point estimates without 95% CI could be extracted or calculated can be found in Tables S2-S3.

We compared the outcomes for the highest available volume threshold to the lowest available volume threshold as provided in the original articles. Risk estimates were pooled using a random effects model, with study weights based on the generic inversed variance method. Risk estimates were pooled separately for: 1) CEA and CAS; 2) RRs, ORs, and HRs; 3) unadjusted and adjusted risk estimates.

Forest plots were constructed to visualize contribution of each study to a pooled estimate. To visualize the associations in studies from which only a point estimate could be extracted, we depicted these studies in the forest plots (displayed in the Appendix) without confidence intervals. Studies excluded from meta-analyses due to overlap in study population with other studies are not displayed in the forest plots.

Construction of forest plots, funnel plots, calculation of pooled estimates, and measures of heterogeneity were performed using the Metafor package for R language environment for statistical computing version 3.1.3.[21]

Heterogeneity

To account for heterogeneity between studies, we used a random effects model with weights per study assigned based on the generic inverse variance method. Heterogeneity across studies was assessed with the Cochran's Q test (if $P < 0.05$ significant heterogeneity exists), and expressed in the I^2-statistic. A prediction interval was constructed and displayed within the forest plots if ≥3

studies were included in the meta-analyses.[22,23] A prediction interval implies that there is a 95% chance that a risk estimate of a subsequent study with comparable characteristics will fall within this prediction interval. Wide prediction intervals indicate more heterogeneity than narrow prediction intervals.

Publication bias

Risk of publication bias is assessed with funnel plots and asymmetry is visually assessed and tested by Egger's regression[24], with a p-value <0.05 indicating asymmetry.[25] Symmetric funnel plots indicate no to low evidence for publication bias. Funnel plots were only constructed when ≥10 studies reported on a certain determinant-outcome relation, because interpretation of these plots is hampered when fewer studies are included.[25]

Sensitivity analysis

We performed the following sensitivity analyses for the primary endpoint: 1) Geographical region: limited to cohorts from North America; 2) Symptomatic status: limited to cohorts with adjustment for symptomatic status; 3) Adjustment for the other volume determinant: limited to cohorts with adjustment for the other volume determinant (e.g. surgeon volume-outcome relationship adjusted for hospital volume); 4) Midyear in which treatment took place (defined as median calendar year of treatment dates): limited to cohorts with midyear of treatment equal or above the median; 5) Volume threshold for low volume: limited to cohorts with low volume equal or above the median; 6) Volume threshold for high volume: limited to cohorts with high volume equal or below the median.

RESULTS

After screening 7021 publications, we identified 87 eligible studies (Figure 1 and Table S4). Two (2.3%) studies were based on data from randomized clinical trials, 85 (97.7%) studies were cohort studies, in which data-collection was prospective (15 [17.2%]), retrospective (57 [65.5%]), or a combination or unknown (15 [17.2%])(Table 1 and Tables S5-S6). For CEA, the relation was assessed with: 1) operator volume in 40 studies with >1,197,878 patients, and 2) hospital volume in 49 studies with >4,257,847 patients; and for CAS: 1) operator volume in 11 studies with 103,051 procedures, and 2) hospital volume in 15 studies with 178,251 procedures (Table S7). An overview of the pooled risk estimates is provided in Table 2.

Risk of bias assessment

Most studies were population-based or multicenter. Incomplete data on outcome did not exceed 20% except for one study. High risk of bias was assigned to studies that retrospectively used administrative databases, especially if these databases implied a selection of patients for enrollment. The use of classification coding systems for ascertainment of treatment and determination of outcome was the main reason leading to the assignment of a high risk of bias (Table S8).

Figure 1. Flowchart detailing the numbers of studies excluded and included at each step of the literature search

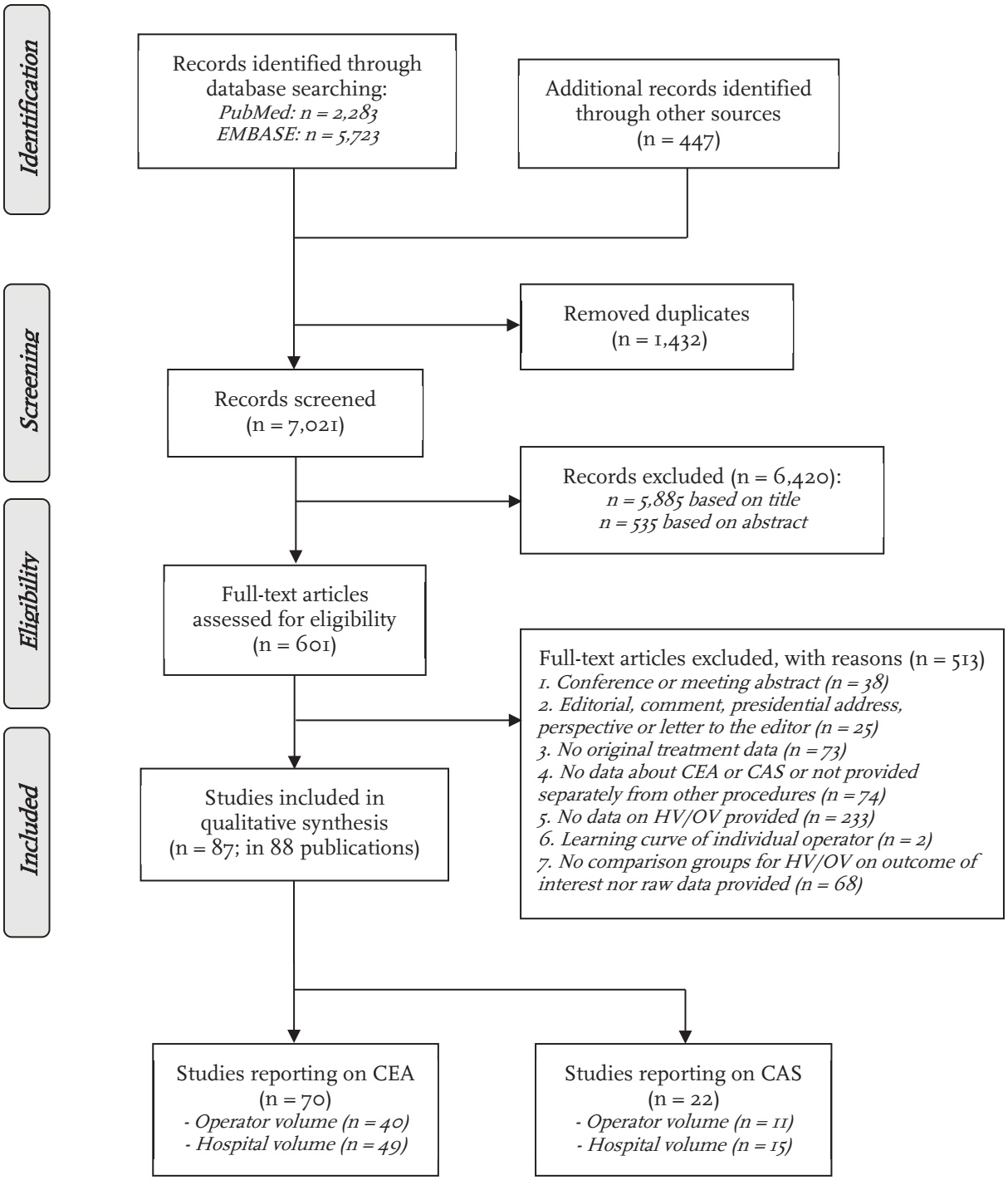


Table 1. Summary of study, patient and disease characteristics of the included studies

Study characteristics	Total[a] No. of studies (%)	CEA No. of studies (%)	CAS No. of studies (%)
Study design			
Cohort	85 (97.7)	69 (98.6)	21 (95.5)
Subgroup of RCT	2 (2.3)	1 (1.4)	1 (4.5)
Data-collection			
Prospective	15 (17.2)	10 (14.3)	5 (22.7)
Retrospective	57 (65.5)	47 (67.1)	14 (63.6)
Combination, other or not reported	15 (17.2)	13 (18.6)	3 (13.6)
Data source			
Clinical	20 (23.0)	17 (24.3)	3 (13.6)
Administrative	57 (65.5)	46 (65.7)	16 (72.7)
Combination, other or unknown	10 (11.5)	7 (10)	3 (13.6)
Continent			
North-America	73 (83.9)	61 (87.1)	16 (72.7)
Europe	8 (9.2)	7 (10.0)	2 (9.1)
Asia	3 (3.4)	0	3 (13.6)
Australia	1 (1.1)	1 (1.4)	0
Transcontinental	2 (2.3)	1 (1.4)	1 (4.5)
Number of operators in studies reporting on operator volume			
≥100 operators	20 (39.2)	16 (40.0)	4 (36.4)
<100 operators	16 (31.4)	16 (40.0)	0
Unknown	15 (29.4)	8 (20.0)	7 (63.6)
Number of hospitals in studies reporting on hospital volume[a]			
≥25 centers	37 (62.7)	30 (61.2)	10 (66.7)
<25 centers	10 (16.9)	10 (20.4)	0
Unknown	12 (20.3)	9 (18.4)	5 (33.3)
Patient characteristics			
Sex			
Reported	66 (75.9)	51 (72.9)	20 (90.9)
≥65% male	17 (25.8)	12 (23.5)	7 (35.0)
Age			
Reported mean or median	59 (67.8)	42 (60.0)	17 (77.3)
Mean or median ≥70 years	29 (49.2)	19 (45.2)	13 (76.5)
Disease characteristics			
Symptomatic status			
Reported	54 (62.1)	41 (58.6)	18 (81.8)
≥50% of the cohort underwent carotid revascularization for symptomatic carotid stenosis	24 (44.4)	20 (48.8)	4 (22.2)
Reported degree of stenosis			
Reported	8 (9.2)	7 (10.0)	3 (13.6)
Duration of hospital stay			
Reported	22 (25.3)	16 (22.9)	7 (31.8)

CAS, carotid stenting; CEA, carotid endarterectomy; RCT, randomized controlled trial.
[a]Five studies reported on CEA and CAS.
Study, patient and disease characteristics per study are provided in Tables S5-S6.

Table 2. Pooled risk estimates per outcome for the relation between operator volume and hospital volume (high-volume vs. low-volume) and procedural outcomes following CEA and CAS

	Operator volume	
	Unadjusted RR [95%-CI] (N of cohorts)	*Adjusted* OR [95%-CI] (N of cohorts)
Procedural outcomes for CEA		
Death or stroke	**0.59 [0.42-0.83]** (N = 9) OR: **0.40 [0.21-0.76]** (N = 1)	**0.50 [0.28-0.87]** (N = 3)
Death	**0.60 [0.52-0.69]** (N = 22)	**0.67 [0.61-0.74]** (N = 10)
Stroke	**0.56 [0.49-0.64]** (N = 14)	**0.55 [0.41-0.75]** (N = 3)
MI	**0.33 [0.20-0.53]** (N = 3)	**0.55 [0.31-0.97]** (N = 1)
Death, stroke, or MI	NA	1.08 [0.64-1.82] (N = 1)
Cranial nerve injury	0.68 [0.15-3.10] (N = 1)	NA
Procedural outcomes for CAS		
Death or stroke	**0.50 [0.32-0.79]** (N = 1)	**0.43 [0.20-0.95]** (N = 1) RR: **0.43 [0.26-0.74]** (N = 1)
Death	**0.57 [0.44-0.74]** (N = 2)	**0.5 [0.4-0.7]** (N = 1)
Stroke	**0.67 [0.50-0.90]** (N = 2)	**0.67 [0.49-0.92]** (N = 2)
MI	NA	NA
Death, stroke, or MI	0.42 [0.17-1.05] (N = 1)	0.4 [0.15-1.07] (N = 1)

	Hospital volume	
	Unadjusted RR [95%-CI] (N of cohorts)	*Adjusted* OR [95%-CI] (N of cohorts)
Procedural outcomes for CEA		
Death or stroke	**0.68 [0.51-0.92]** (N = 9)	**0.62 [0.42-0.90]** (N = 5) RR: **0.74 [0.60-0.90]** (N = 1)
Death	**0.71 [0.62-0.82]** (N = 17)	**0.78 [0.72-0.84]** (N = 12) RR: 0.74 [0.53-1.02] (N = 1)
Stroke	**0.83 [0.76-0.90]** (N = 11)	**0.62 [0.50-0.77]** (N = 3)
MI	**0.65 [0.42-0.99]** (N = 4)	1.22 [0.96-1.56] (N = 2)
Death, stroke, or MI	0.70 [0.41-1.20] (N = 1)	1.48 [0.19-11.70] (N = 2)
Cranial nerve injury	0.23 [0.04-1.39] (N = 2)	NA
Procedural outcomes for CAS		
Death or stroke	0.72 [0.49-1.06] (N = 2)	**0.46 [0.26-0.80]** (N = 1) RR: 0.93 [0.50-1.69] (N = 1)
Death	**0.70 [0.51-0.98]** (N = 4)	**0.59 [0.46-0.77]** (N = 2) RR: 0.65 [0.28-1.52] (N = 1) HR: 1.36 [0.74-2.49] (N = 1)
Stroke	**0.81 [0.71-0.92]** (N = 4)	**0.76 [0.62-0.92]** (N = 2) HR: 1.04 [0.62-1.74] (N = 1)
MI	1.46 [0.19-11.00] (N = 1)	HR: 0.38 [0.04-3.34] (N = 1)
Death, stroke, or MI	0.94 [0.44-2.00] (N = 1)	HR: 1.10 [0.75-1.63] (N = 1)

CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MI, myocardial infarction; N, number; NA, no cohorts available; OR, odds ratio; RR, relative risk.
All risk estimates represent the comparison of high volume with low volume taken as reference category.
Pooled estimates are calculated based on a random effects model weighting the individual cohorts with the generic inversed variance method. Statistically significant risk estimates are displayed in a **bold** font. The references of the individual studies that contributed to the meta-analyses are provided in Table S10.

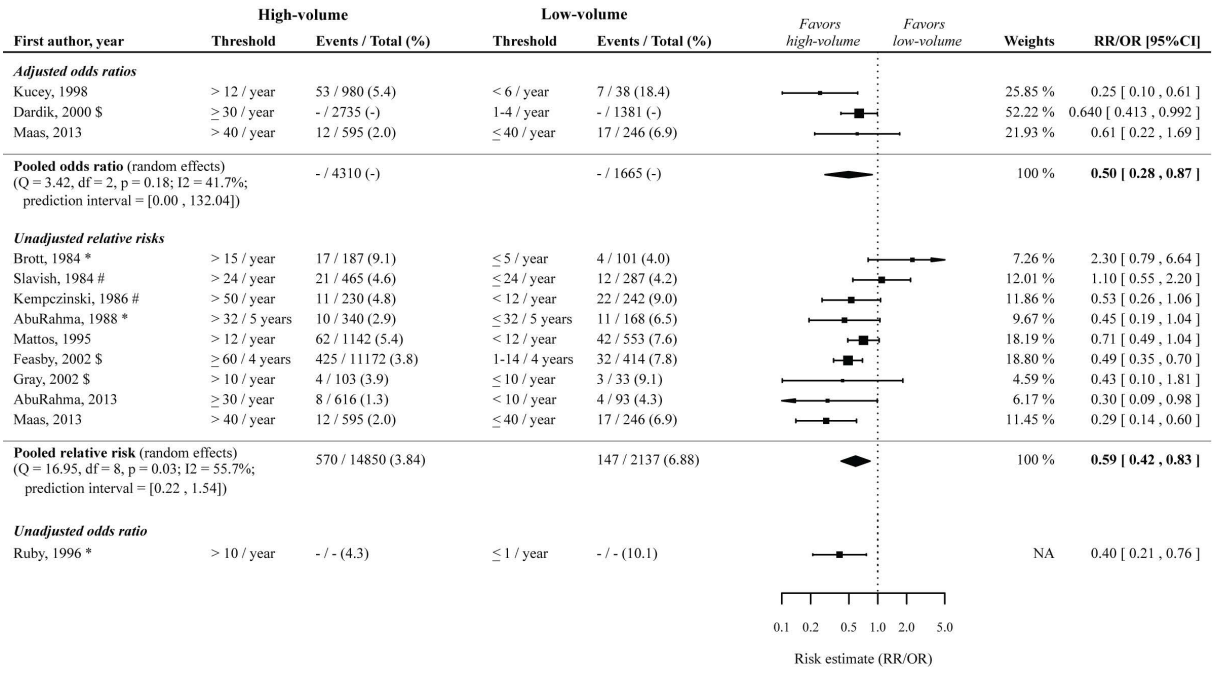
CEA operator volume

High operator volume compared to low operator volume was significantly associated with a decreased risk of procedural death or stroke following CEA, with a pooled adjusted OR of 0.50 (95% CI 0.28-0.87; 3 cohorts),[26-28] with a pooled unadjusted RR of 0.59 (95% CI 0.42-0.83; 9 cohorts),[28-36] and with an unadjusted OR of 0.40 (95% CI 0.21-0.76; 1 cohort).[37] (Figure 2; Table 2). The pooled adjusted ORs and pooled unadjusted RRs, with low operator volume taken as reference, showed that high operator volume is significantly associated with a decreased risk of procedural death and procedural stroke separately, and procedural MI following CEA (Table 2; Figures S1-S3). The adjusted association for procedural death, stroke or MI following CEA, and the unadjusted association for procedural cranial nerve injury were not statistically significant (Table 2; Figures S4-S5).

Among the studies reporting unadjusted RRs for procedural death or stroke, procedural death, and procedural stroke, most prediction intervals were narrow and did not include 1 except for the outcome procedural death or stroke.

Within the meta-analyses of the adjusted ORs for these outcomes the prediction intervals were wider and including 1 (except for the outcome procedural death), possibly due to the low number of studies reporting adjusted ORs.

Figure 2. Risk estimates and meta-analysis for the association between CEA operator volume (high vs. low volume) for the outcome procedural death or stroke.



Pooled estimates are based on a random effects model. Point sizes of the individual studies are proportional to the standard error of the specific study. Point estimates without confidence intervals were not included in the meta-analyses, and can be found in Figure S19.The timeframe for the measured outcomes is depicted as follows: no symbol 30-days outcome, * perioperative, # postoperative, $ in-hospital, § not further specified.
CEA, carotid endarterectomy; CI, confidence interval; NA, not applicable; OR, odds ratio; RR, relative risk.

CEA hospital volume

High hospital volume compared to low operator volume was significantly associated with a decreased risk of procedural death or stroke following CEA, with a pooled adjusted OR of 0.62 (95% CI 0.42-0.90; 5 cohorts),[20,26,38-40] with an adjusted RR of 0.74 (95% CI 0.60-0.90; 1 cohort),[41] and with an pooled unadjusted RR of 0.68 (95% CI 0.51-0.92; 9 cohorts).[20,36,39,41-46] (Figure 3; Table 2).

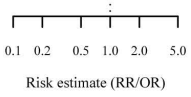
The pooled adjusted ORs and pooled unadjusted RRs, with low operator volume taken as reference, showed that high hospital volume is significantly associated with a decreased risk of procedural death and stroke separately following CEA. (Table 2; Figures S6-S7). The pooled unadjusted RR showed that high hospital volume was significantly associated with a decreased risk of procedural MI following CEA. The adjusted OR showed that high hospital volume is not significantly associated with a decreased risk of procedural MI

following CEA. The associations for procedural death, stroke or MI, and procedural cranial nerve injury following CEA were not statistically significant. (Table 2; Figures S8-S10).

Among studies reporting on procedural death or stroke, procedural death, and procedural stroke, the prediction intervals for studies reporting unadjusted RRs for procedural stroke, and adjusted ORs for procedural death were below 1. The other prediction intervals were wider, but except for the prediction interval for procedural stroke (prediction interval: 0.10-3.85) the upper bound did not exceed 2.

Figure 3. Risk estimates and meta-analysis for the association between CEA hospital volume (high vs. low volume) for the outcome procedural death or stroke

	High-volume		Low-volume				
First author, year	**Threshold**	**Events / Total (%)**	**Threshold**	**Events / Total (%)**	*Favors high-volume*	*Favors low-volume*	**Weights**	**RR/OR [95%CI]**
Adjusted odds ratios								
Fisher, 1989	> 40 / year	9 / 457 (2.0)	≤ 5 / year	9 / 158 (5.7)			11.25 %	0.32 [0.12 , 0.82]
Cebul, 1998	> 62 / year	- / - (2.4)	< 62 / year	- / - (7.1)			12.83 %	0.29 [0.12 , 0.69]
Dardik, 2000 *	≥ 50 / year	- / 5585 (-)	1-15 / year	- / 451 (-)			22.31 %	0.744 [0.436 , 1.270]
Giacovelli, 2010 $	> 123 / year	- / - (-)	1-33 / year	- / - (-)			34.01 %	0.85 [0.66 , 1.09]
Huibers, 2016	> 75 / year	26 / 823 (3.2)	< 40 / year	19 / 422 (4.5)			19.60 %	0.68 [0.37 , 1.26]
Pooled adjusted OR (random effects) (Q = 8.57, df = 4, p = 0.07; I2 = 54.5%; prediction interval = [0.19 , 1.96])		- / - (-)		- / - (-)			100 %	**0.62 [0.42 , 0.90]**
Adjusted relative risk								
Kuehnl, 2016 $	80-734 / year	1759 / 82338 (2.1)	1-10 / year	136 / 3251 (4.2)			NA	0.74 [0.60 , 0.90]
Unadjusted relative risks								
Kempczinski, 1986 #	> 100 / year	11 / 140 (7.9)	< 50 / year	21 / 285 (7.4)			10.85 %	1.07 [0.53 , 2.15]
Fisher, 1989	> 40 / year	9 / 457 (2.0)	≤ 5 / year	9 / 158 (5.7)			7.65 %	0.35 [0.14 , 0.86]
Bratzler, 1996	≥ 100 / 2 years	30 / 676 (4.4)	< 100 / 2 years	10 / 137 (7.3)			10.91 %	0.61 [0.30 , 1.21]
Karp, 1998	> 50 / year	26 / 1113 (2.3)	1-10 / year	7 / 118 (5.9)			8.72 %	0.39 [0.17 , 0.89]
Roddy, 2000 $	≥ 50 / year	113 / 7419 (1.52)	12-23 / year	5 / 446 (1.14)			7.89 %	1.36 [0.56 , 3.31]
Peck, 2001	404 / 2 years	13 / 404 (3.2)	67-89 / 2 years	3 / 156 (1.9)			4.66 %	1.67 [0.48 , 5.79]
Kuhan, 2001	435 / 8 years	17 / 435 (3.9)	306 / 8 years	12 / 306 (3.9)			10.33 %	1.00 [0.48 , 2.06]
Huibers, 2016	> 75 / year	26 / 823 (3.2)	< 40 / year	19 / 422 (4.5)			13.39 %	0.70 [0.39 , 1.25]
Kuehnl, 2016 $	80-734 / year	1759 / 82338 (2.1)	1-10 / year	136 / 3251 (4.2)			25.61 %	0.51 [0.43 , 0.61]
Pooled unadjusted RR (random effects) (Q = 15.93, df = 8, p = 0.04; I2 = 46.4%; prediction interval = [0.32 , 1.46])		2004 / 93805 (2.14)		222 / 5279 (4.21)			100 %	**0.68 [0.51 , 0.92]**



Pooled estimates are based on a random effects model. Point sizes of the individual studies are proportional to the standard error of the specific study. Point estimates without confidence intervals were not included in the meta-analyses, and can be found in Figure S20. The timeframe for the measured outcomes is depicted as follows: no symbol 30-days outcome, * perioperative, # postoperative, $ in-hospital, § not further specified.
CEA, carotid endarterectomy; CI, confidence interval; OR, odds ratio; RR, relative risk.

CAS operator volume

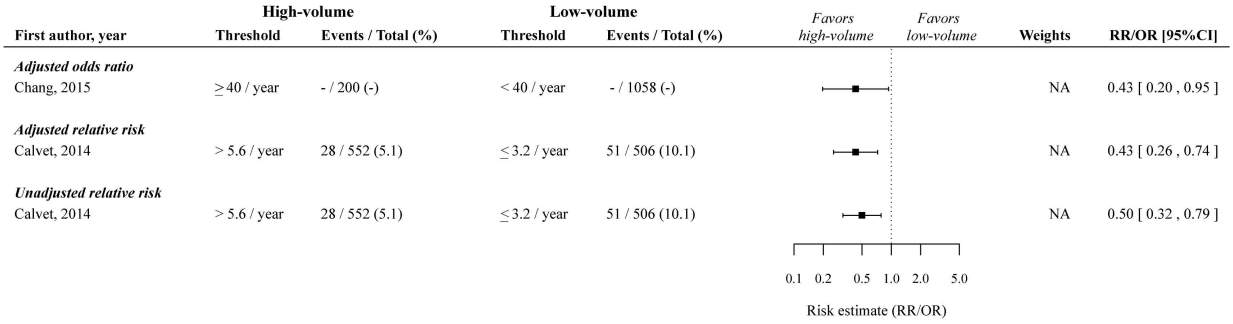
High operator volume compared to low operator volume was significantly associated with a decreased risk of procedural death or stroke following CAS, with an adjusted OR of 0.43 (95% CI 0.20-0.95; 1 cohort),[47] with an adjusted RR of 0.43 (95% CI 0.26-0.74; 1 cohort),[48] and with an unadjusted RR of 0.50 (95% CI 0.32-0.79; 1 cohort)[48] (Figure 4; Table 2).

The pooled adjusted ORs and pooled unadjusted RRs, with low operator volume taken as reference, showed that high operator volume is significantly associated with a decreased risk of procedural death and stroke separately following CAS (Table 2; Figures S11-S12).

No studies reported on procedural MI after CAS, and the association for procedural death, stroke or MI following CAS was not statistically significant (Table 2; Figures S13-S14).

No substantial heterogeneity was found in the three meta-analyses performed for CAS operator volume and no prediction intervals could be estimated because the number of studies per meta-analysis was ≤2.

Figure 4. Risk estimates and meta-analysis for the association between CAS operator volume (high vs. low volume) for the outcome procedural death or stroke



No pooled estimates are provided, because only one study per category was included. Point estimates without confidence intervals were not included in the meta-analyses, and can be found in Figure S21. The timeframe for the measured outcomes is depicted as follows: no symbol 30-days outcome, * perioperative, # postoperative, $ in-hospital, § not further specified.
CAS, carotid artery stenting; CI, confidence interval; NA, not applicable; OR, odds ratio; RR, relative risk.

CAS hospital volume

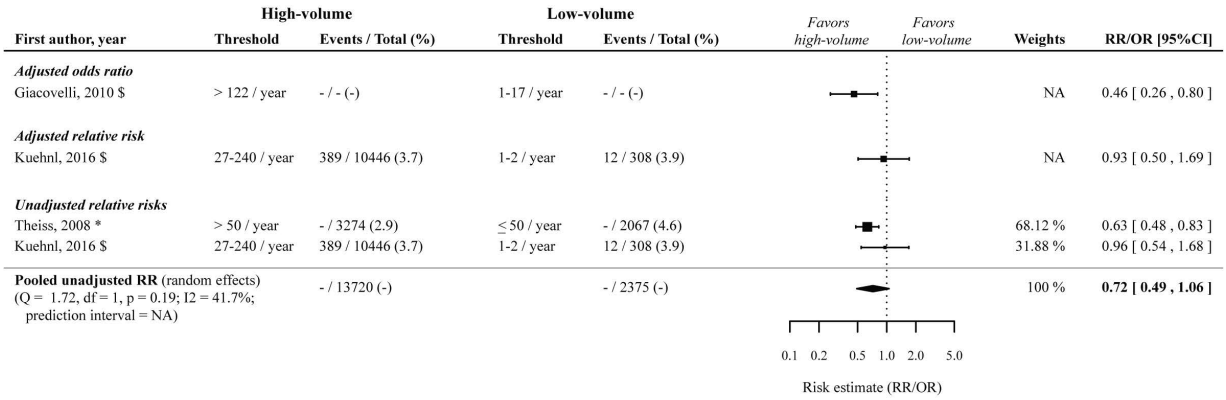
High hospital volume compared to low hospital volume was significantly associated with a decreased risk of procedural death or stroke following CAS, with an adjusted OR of 0.46 (95% CI 0.26-0.80; 1 cohort),[40] , and not significantly associated with an adjusted RR of 0.93 (95% CI 0.50-1.69; 1 cohort),[41] and a pooled unadjusted RR of 0.72 (95% CI 0.49-1.06; 2 cohorts).[41,49] (Figure 5; Table 2).

The pooled adjusted ORs and pooled unadjusted RRs, with low hospital volume taken as reference, showed that high hospital volume is significantly associated with a decreased risk of procedural death and stroke separately following CAS. (Table 2; Figures S15-S16).

The associations for procedural MI, and procedural death, stroke or MI following CAS were not statistically significant. (Table 2; Figures S17-S18).

Cochran's Q was >0.05 for all five meta-analyses for the CAS hospital volume-outcome relationship. Two prediction intervals could be estimated for studies reporting unadjusted RRs for procedural stroke (prediction interval: 0.60-1.08), and unadjusted RRs for procedural death (prediction interval: 0.22-2.21).

Figure 5. Risk estimates and meta-analysis for the association between CAS hospital volume (high vs. low volume) for the outcome procedural death or stroke



No pooled estimates are provided, because only one study per category was included. The timeframe for the measured outcomes is depicted as follows: no symbol 30-days outcome, * perioperative, # postoperative, $ in-hospital, § not further specified.

CAS, carotid artery stenting; CI, confidence interval; NA, not applicable; OR, odds ratio; RR, relative risk.

Publication bias

Asymmetry in the funnel plots was found for studies presenting adjusted associations between CEA hospital volume and procedural death (Egger's regression p=0.0012), indicating that there is statistical evidence for publication bias. No asymmetry was found for studies presenting other unadjusted and adjusted associations, indicating that there is no statistical evidence for publication bias for these procedural outcomes (Figure 6).

Figure 6. Funnel plots

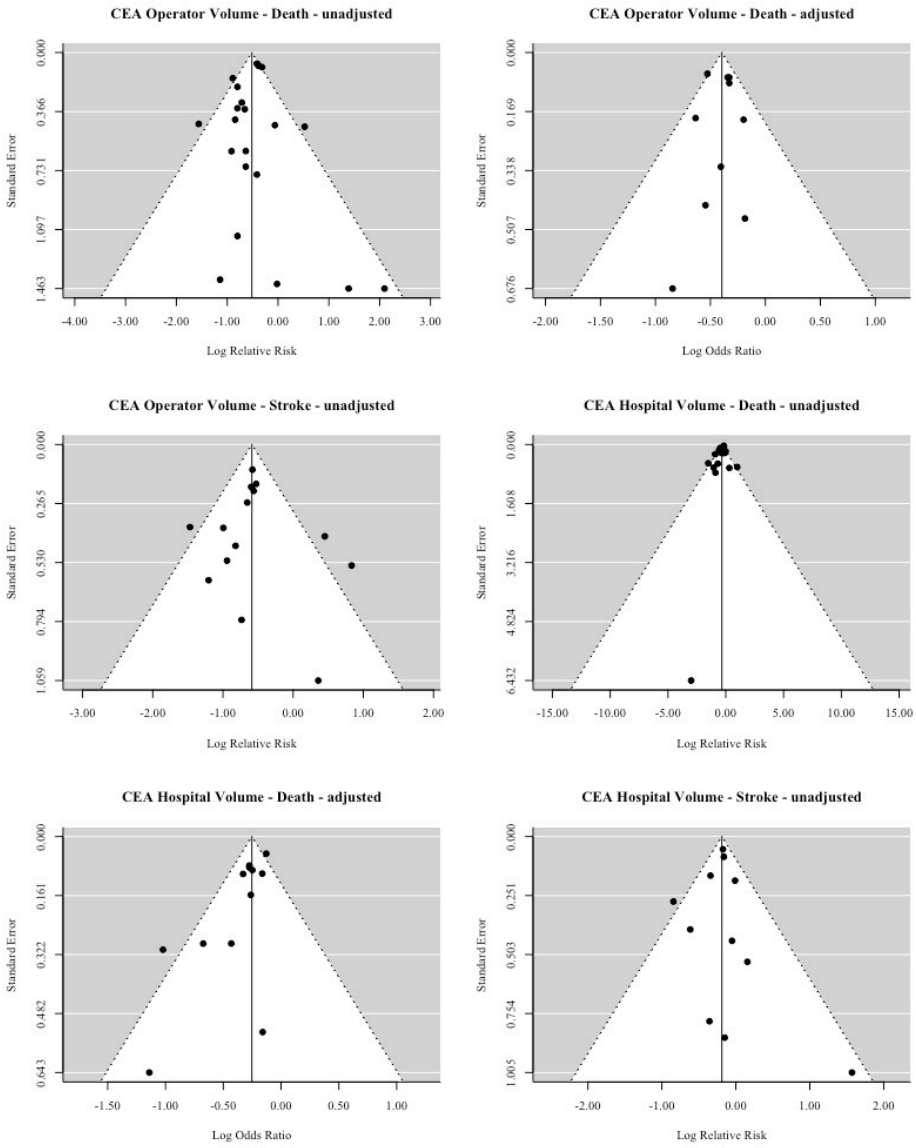


Figure 6. Funnel plots for all determinant-outcome relations with at least 10 studies. Adjusted or unadjusted in the title refers to the effect estimates under study, i.e. unadjusted/crude relative risks or adjusted odds ratios. Statistically significant asymmetry, indicating statistical evidence for publication bias, was only found within the funnel plot for the reported adjusted associations between CEA hospital volume and death with an Egger's regression p=0.0012.

Sensitivity analysis

Limited to studies from North America, we found similar associations between CEA operator and hospital volume and procedural death or stroke (Table S9). For CAS, no studies were found from North America reporting on procedural death or stroke. We found only one study reporting on operator volume that adjusted for symptomatic status of the patients undergoing CEA and no studies reporting on hospital volume adjusted for symptomatic status. We found similar results if

the inclusion for analysis was restricted to studies that adjusted for the other determinant. Limited to more recently treated patients, we found similar results (i.e. direction and size of risk estimate) for CEA operator volume, CAS operator and CAS hospital volume and procedural death or stroke. However, the 95%-CI of the association between CEA hospital volume and procedural death or stroke widened and included one, due to the lower number of included studies.

When limited to studies with higher low-volume thresholds or studies with lower high-volume threshold the direction and size of the association between CEA operator or hospital volume and procedural death or stroke remained stable. In a few comparisons, the risk estimates became statistically non-significant, because the pooled risk estimates had wider 95%-CI due to the lower number of cohorts included in these sensitivity analyses. For CAS, the sensitivity analyses with volume thresholds showed similar results compared to the primary analyses.

Discussion

Our systematic review and meta-analysis shows a decreased risk of procedural death and stroke following CEA and CAS in high operator and high hospital volume. For CEA, the unadjusted and adjusted pooled risk estimates for procedural death or stroke, procedural death and procedural stroke almost all show better outcomes in high volume operators and hospital. For CAS, similar results were found in a limited number of studies. The association between operator or hospital volume and procedural MI; procedural death, stroke or MI; and procedural cranial nerve injury has been less extensively studied, leading to less robust results. Importantly, we found limited evidence for publication bias.

Historically, two explanations have been proposed for the observed association between volume and outcome: The practice-makes-perfect hypothesis (note that this term has been criticized for being used in volume assessment but rather describes learning curve assessment[50]), assumes that the increasing experience of an operator or hospital leads to a reduction in adverse events. The selective-referral-pattern hypothesis stresses the influence of higher number of patient referrals to operators and hospital with better outcomes.[51] The latter hypothesis assumes high volume operators and hospitals select lower risk patients. However, in our meta-analyses, pooled unadjusted risks for death or stroke were comparable to adjusted risks. Furthermore, hospital readmission rates may be partly linked to hospital quality, regardless of patient-related factors.[52] It is often assumed that the experience or skill of the operator has an important impact on outcomes.[53] This is underlined by a study in which operator volume remained statistically significantly associated with CEA procedural death after extra adjustment for hospital volume.[54]

Our literature search was extensive and the inclusion of studies in our study was only influenced by suitability for the analyses. Our findings strengthen the evidence that operator and hospital volume influence the outcome following CEA and CAS.[55]

Nonetheless, our study has several limitations. First, there was considerable heterogeneity in volume definitions and thresholds. For this reason, the magnitude of the effect could only be

measured for the dichotomized determinant volume groups: high versus low. Since most original studies did not pre-specify thresholds and possibly selected thresholds to maximize differences in outcome between volume groups, bias might be introduced. Next to that, not all studies provided data on annual volume, but sometimes different timeframes were used. Second, the majority of the included studies used administrative data as data source that might be of inferior quality with regard to symptom status, high-risk status, and perioperative stroke.[56,57] Third, individual operator experience or 'learning curve' is knowingly not included as a determinant in this study.[58-61] The experience prior to the measured timeframe is unknown. The influence of developing clinical practice and the position of the operator on the learning curve might be underestimated, and the influence of other provider characteristics such as academic status of the hospital and experience with carotid interventions in high-risk patients is unknown.[62] Fourth, the assessment of the relationship between volume and outcome is hampered since not all studies adjusted for characteristics that are known to influence outcome following carotid revascularization (Tables S5-S6).[6,63-65] Fifth, we may have missed publications where operator and hospital volume was assessed but not clearly reported. Sixth, despite our efforts to prevent double-counting of patients by excluding overlapping datasets from meta-analyses, studies based on administrative datasets could potentially still have included overlapping patient groups.

Our results indicate an association between increasing volume and decreasing procedural death and stroke. Studies investigating determinants of outcome following carotid revascularization should adjust for operator volume and hospital volume. Heterogeneity in thresholds and definitions of determinants and outcomes emphasizes the need for clear definitions in order to improve the comparability of studies. Our findings question the decision of the Leapfrog initiative to drop volume standard for CEA as safety standard in surgical procedures.[11,17] The heterogeneity in the identified studies cannot justify direct introduction of set volume-thresholds, but do call for a closer examination of volume-effects within carotid revascularization.

The possibility of another relationship besides a dichotomized high versus low volume groups might be clinically relevant. For this reason, we extracted data from studies in which the volume-

outcome relation was assessed continuously. The possibility of a plateau phase in which the effect of additional cases per year after a certain number minimally affects outcomes should be considered, since this was found for many surgical procedures.

In conclusion, our study shows a decreased risk of death and stroke following CEA and CAS in high operator and high hospital volume. The association for CAS has been studied in fewer studies. The relationship of operator and hospital volume with procedural MI and procedural cranial nerve injury has less extensively been studied and therefore remains uncertain. Our results indicate that aiming for a high operator and hospital volume may help minimize adverse events following carotid revascularization. Further research is needed to establish the optimum volume thresholds balancing a minimum adverse event rate and practical feasibility.

Author contributions

MHFP, ECB, GJdB conceived the original idea for the study. All authors were involved in acquisition, analysis, or interpretation of data. MHFP and ECB performed the statistical analysis. The manuscript was drafted by MHFP, ECB, and GJdB with input from all co-authors. Critical revision of the manuscript for important intellectual content was done by all authors. Study supervision was done by GJdB. GJdB is guarantor for this article. MHFP and ECB contributed equally to this article and share first authorship.

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Supplementary material

Appendix S1: Protocol

Appendix S2: Checklists for reporting standards

Appendix S3: Search strategies

Table S1. Overview of studies with non-quantified data in which the volume outcome relation was assessed continuously

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Figure S19. Risk estimates and meta-analysis for the association between CEA operator volume for the outcome procedural death or stroke (including point estimates)

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Figure S21. Risk estimates and meta-analysis for the association between CAS operator volume for the outcome procedural death or stroke (including point estimates)

Supplementary material can be found at the journal website: http://links.lww.com/SLA/B441

Supplementary material is also attached to this dissertation and can be found here

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A Systematic Review and Meta-analysis of Complication Rates after Carotid Procedures Performed by Different Specialties

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Abstract

Objective Different competencies and skills are required and obtained during medical specialization. However, whether or not these impact on procedural outcomes of carotid endarterectomy (CEA) or carotid artery stenting (CAS) is unclear. We assessed the reported association between operator specialization and procedural outcomes following CEA or CAS to determine whether CEA and CAS should be performed by specific specialties.

Methods We systematically searched PubMed and EMBASE up to 21 August, 2017 for randomized clinical trials and observational studies that compared two or more specialties performing CEA or CAS for symptomatic and asymptomatic carotid artery stenosis. The composite primary outcome was procedural stroke or death (i.e., occurring within 30-days of the procedure or prior to discharge). Risk estimates were pooled with a generic inverse variance random effects model.

Results A total of 35 studies (26 providing data on CEA; 8 on CAS; one both CEA and CAS) were included, describing 256,033 CEA and 38,605 CAS procedures. For CEA, decreased risk of procedural stroke or death for operations performed by vascular surgeons compared to neurosurgeons was found with pooled unadjusted relative risk (RR) of 0.63 (95% CI 0.46 to 0.86; 7 studies) and RR of 0.81 (95% CI 0.66 to 0.99; 6 studies) when compared to general surgeons. An increased risk of procedural stroke or death for operations performed by neurosurgeons compared to cardiothoracic surgeons was found with a pooled unadjusted RR of 1.22 (95% CI 1.02-1.46). No studies adjusted for potential confounding and no significant unadjusted associations were found in other comparisons of operator specialty for the primary outcome. For CAS, no differences in procedural stroke or death were found by operator specialty.

Conclusions Studies were at high risk of bias mainly due to potential confounding by patient selection for CEA and CAS. Current evidence is insufficient to restrict CEA or CAS to specific specialties.

Registration This systematic review was registered *(PROSPERO CRD42017071959).*

Introduction

Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are commonly performed vascular procedures and a low procedural death and stroke rate is necessary to achieve long-term clinical benefit, because both procedures are performed as prophylaxis for future stroke.[1] Patient characteristics, such as age, smoking, coronary heart disease, chronic renal insufficiency, diabetes, type of preprocedural neurologic symptom, and contralateral carotid stenosis, are known to influence outcome after carotid revascularization.[2-6] Procedural characteristics that influence outcome are timing of intervention after the neurologic event[7,8] and patch-use.[9] Type of anesthesia,[10,11] shunt use during CEA,[12] and use of cerebral protection devices during CAS have not been shown to influence procedural outcomes.[13]

Operator characteristics have recently received more attention,[14] resulting in volume thresholds,[15-19] and which have driven reconfiguration of vascular centers with the creation of high-volume 'hubs'.[20]

Operator specialty has been proposed to influence patient outcomes after vascular procedures,[21] and may be particularly important for CEA and CAS, since these procedures are traditionally performed by a large variety of specialties with different training backgrounds.[22] However, reports of a relationship between specialty and outcome after carotid revascularization vary between studies and have not systematically reviewed. Consequently, there is no consensus whether carotid revascularization should be performed by specific specialties.

We aimed to systematically review and pool risk estimates on the association between operator specialty and procedural outcome after carotid revascularization with CEA or CAS.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted with a predefined protocol that has been registered prospectively in the international prospective registry for systematic reviews (PROSPERO): CRD42017071959. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations,[23] and our study adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Appendix S1).[24]

Data sources and searches

We searched PubMed and EMBASE on August 21, 2017 for studies describing (subgroup analyses of) randomized clinical trials (RCTs) and observational studies (Appendix S2).

Eligibility criteria

Inclusion criteria: 1) full-text articles published in peer-reviewed journals; 2) written in English, French, German, Spanish, or Dutch; 3) presenting original data on patients undergoing either CEA or CAS for asymptomatic or symptomatic carotid stenosis; 4) comparing two or more operator specialties; 5) presenting effect estimates or providing raw data with which effect estimates could be calculated.

Study selection

Two authors (MHFP and ECB) independently screened all titles and abstracts for eligibility and subsequently assessed full-text copies for final inclusion in this study. Reasons for exclusion after full-text evaluation were recorded. Reference lists of included articles and identified reviews were checked for further relevant studies. In case of disagreement, discrepancies were resolved between three authors (MHFP, ECB and GJdB).

Data extraction

The following study characteristics were extracted from the included studies by two authors (MP and EB) independently: Methods: study design, design of data-collection,

data source, setting study, number of study centers, number of operators, geographic area (country and continent) of study, study years, and sample size (patients/procedures); Patient characteristics: sex, age, cardiovascular risk factors (adhering to the definitions of the individual studies); Disease characteristics: symptomatic or asymptomatic status, degree of stenosis, duration of hospital stay; Determinant: different specialty groups; Outcome: definition of the outcome as used by the authors, specification of the timeframe of outcome measurement (e.g. 30-days or in-hospital), number of surgeons per specialty, number of patients/procedures per specialty, number of events per specialty, unadjusted relative risks (RRs) or odds ratios (ORs), adjusted RRs, ORs or hazard ratios (HRs) with corresponding 95%-confidence intervals (CI), and the adjustment factors where applicable.

Outcome measures

Primary

The primary outcome was procedural stroke or death, either in-hospital or 30-days (using authors' description of outcome).

A composite endpoint has the potential disadvantage of opposite directions of the risks of its constituents. For example, a higher risk of death and a lower risk of stroke within the same comparison. However, these two clinically relevant procedural outcomes are often reported together.

Secondary

The secondary outcomes were procedural: 1) death; 2) stroke; 3) MI; 4) combined death, stroke or MI; 5) postoperative cranial nerve deficit after CEA.

Quality assessment

Two authors (MHFP and ECB) independently used an adapted version of the Newcastle-Ottawa Scale to assess: patient selection (representativeness of study cohort and ascertainment of intervention), comparability of case-mix between specialties, and

assessment of outcome and addressing of incomplete data. An overview of criteria to assign high or low risk of bias can be found in the PROSPERO protocol.

Statistical analyses

We obtained RRs, ORs and HRs with 95%-CI or we calculated RRs (using number of patients per event or the number of procedures if the number of patients was not provided). If no events occurred, we added 0.5 to the events and procedures of specialties to estimate an unadjusted RR.[25] We only used the relative risks and did not use the absolute risks per specialty in the statistical analysis, since the absolute risks might change between settings, cohorts and over time and should therefore not be compared directly.

We used the definitions of the operator specialty as provided by the original articles and compared different specialties in the following order, for CEA: vascular surgeons, neurosurgeons, general surgeons, cardiothoracic surgeons; and for CAS: cardiologists, radiologists, vascular surgeons, neurosurgeons. Cardiovascular surgeons, cardiothoracic surgeons, cardiac surgeons and thoracic surgeons were considered cardiothoracic surgeons. Interventional cardiologists were considered cardiologists. Interventional radiologists, neuroradiologists and interventional neuroradiologists were considered radiologists.

We pooled risk estimates with a random effects model to account for heterogeneity between studies. Study weights were based on the generic inverse variance method. We included only the largest study in the meta-analysis if studies described (partly) overlapping data for a specific outcome. We performed separate analyses for: 1) CEA and CAS; 2) RRs, ORs, and HRs; 3) unadjusted and adjusted risk estimates. R version 3.1.3 was used for all analyses.[26]

Heterogeneity

Heterogeneity across studies was assessed with the Cochran's Q test, I^2-statistic and prediction intervals.[27,28] Prediction intervals were calculated if ≥3 studies were included in a meta-analysis. Prediction intervals should be interpreted as follows: there is a 95% chance that a risk estimate of a subsequent study with comparable characteristics will fall within the limits of the prediction interval. Wide prediction intervals indicate more heterogeneity than narrow prediction intervals. Heterogeneity was considered minor if I^2 <50%, Cochran's Q p>0.05, and narrow prediction intervals were found. Otherwise, the heterogeneity was considered substantial.

Publication bias

Risk of publication or reporting bias was assessed with funnel plots. Symmetric funnel plots indicate low evidence for publication or reporting bias. Potential asymmetry was assessed visually and tested by Egger's regression.[29] A p-value of <0.05 indicates asymmetry.[22] Funnel plots were constructed if ≥10 studies were included in a meta-analysis.[22]

Sensitivity analyses

Sensitivity analyses for the primary outcome were performed with studies: 1) reporting ≥80% symptomatic patients or stratified risk estimates by symptomatic patients; 2) reporting ≥80% asymptomatic patients or stratified risk estimates by asymptomatic patients; 3) based on clinical data and data from registries; 4) of high quality. High quality was assigned to studies with prospective data-collection, no patient selection, and case-mix adjustment.

RESULTS

After screening 7,021 publications, 35 eligible studies were identified (Figure 1).[5,17,18,30-61] Twenty-six studies reported CEA data, eight CAS data, and one both. In total, 256,033 CEA and 38,605 CAS procedures were described. Three studies were based on data from one RCT[17,18,59] and 32 studies were observational studies. All studies described procedures performed in North America (Table 1).

The number of patients per specialty is provided in Table 2. The number of events and patients per outcome is provided in Table 3.

Risk of bias assessment

Most studies applied no selection of patients based on risk factors that could have potentially affected outcomes when enrolling in the study. Few studies adjusted for patient variables in their analyses of the association between operator specialty and procedural outcomes, and seven studies adjusted for surgeon and/or hospital variables. Potential confounding due to the selection of patients by specialty could have affected the observed outcomes. Outcomes were almost never assessed blindly. Missing data in ≥20% of the patients was very uncommon. We found no study of high quality reporting on the primary outcome. (Table S1)

Figure 1. Flowchart

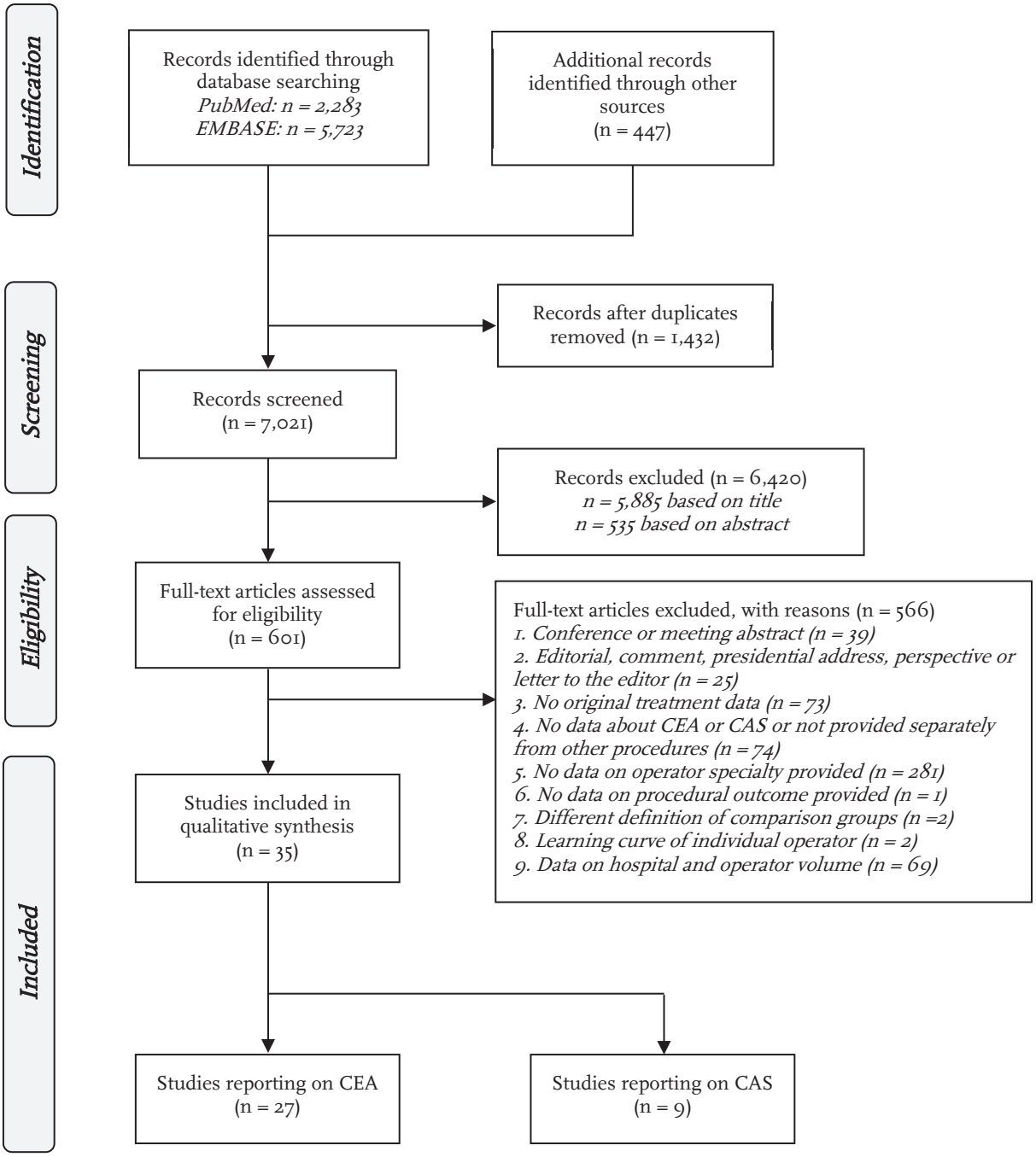

Table 1. Overview of study characteristics

	CEA (27 studies) No. of studies (%)	CAS (9 studies) No. of studies (%)
Study characteristics		
Study approach		
Cohort	26 (96.3%)	6 (66.7%)
Subgroup of RCT	1 (3.7%)	3 (33.3%)
Population-based	9 (33.3%)	2 (22.2%)
Multicenter	22 (81.5%)	8 (88.9%)
Data-collection		
Prospective	4 (14.8%)	6 (66.7%)
Retrospective	22 (81.5%)	3 (33.3%)
Unknown	1 (3.7%)	0
Data source		
Clinical	12 (44.4%)	5 (55.6%)
Administrative	15 (55.6%)	4 (44.4%)
Continent		
North-America	27 (100%)	9 (100%)
Number of operators		
≥100 operators	7 (25.9%)	6 (66.7%)
<100 operators	13 (48.1%)	0
Unknown	7 (25.9%)	3 (33.3%)
Patient characteristics		
Sex		
Reported	23 (85.2%)	7 (77.8%)
≥66% male	4 (17.4%)	1 (14.3%)
Age		
Reported	15 (55.6%)	8 (88.9%)
Mean or median ≥70 years	7 (46.7%)	4 (50.0%)
Disease characteristics		
Reported symptomatic status	18 (66.7%)	7 (77.7%)
≥50% symptomatic patients	8 (44.4%)	0 (NA)
Reported degree of stenosis	6 (22.2%)	2 (22.2%)
Reported duration of hospital stay	8 (29.6%)	3 (33.3%)

CAS, carotid stenting; *CEA*, carotid endarterectomy; *RCT*, randomized clinical trial

Table 2. Overview of procedures per specialty

	CEA Procedures, No. (%)	CAS Procedures, No. (%)
Vascular surgeons	129 282 (50.5)	2973 (7.7)
Neurosurgeons	12 388 (4.8)	170 (0.4)
General surgeons	45 083 (17.6)	N/A
Cardiothoracic surgeons	29 630 (11.6)	N/A
Cardiologists	N/A	9019 (23.4)
Radiologists	N/A	1952 (5.1)
Specialties combined[a]	39 650 (15.5)	24 491 (63.4)
Total	**256 033**	**38 605**

CAS, carotid artery stenting; *CEA*, carotid endarterectomy; *N/A*, not available.
[a] Different specialties were combined in one group for the analyses in the original studies.

Table 3. Overview of number of events, patients, and studies per outcome

	CEA		CAS	
	Events / patients, No. (%)	No. of studies	Events / patients, No. (%)	No. of studies
Procedural outcomes				
Stroke or death	1749 / 45 135 (3.88%)	14	>175‡ / 11 143 (N/A)	4
Death	>1036* / 197 814 (N/A)	14	236 / 28 041 (0.84%)	3
Stroke	>1997† / 186 541 (N/A)	16	1029 / 28 666 (3.59%)	4
MI	1040 / 104 573 (0.99%)	6	463 / 24 665 (1.88%)	3
Death, stroke or MI	4558 / 96 345 (4.80%)	4	>253§ / 12 289 (N/A)	5
Cranial nerve deficit	124 / 43 840 (0.28%)	3	NA	NA

CAS, carotid artery stenting; *CEA*, carotid endarterectomy; *MI*, myocardial infarction; *NA*, not applicable; *N/A*, not available.

* The number of patients with procedural death after CEA was not provided in two studies. † The number of patients with procedural stroke after CEA was not provided in one study. ‡ The number of patients with procedural stroke after CAS was not provided in one study. § The number of patients with procedural death, stroke or MI combined after CAS was not provided in one study.

Operator specialty and outcome after CEA

Unadjusted analyses showed a significantly decreased risk of procedural stroke or death for vascular surgeons compared to neurosurgeons (RR 0.63 (95% CI 0.46-0.86); 7 studies) and compared to general surgeons (RR 0.81 (95% CI 0.66-0.99); 6 studies). An increased risk of procedural stroke or death was found for neurosurgeons compared to cardiothoracic surgeons (RR 1.22 (95% CI 1.02-1.46); 4 studies) (Table 4).

Unadjusted analyses showed a decreased risk of procedural death for vascular surgeons compared to general surgeons (RR 0.70 (95% CI 0.58-0.85); 11 studies), and an increased risk of procedural death was found for neurosurgeons compared to general surgeons (RR 1.50 (95% CI 1.04-2.15); 9 studies), compared to cardiothoracic surgeons (RR 1.80 (95% CI 1.16-2.79); 7 studies (Table S2).

Unadjusted analyses showed a decreased risk of procedural stroke for vascular surgeons compared to neurosurgeons (RR 0.57 (95% CI 0.46-0.72); 11 studies), to general surgeons (RR 0.69 (95% CI 0.60-0.79); 10 studies) and to cardiothoracic surgeons (RR 0.70 (95 CI 0.58-0.86); 8 studies). The risk of procedural stroke for vascular surgeons compared to general surgeons remained significant in the meta-analysis of adjusted risk estimates (RR 0.70 (95% CI 0.58-0.83); 5 studies) (Table S2).

The (pooled) estimates for the outcomes procedural MI, procedural death, stroke or MI combined, and cranial nerve deficit are provided in Table S2. Heterogeneity was minor in most pooled analyses.

Table 4. Pooled risk estimates for the relation between specialties and procedural stroke or death after CEA

Index specialty		Reference specialty	Unadjusted RR (95% CI)	No. of studies	Cochran's Q	I^2	Prediction interval[a]
Vascular surgeons	vs	Neurosurgeons	**0.63 (0.46-0.86)**	7[31,36,37,40,42,45,46]	df: 6; Q: 11.832; p=0.07	54.3%	0.27-1.48
	vs	General surgeons	**0.81 (0.66-0.99)**	6[31,32,37,40,42,45]	df: 5; Q: 6.560; p=0.26	0.0%	0.61-1.07
	vs	Cardiothoracic surgeons	0.87 (0.63-1.19)	5[31,32,40,42,45]	df: 4; Q: 5.280; p=0.26	25.8%	0.39-1.94
Neurosurgeons	vs	General surgeons	1.53 (0.85-2.74)	5[31,37,40,42,45]	df: 4; Q: 11.682; p=0.02	63.2%	0.24-9.77
	vs	Cardiothoracic surgeons	**1.22 (1.02-1.46)**	4[31,40,42,45]	df: 3; Q: 2.150; p=0.54	0.0%	0.82-1.81
General surgeons	vs	Cardiothoracic surgeons	1.16 (0.85-1.57)	5[31,32,40,42,45]	df: 4; Q: 3.660; p=0.45	12.5%	0.58-2.31

CI, confidence interval; *df*, degrees of freedom; *RR*, relative risk.
The risk estimates in a **bold font** are considered statistically significant. Data on risk estimates for comparisons with specialty groups combined as reference category are provided in Table S2.
[a] Only estimated if ≥3 studies were included in the meta-analyses.

Operator specialty and outcome after CAS

We found no associations between operator specialty and procedural stroke or death (Table 5), or death and stroke separately (Table S3).

The (pooled) estimates for the outcomes procedural MI, and procedural death, stroke or MI combined are provided in Table S3. No substantial heterogeneity was found in the meta-analyses.

Table 5. Risk estimates for the relation between operator specialty and procedural stroke or death after CAS

Index specialty		Reference specialty	Unadjusted RR (95% CI)	No. of studies
Cardiologists	vs	Radiologists	0.95 (0.47-1.90)	[1 study][41]
	vs	Vascular surgeons	0.81 (0.49-1.32)	[1 study][41]
	vs	Neurosurgeons	0.64 (0.16-2.56)	[1 study][41]
Radiologists	vs	Vascular surgeons	0.85 (0.39-1.82)	[1 study][41]
	vs	Neurosurgeons	0.68 (0.15-3.03)	[1 study][41]
Vascular surgeons	vs	Neurosurgeons	1.27 (0.30-5.26)	[1 study][41]

CI, confidence interval; RR relative risk.
Data on risk estimates for comparisons with specialty groups combined as reference category are provided in Table S3.

Publication bias

None of the four constructed funnel plots showed statistical evidence for asymmetry indicating that there is no statistical evidence for publication bias (Figure S1).

Sensitivity analyses

Two studies reported on the primary outcome by symptomatic status,[31,32] five studies were based on clinical data[31,32,36,37,45] and three studies used administrative data.[40,42,46] In these sensitivity analyses, the associations between operator specialty and the primary outcome were comparable to the main analyses with regard to magnitude and direction of the association. (Table S4). No studies of high quality reported on the primary outcome.

Discussion

Our study showed that vascular surgeons had a lower unadjusted risk of stroke or death after CEA compared to neurosurgeons and general surgeons. Neurosurgeons had a higher unadjusted risk of stroke and death after CEA compared to cardiothoracic surgeons. Studies did not adjust for selection of patients for CEA by speciality. We found no associations for procedural stroke or death after CAS.

Several explanations have been suggested for the relationship between operator specialty and procedural outcomes that might explain our findings: the effect of higher volume for more specialized surgeons, different patient selection, and experience of the healthcare team.[62] These and other possible confounding factors were, however, not addressed in the included studies.

In a recent study, operator specialization has been associated with a lower risk of death after CEA.[63] However, the approach of this study was criticized because operator specialization was defined as the percentage CEAs of all procedures performed by an operator, but did not account for the absolute number of CEAs performed. As a result, a surgeon with a lower number of CEAs could be considered more specialized than a surgeon with a higher number of CEAs. Specialization should instead be understood as the relative number of CEAs supplemented by the total number of CEAs, since operator volume and learning curve have been shown to be associated with lower procedural risks.[14]

In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), CEA and CAS performed by vascular surgeons were compared. A lower risk of periprocedural stroke was found after CEA and a lower risk of periprocedural MI after CAS, but no

significant difference was found for the composite periprocedural outcome of stroke, MI, or death.[59]

Our literature search was extensive and we used predefined selection criteria for inclusion. We report the first systematic review and meta-analysis that quantified the association between operator specialty and procedural outcomes for CEA and CAS by pooling risk estimates from different studies. The current literature has several limitations. First, the definition of operator specialty differed between studies, ranging from practice designations, training level of operators, and self-reporting of specialty. Furthermore, specialty training can differ between programs among countries and the training of surgeons developed separately over the years. However, we decided not to restrict our search to more recent articles with lower procedural risks, as a consequence of improved medical therapy, because we did not use absolute numbers but risk ratios. This seems justified since we found no evidence for differential improvement over time across specialties. Second, operator or hospital experience and the 'learning curve' are not included as determinants in this study. Also, patient and disease characteristics that are known to influence outcome after carotid revascularization, such as symptomatic status, were not used as adjustment factors in most included studies and the published data did not allow for stratification of these characteristics. The same holds for operator-specific characteristics that have been found to be associated with mortality for surgery in general, for example age and sex of the operator.[64,65] Third, assessment of the outcome measures was not standardized between studies and often not performed, or reported to be performed, by an (independent) neurologist in case of procedural stroke. Fourth, some studies used administrative databases that might be of inferior reporting quality and most studies used retrospective data-collection. Fifth, we tried to exclude overlapping datasets from meta-analyses to prevent double counting of patients, but some meta-

analyses could potentially still have included overlapping patient groups. Sixth, generalizability of our findings might be limited since only studies from North America were available. Finally, we may have missed publications in which operator specialty was assessed but buried in a few words within the body of the text.

In future research, prospective, long-term evaluations of operator experience, including any learning-curve, operator and hospital volumes are needed. In addition, identification of specialty-specific skills and competencies which may reduce the risk of adverse procedural outcomes need to be explored.

In conclusion, vascular surgeons showed a lower unadjusted risk of stroke and death after CEA compared to neurosurgeons and general surgeons. Neurosurgeons showed a higher unadjusted risk of stroke and death after CEA compared to cardiothoracic surgeons. No associations between specialty and procedural outcomes after CAS were found for the primary outcome. There is insufficient evidence that CEA or CAS should be performed by specific specialties, since most studies did not adjust for case-mix differences and were therefore at high risk of bias mainly due to confounding by indication.

Contributions

Conception and design: MP, EB, GB

Analysis and interpretation: MP, EB, AH, RB, MS, MB, GB

Data collection: MP, EB

Writing the article: MP, EB

Critical revision of the article: MP, EB, AH, RB, MS, MB, GB

Final approval of the article: MP, EB, AH, RB, MS, MB, GB

Statistical analysis: MP, EB

Obtained funding: Not applicable

Overall responsibility: GB

MP and EB contributed equally to this article and share co-first authorship.

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SUPPLEMENTARY MATERIAL

Appendix S1: Checklists for reporting standards

Appendix S2: Search strategies

Figure S1 Publication bias

Table S1: Risk of bias summary

Table S2: Procedural outcome after carotid endarterectomy (CEA): Unadjusted risk estimates

Table S3: Procedural outcome after carotid endarterectomy (CEA): Adjusted risk estimates

Table S4: Procedural outcome after carotid endarterectomy (CAS): Unadjusted risk estimates

Table S5: Procedural outcome after carotid endarterectomy (CAS): Adjusted risk estimates

Table S6: Sensitivity analysis for carotid endarterectomy (CEA) for the primary outcome with studies reporting ≥80% symptomatic patients and with studies reporting ≥80% asymptomatic patients

Table S7: Sensitivity analysis for carotid endarterectomy (CEA) for the primary outcome with studies based on clinical data and studies based on data from registries

Supplementary material can be found at the journal website:
https://www.jvascsurg.org/action/showPdf?pii=S0741-5214%2820%2930120-8

Supplementary material is also attached to this dissertation and can be found here

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Timing of Procedural Stroke and Death in Asymptomatic Patients Undergoing Carotid Endarterectomy: Individual Patient Analysis from Four RCTs

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On behalf of the Carotid Stenosis Trialists' Collaboration

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Abstract

Background The effectiveness of carotid endarterectomy (CEA) for stroke prevention depends on low procedural risks. We aimed to assess frequency and timing of procedural complications after CEA, which may clarify underlying mechanisms and help inform safe discharge policies.

Methods Individual patient data (N=8 752) were obtained from four large trials (VACS, ACAS, ACST-1, and GALA; 1983-2007). Patients undergoing CEA for asymptomatic carotid artery stenosis (N=3 694) directly after randomization were used for the present analysis. We divided the timing of procedural death and stroke into intraoperative day 0, postoperative day 0, day 1-3, and days 4-30.

Results In total, 103 (2.8%) patients had serious procedural complications (18 fatal strokes, 68 non-fatal strokes, 11 fatal myocardial infarctions, and 6 deaths from other causes). Of the 86 strokes, 67 (78%) were ipsilateral, 17 (20%) were contralateral, and two (2%) were vertebrobasilar. Forty-five strokes (52%) were ischaemic, 9 (10%) haemorrhagic and stroke subtype was not determined in 32 (37%) patients. Half the strokes happened on the day of CEA. Of all serious complications, 44 (43%) occurred on day 0 (20 intraoperative, 17 postoperative, and 7 with unclear timing), 23 (22%) occurred on days 1-3, and 36 (35%) on days 4-30.

Conclusions At least half of the procedural strokes in this study are ischaemic and ipsilateral to the treated artery. Half of all procedural complications occurred on the day of surgery, but one third after day 3 when many patients have been discharged. Reported in-hospital stroke or death rates might underestimate true risks after CEA.

Introduction

Net benefit of carotid endarterectomy (CEA) for carotid artery stenosis is partly determined by the risk of procedural complications. Three randomized clinical trials (RCTs) in asymptomatic patients with high-grade carotid stenosis compared endarterectomy plus medical therapy with medical therapy alone: The Veterans Administration Cooperative Study (VACS);[1] The Asymptomatic Carotid Atherosclerosis Study Group (ACAS);[2] and the Asymptomatic Carotid Surgery Trial (ACST-1).[3,4] The 30-day death or stroke risk ranged from 2.3% to 4.6%, but this included strokes that occurred during diagnostic angiography, performed commonly in the early US trials.[1,2] More recently, the General Anaesthesia versus Local Anaesthesia (GALA) RCT compared general and local anaesthesia in patients undergoing CEA.[5] No differences were found in cardiovascular outcomes between groups up to 30 days after CEA.

Several risk prediction models for the procedural hazards of CEA have been published, but their predictive performance and clinical applicability are limited.[6] Although risk models might inform patients about their risks and benefits of CEA by applying predictors of adverse outcomes to individual patients, it remains unclear when and how procedural complications might be prevented.[7] A detailed analysis of the timing of procedural events and stroke subtype might help inform safe discharge policies and may critically review reporting of in-hospital complication rates after CEA.

We aimed to assess frequency and timing of procedural complications after CEA for asymptomatic carotid stenosis in order to inform future operative policies.

MATERIAL AND METHODS

Data sources

Individual patient data from four RCTs were obtained: VACS,[1] ACAS,[2] ACST-1,[3,4] and GALA.[5] Details on the individual trials are published elsewhere.[8-11] In summary, the VACS, ACAS, and ACST-1 RCTs compared CEA plus medical treatment versus medical treatment alone. In the VACS, 444 male patients with ≥50% stenosis were randomized (1983-1987). ACAS randomized 1 662 patients <80 years with ≥60% stenosis (1987-1993).

ACST-1 randomized 3 120 patients with ≥60% stenosis (1993-2003). GALA randomized 3 526 (1362 asymptomatic and 2 164 symptomatic) patients with carotid artery stenosis regardless of degree of stenosis between either loco-regional (LA) or general anaesthesia (GA) (1999-2007).

Assessment of carotid stenosis

All patients in VACS underwent intra-arterial angiography after randomization to determine the operability of the carotid stenosis,[8] and all patients in ACAS underwent duplex ultrasound (DUS), with additional intra-arterial angiography in patients allocated to CEA.[9] Though angiography was not required in ACST-1, some patients did have this.[4] In GALA, degree of stenosis was assessed by DUS in 1 259 (92.4%) of the 1 362 asymptomatic patients.[5]

Outcome measures

The primary outcome was timing of procedural (30-day) death and any non-fatal stroke after CEA among patients with asymptomatic carotid artery stenosis.

Data-collection

We collected baseline characteristics (age, sex, medical history, blood pressure), medication use (antihypertensive, lipid-lowering, antithrombotic medication, and anticoagulants at the time of the CEA), disease characteristics (degree of ipsilateral and contralateral stenosis, cerebral infarct on imaging), CEA characteristics (type of anaesthesia, shunt use, patch use), and timing of the complication with respect to the CEA. For procedural strokes, we also collected the following data: type of stroke (ischaemic, haemorrhagic), severity (fatal, disabling, non-disabling), territory (carotid, vertebrobasilar), and side (ipsilateral, contralateral).

Definition of outcomes and ascertainment of timing of complications

Procedural stroke was defined as an acute deficit of focal neurological function which led to symptoms lasting >24 hours, resulting from intracranial vascular disturbance (ischaemia or haemorrhage) occurring within 30 days after CEA. We used the adjudicated procedural complications from the original RCTs.[8-11] For the current analysis, two authors (MHFP and DRM) independently analysed the collected data of patients with procedural complications that occurred on day 0 to determine whether the complication occurred during (intraoperative) or after the CEA (postoperative). Consistent with previous studies, 'intraoperative' was defined as any complication that occurred before the patient left the operation room in patients where CEA was performed under LA, or before the patient was fully awake, in patients where CEA was performed under GA.[12] 'Postoperative' was defined as any complication that occurred after the patient left the operation room in patients where CEA was performed under LA, or after the patient awoke, when the CEA was performed under GA. For the timing of fatal procedural strokes, we used the date at which the stroke occurred to determine the timing of stroke, not the date of death. Timing was classified as: "timing unclear" if the complication occurred on day 0 but exact timing could not be determined. Uncertainties were discussed with a senior author (GJdB).

Statistical analyses

We included the first CEA of patients allocated immediate CEA from the VACS, ACAS and ACST-1 RCTs and all asymptomatic CEAs from GALA. We excluded patients who did not adhere to allocated treatment (8 patients in VACS, 97 ACAS, 134 in ACST-1, and 28 asymptomatic patients in GALA). Crossover patients from the medical therapy group (29 patients in VACS, 305 in ACAS, and 407 in ACST-1) were also excluded, since some characteristics at the time of deferred CEA and qualifying event for the deferred CEA were not systematically recorded in all RCTs. Angiography-related pre-procedural strokes were also excluded.

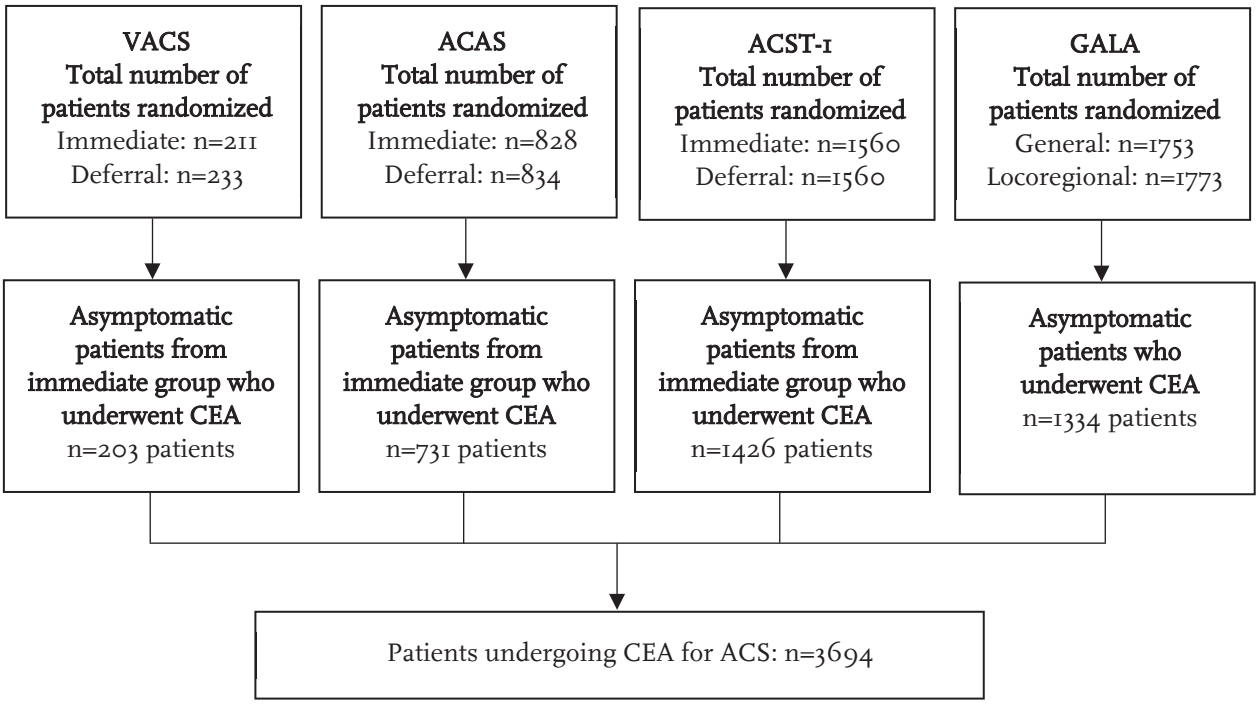
Patient, disease and procedural characteristics are reported with descriptive statistics. Categorical variables are reported as absolute number and percentage and continuous variables as mean and

standard deviation (SD). The timing was divided into four intervals from CEA: intraoperative day 0, postoperative day 0, day 1-3 and day 4-30.

RESULTS

The present study includes 3 694 patients who underwent the allocated CEA for asymptomatic carotid artery stenosis (203 from VACS, 731 from ACAS, 1 426 from ACST-1, and 1 334 from GALA). (Figure 1).

Figure 1. Study flow chart



VACS, Veterans Administration Cooperative Study; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial; GALA, General anaesthesia versus local anaesthesia for carotid surgery; CEA, carotid endarterectomy.

A total of 103 (2.8%) patients had a stroke or died during the 30-day procedural period. Of these, 67 patients (65%) in VACS, ACAS and ACST-1 were randomized to immediate CEA; in GALA 19 (18%) patients were randomized to general anaesthesia and 17 (17%) to local anaesthesia. Patient, disease and procedural characteristics are provided in Table 1.

Table 1. Patient and disease characteristics

	Patients with a procedural stroke or death (N = 103)	Patients without a procedural stroke or death (N = 3591)
Patient characteristics		
Age at CEA, y	68.9 ± 7.9	68.3 ± 7.8
Male sex	65 (63.1%)	2496 (69.5%)
Systolic blood pressure, mmHg	148 ± 19.5	147 ± 20.2
Diastolic blood pressure, mmHg	83 ± 11.2	81 ± 10.4
Diabetes mellitus	34 (33.0%)	899 (25.0%)
Ischaemic heart disease	41 (39.8%)	1346 (37.8%)
Prior contralateral symptoms	32 (31.1%)	782 (21.8%)
Medical therapy		
Anti-platelet therapy	73 (77.7%)	2725 (77.8%)
Anticoagulant	3 (3.2%)	91 (2.6%)
Antihypertensive therapy	55 (68.8%)	2086 (69.8%)
Lipid-lowering therapy	30 (38.0%)	972 (32.5%)
Disease characteristics		
Ipsilateral stenosis >80%	39 (42.9%)	1435 (42.2%)
Contralateral stenosis >60%	35 (38.5%)	974 (28.7%)
Contralateral occlusion	16 (17.6%)	353 (10.4%)
Brain infarct on imaging	27 (33.8%)	947 (33.4%)
Intra-operative care		
General anaesthesia	30 (61.2%)	1294 (64.3%)
Intraoperative shunt	31 (51.7%)	837 (38.0%)
Patch angioplasty	22 (36.7%)	844 (38.3%)

Categorical variables are reported as absolute number and percentage and continuous variables as mean and standard deviation (SD).
CEA, carotid endarterectomy.

Of 103 procedural complications, 86 were strokes and 17 were non-stroke related deaths. Of 86 strokes, 18 (21%) were fatal, 23 (27%) were disabling, and 45 (52%) were non-disabling. Sixty-seven (78%) were ipsilateral to the operated artery, 17 (20%) contralateral and two (2%) were vertebrobasilar. Forty-five strokes (52%) were ischaemic, nine (11%) were haemorrhagic, and in 32 (37%) patients (6 patients from VA, 12 from ACAS, 5 from ACST-1 and 9 from GALA) stroke subtype could not be determined.

Timing and severity of procedural stroke or death

Forty-three (50%) procedural strokes occurred on the day of the procedure, 18 (21%) between day 1 and 3, and 25 (29%) between day 4 and 30. Of the procedural strokes on the day of the procedure, 19 (44%) were intraoperative and 17 (40%) were postoperative. Forty-four (43%) procedural deaths and strokes occurred on the day of procedure, 23 (22%) between day 1 and 3, and 36 (35%) between day 4 and 30. Six (54.5%) of the 11 fatal myocardial infarctions occurred

between day 4 and 30. (Table 2 & Figure 2). The severity of procedural strokes by timing after CEA is provided in Figure 3.

Table 2. Procedural deaths and strokes by timing after CEA

	Total	Day of the procedure				Day 1-3	Day 4-30
		Intraoperative	Postoperative	Unclear timing	Total day 0		
Death / stroke per RCT (%)							
VACS	12	-	-	3 (25)	3 (25)	5 (42)	4 (33)
ACAS	13	2 (15)	2 (15)	1 (8)	5 (38)	3 (23)	5 (38)
ACST-1	42	12 (29)	10 (24)	-	22 (52)	7 (17)	13 (31)
GALA	36	6 (17)	5 (14)	3 (8)	14 (39)	8 (22)	14 (39)
Procedural outcome in all RCTs combined (%)							
Stroke or death (%)	103	20 (19)	17 (17)	7 (7)	44 (43)	23 (22)	36 (35)
Stroke (%)	86	19 (22)	17 (20)	7 (8)	43 (50)	18 (21)	25 (29)
Fatal MI (%)	11	1 (9)	-	-	1 (9)	4 (36)	6 (55)
Any death (%)	35	4 (11)	4 (11)	-	8 (23)	8 (23)	19 (54)

MI, myocardial infarction. RCT, randomized clinical trial.

Figure 2. Timing of procedural strokes and deaths between days 0 and 30 after CEA and on the day of procedure

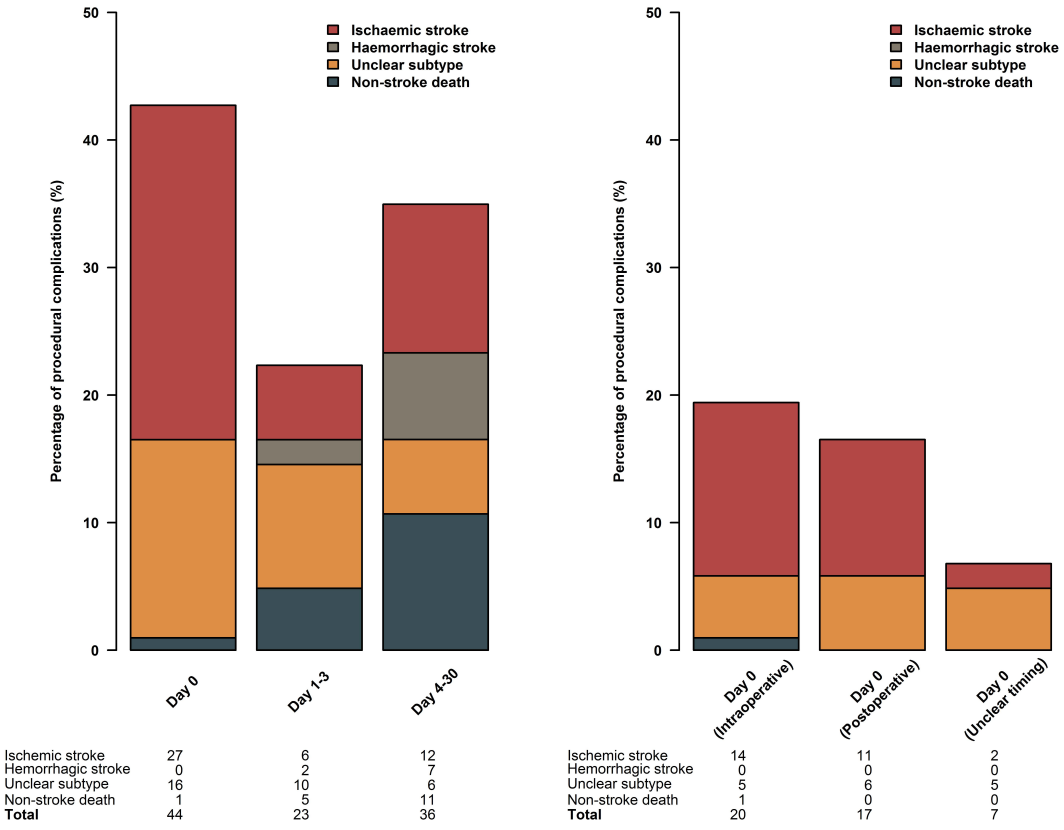
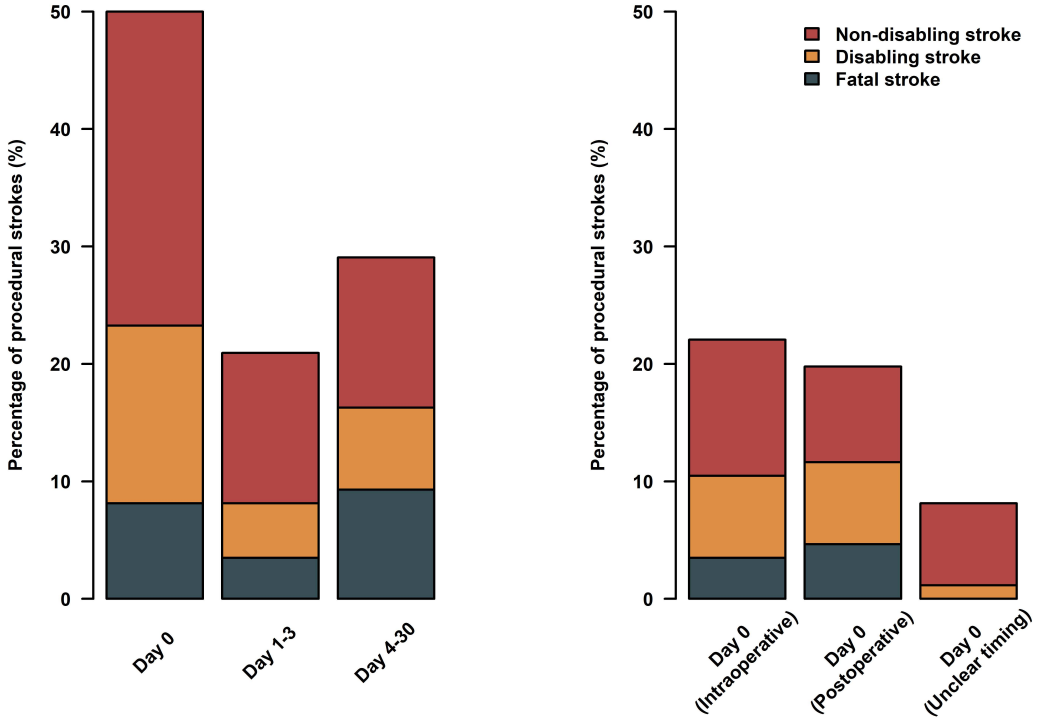


Figure 3. Severity of procedural strokes by timing after CEA between days 0 and 30 after CEA and of the day of procedure



	Day 0	Day 1-3	Day 4-30
Non-disabling stroke	23	11	11
Disabling stroke	13	4	6
Fatal stroke	7	3	8
Total	43	18	25

	Day 0 (Intraoperative)	Day 0 (Postoperative)	Day 0 (Unclear timing)
Non-disabling stroke	10	7	6
Disabling stroke	6	6	1
Fatal stroke	3	4	0
Total	19	17	7

Discussion

In this individual patient data analysis from four randomized clinical trials, half of procedural complications occurred after the day of operation and one third of the complications occurred between day 4 and 30. At least half of the procedural strokes were ischaemic and ipsilateral to the treated artery. Half the strokes occurred after the day of the procedure.

Our findings are consistent with a previous study in symptomatic patients who reported that about half of the events also occurred on the day of the CEA.[13] This study also found that patients who underwent carotid artery stenting were at greater risk of complications at the day of the procedure compared to CEA, but not for complications beyond the day of the operation.

Previous studies showed that the pathogenesis of stroke may vary with the time interval from intervention.[7,12,14-17] It was concluded that early strokes could be due to thrombosis or thrombotic occlusion of the carotid artery sometimes associated with hypotension, while later strokes could be due to hyperperfusion. Data from ACST-1 revealed the same results with most post procedural events being related to hyperperfusion.[12] Understanding the patho-physiological mechanism of procedural stroke informs the surgeon about specific technical aspects (in, for example, cases of residual stenosis) and the application of additional protective measures, such as use of dual antiplatelet therapy to prevent increased thrombo-embolisation, or additional postoperative TCD monitoring to prevent hyperperfusion might results in lower procedural stroke risk.

Procedural complication rates after CEA in asymptomatic patients have decreased since recruitment of the included RCTs .[18] Reasons for this decrease may include improvements in medical treatment, better patient selection, and possibly the increased understanding of the mechanisms of procedural strokes and increased attention to postoperative blood pressure control. There is also a trend towards centralization of CEA in high volume centres with high volume surgeons.[19]

Stroke risk factors include age, smoking, diabetes mellitus, ischaemic heart disease, heart and renal failure.[20] Contralateral stenosis or occlusion and use of patch angioplasty have been

implicated.[21,22] Hyperperfusion syndrome (HPS) can lead to intracerebral haemorrhage and intra-arterial blood pressure monitoring for the first 3-6 hours postoperatively, followed by hourly non-invasive blood pressure monitoring for the first 24 hours, may help prevent HPS and enable early intervention.[23-25] Furthermore, transcranial doppler (TCD) monitoring during and after CEA identifies patients at high risk of developing cerebral hyperperfusion.[25,26] Intra-operative monitoring might also include measuring stump pressure, near-infrared spectroscopy, assessment of backflow in the internal carotid artery following clamping. Residual thrombus and large intimal flaps might be identified before blood flow restoration by angioscopy or, after blood flow restoration, by angiography or DUS. Residual stenosis might also be discovered by angiography or DUS. Despite, the evidence for these monitoring options is low, and therefore the recent ESVS guidelines leave to the operator to decide whether to use of either of these intra-or post procedural measures.[27]

Our study has some limitations. Procedural stroke and death were included but not non-fatal myocardial infarctions, retinal infarctions, hematomas, and cranial nerve injury. Recruitment of patients in the four RCTs stopped more than a decade ago. The inclusion of patients who underwent CEA for mild stenosis. Data on management of procedural strokes was not systematically collected. The high number of procedural strokes in which the stroke subtype was not reported. Stroke severity was not assessed with the same standardized outcome scale, but reporting of strokes in the included RCTs allowed to determine strokes severity, in terms of non-disabling, disabling or fatal. We were not able to identify risk factors for early and late procedural complications due to the limited number of outcomes. Minor deficits may have been missed in the operation room, but noticed later when a neurologist examined the patient, leading to an underestimation of intraoperative strokes.

In conclusion, at least half of the procedural strokes in this study were ischaemic and most were ipsilateral to the treated artery. Half of all procedural complications occurred on the day of surgery, but one third of complications occurred after day 3 when many patients have been discharged. Reported in-hospital stroke or death rates might underestimate true risks after CEA.

Intensive medical therapies, particularly antihypertensive and antithrombotic regimes, should be used for optimal procedural stroke prevention. In addition, patients should be informed about signs and symptoms of stroke and should receive clear instructions about seeking emergent medical help lest stroke occurs after discharge.

Contributions

MP, RB, DM, GdB, and AH designed the study plan. MP, DM and HP cleaned the data. MP performed the statistical analysis. MP wrote the first version of the article. All authors contributed to data interpretation, critical revision of the article, and approved the final version. All authors gave final approval to submit for publication. MP, RB and DRM are joint first authors. SL, GdB. and AH. are joint senior authors.

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CSTC collaboration

Involvement of the authors in the CSTC Steering Committee is as follows: Ale Algra, Jacoba Greving (coordinator); EVA-3S: Jean-Pierre Becquemin, David Calvet, Jean-Louis Mas; ICSS: Leo Bonati (chair), Martin Brown, Jeroen Hendrikse; SPACE and SPACE-2: Hans-Henning Eckstein, Gustav Fraedrich, Olav Jansen, Peter Ringleb; CREST and CREST-2: Thomas Brott, George Howard, Gary Roubin; ACST-1 and ACST-2: Richard Bulbulia, Alison Halliday; trial statistician: John Gregson. The members of the Steering Committees and a list of Investigators contributing data to the trials including those in this pooled analysis can be found in earlier publications.

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II

External Validation of Risk Prediction Models to Improve Selection of Patients for Carotid Endarterectomy

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Submitted

Abstract

Background and purpose: The net benefit of carotid endarterectomy (CEA) is determined partly by the risk of procedural stroke or death. Current guidelines recommend CEA if 30-day risks are <6% for symptomatic stenosis and <3% for asymptomatic stenosis. We aimed to identify prediction models for procedural stroke or death after CEA and to externally validate these models in a large registry of patients from the United States.

Methods: We conducted a systematic search in MEDLINE and EMBASE for prediction models for procedural outcomes after CEA. We validated these models with data from patients who underwent CEA in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP, 2011-2017). We assessed discrimination and calibration. We determined the number of patients with predicted risks that exceeded recommended thresholds of procedural risks to perform CEA.

Results After screening 788 reports, 15 studies describing 17 prediction models were included. Nine were developed in populations including both asymptomatic and symptomatic patients, two in symptomatic and five in asymptomatic populations. In the external validation cohort of 26,293 patients who underwent CEA, 717 (2.6%) developed a stroke or died within 30-days. C-statistics varied between 0.52 and 0.64 using all patients, between 0.51 and 0.59 using symptomatic patients, and between 0.49 to 0.58 using asymptomatic patients. The Ontario Carotid Endarterectomy Registry (OCER) model that included symptomatic status, diabetes mellitus, heart failure and contralateral occlusion as predictors, showed best discrimination and good concordance between predicted and observed risks. This model identified 4.5% of symptomatic and 2.1% of asymptomatic patients with procedural risks that exceeded recommended thresholds.

Conclusions: Of the 17 externally validated prediction models, the OCER risk model had most reliable predictions of procedural stroke or death after CEA and can inform patients about procedural hazards and help focus CEA toward patients who would benefit most from it.

Introduction

Carotid endarterectomy (CEA) aims to prevent long-term stroke and should be performed in patients who may derive greatest benefit in terms of stroke risk reduction. Symptomatic patients who have had a recent stroke or transient ischemic attack (TIA) related to an ipsilateral high-grade stenosis are recommended to undergo CEA in addition to medical therapy.[1-5] The absolute benefits of CEA have become smaller due to improvement of medical preventive therapy in patients without recent symptoms related to the carotid stenosis.[6-9] The net benefit depends not only on the long-term reductions in stroke risk, but is also determined by the procedural hazards of CEA.

Current guidelines recommend to consider CEA in patients who have a risk of procedural stroke or death of less than 6% in symptomatic patients and 3% in asymptomatic patients who also have a life expectancy of five years.[1,10] Risk prediction models might help to inform patients about procedural hazards and possibly patient selection for CEA by providing individualized risk estimations by taking several patient and disease characteristics into account.[11] Before implementation of risk prediction models in clinical practice, validation to assess discrimination and calibration should be performed in generalizable data with representative absolute procedural risks of patients who underwent CEA. We conducted a systematic review of published studies of prediction models for procedural stroke or death after CEA and then externally validated these models in a large contemporary registry of patients who underwent CEA in the United States.

METHODS

Systematic review

We conducted a systematic review according to a protocol that we registered (PROSPERO CRD42019141835), and report the results of our systematic review consistent with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[12]

Search strategy

We performed electronic searches in MEDLINE (via PubMed interface) and EMBASE (via EMBASE interface) from December 2016 to January 1, 2020 to update a previous systematic review of risk prediction models for outcomes after carotid revascularization (Table S1).[11]

Eligibility criteria

We included studies that: (1) addressed development (with or without internal or external validation) of prognostic prediction models to select patients for CEA using procedural (in-hospital or 30-days) risk of stroke or death as predicted outcome; (2) in patients with carotid artery stenosis; (3) regardless of symptomatic status; (4) using predictors that are available before the intervention and can be used for patient selection; (5) based on data from observational studies or randomized clinical trials; (6) without restrictions on baseline characteristics such as age, sex, or ethnicity and; (7) were published in peer-reviewed journals without any language restrictions.

Screening process and data extraction

Two authors (MHFP and KD) independently screened all titles and abstracts of the retrieved references and subsequently independently reviewed full-text copies for final inclusion in this study. We performed backward citation searching using the bibliographies of included studies. Two authors (MHFP and RARH) independently extracted the following data from the included prediction models based on the CHARMS checklist:[13] source of data, study setting, geographic area (country and continent), study years, modelling method (eg, logistic model), proportion of participants with missing data, handling of missing data, appropriateness of modelling assumptions, methods for predictor selection, shrinkage of predictor weights, number of outcome events, number of participants, degree of stenosis, number and type of predictors

(diagnostic variables) used in the final model, number of outcome events per variable, presentation of model, model performance (discrimination and calibration). In studies that reported internal validation of prediction models, we extracted the following additional data: method of internal validation (e.g., cross-validation, bootstrap); whether the model was adjusted or updated after internal validation. In studies reporting external validation of a prediction model, we extracted the following additional data: type of external validation (e.g., geographical and/or temporal distinct population); whether authors of the external validation also developed the original model; performance of the model before or after model recalibration.

Critical appraisal

One author (RARH) assessed the included prediction models for the risk of bias and applicability using the Prediction model Risk Of Bias ASsessment Tool (PROBAST) and the assessment was supervised by one author (JAAD).[14] The assessment of risk of bias consisted of four domains (participants; predictors; outcome; and analysis) and the applicability consisted of three domains (participants; predictors; and outcome). Risk of bias and applicability was judged as low, high or unclear for each domain.[15] Each model was evaluated separately if multiple models were developed in one study.

External validation

For external validation, we adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[16]

External validation cohort

We used a prospectively maintained cohort of patients who were registered between January 2011 and December 2017 in the Targeted Vascular module of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) registry for external validation of the prediction models identified in our systematic review.[17] In 2017, 708 participating hospitals collected data of patients who underwent a carotid intervention, including 30-days procedural outcomes. Classification of procedures was based on Current Procedural Terminology.[18] Trained surgical clinical reviewers in each hospital collected data from medical charts and operative case logs using strict variable definitions to maintain uniformity across hospitals. Patients were

contacted by letter or phone calls at 30-days after the carotid intervention to obtain data on procedural complications after discharge, if necessary. In addition, the ACS-NSQIP performed random reliability auditing to minimize information bias. Definition of variables in ACS-NSQIP and their validity have been investigated in previous reports.[19]

The Targeted Vascular Module of the ACS-NSQIP recorded additional disease- and procedure-related data and outcomes that were deemed crucial by vascular surgeons in a subset of 29 participating hospital of all hospitals performing vascular interventions.

Predicted outcome

We externally validated the prediction models for stroke or death within 30-days after CEA. Procedural strokes were defined as any new acute focal neurological deficit lasting more than 24 hours or postoperative radiological signs of new infarction.

Statistical analysis

Characteristics of the external validation cohort were summarized using standard methods. Missing data were imputed using chained equation with the MICE package in R. The imputation model included the predicted outcome of procedural death or stroke and predictors of the included prediction models. The algorithm started with the lowest proportion of missing data. The imputation continued until convergence of each predictor with a maximum of 20 iterations for each imputed dataset. Fifteen imputed datasets were computed (Table 2). The number of imputed datasets was determined by taking the highest percentage of missing values and round that to the closest multiple of five.[20,21] The imputation was evaluated graphically with convergence plots.

The regression formula, including the intercept and beta-coefficients (predictor weights) that allows calculation of the predicted probabilities, was used to calculate the 30-day risk of stroke or death for each patient. We contacted authors to provide the regression formula if it was not provided in the original report. If the authors could not provide the regression formula, we calculated a sum score (total points) for each participant by summing the scores of the score chart assigned to each predictor in the original reports. We matched the predictors with the variables in the external validation cohort. Proxies were used if a direct match was not available. An overview

of the proxies is provided in Table S2. Predictors were excluded from the external validation if no proxy was available. The risk equations to calculate the predicted probabilities used in our external validation are provided in Table S3.

We assessed the predictive performance in terms of discrimination and calibration of the included prediction models. Discrimination was assessed using c-statistics. C-statistics were calculated per imputed dataset and results were combined using Rubin's rules.[22,23] Calibration was assessed using calibration plots showing the predicted risks calculated with the prediction models against the observed risks in the external validation cohort. The predicted probabilities were split in deciles to enable comparison between calibration plots and the mean predicted and observed risk with corresponding 95% confidence intervals was calculated for each decile. We used a lower number of groups (with a minimum number of 500 patients for each group to obtain precise estimates) for models that did not allow splitting in deciles because the variation of probabilities was too limited. Calibration plots were created for each imputed dataset and we found that the calibration plots did not differ materially across the imputed datasets. The calibration plots using the fifteenth imputed dataset were therefore presented. We recalibrated the prediction models to the mean incidence of 30-days stroke or death in our external validation cohort to adapt the models to current clinical practice and because some models were developed with either stroke alone or death alone as predicted outcome or were restricted to outcomes that occurred in-hospital. For this, we re-estimated the intercept (referred to as 'recalibration-in-the-large' or 'updating the intercept') by fitting a logistic model with a fixed slope and the intercept as the only free parameter.[24]

Three assessments of discrimination and calibration were performed: 1) including all patients who underwent CEA regardless of symptomatic status; 2) in patients who underwent CEA for symptomatic carotid artery stenosis; and 3) for CEA in patients with asymptomatic carotid stenosis.

We calculated the number of symptomatic patients with risk of procedural stroke or death exceeding 6% and 4% and the number of asymptomatic patients with risk of procedural stroke or

death exceeding 3% and 2%. We performed sensitivity analysis in complete cases. R version 3.5.1 was used for statistical analyses and constructing figures.

Results

After screening of 788 unique reports and assessing the full-texts of 59 for eligibility, we included 15 studies reporting 17 prediction models (Figure 1 and Table S4).[25-39] Two (12%) models were developed in populations of symptomatic patients,[34,35] five (29%) models in populations of asymptomatic patients,[36-38] and nine (53%) in populations of both symptomatic and asymptomatic patients (Table 1). Symptomatic status was included as predictor in these nine prediction models[25-33] of which one used qualifying event as predictor.[29] Other predictors used frequently in the 17 included models were age in eight (47%),[26-30,33,37,39] sex in seven (41%),[29,33,35,36,38] heart failure in eleven (65%),[25-31,38,39] coronary heart disease in seven (41%),[25,29,36-38] and degree of contralateral stenosis in seven (47%).[26,28,30,31,34,36,38] An overview of the included predictors is provided in Figure 2. The number of predictors varied from three to eleven. The number of patients used for development varied from 218 to 39,411. Four (24%) models considered outcome events before discharge[26-28,39] and thirteen (76%) outcome events during 30-days after CEA.[25,29-38] Nine models (59%) were internally validated (Table S5).[29,30,35-39]

Figure 1. Flowchart of literature search

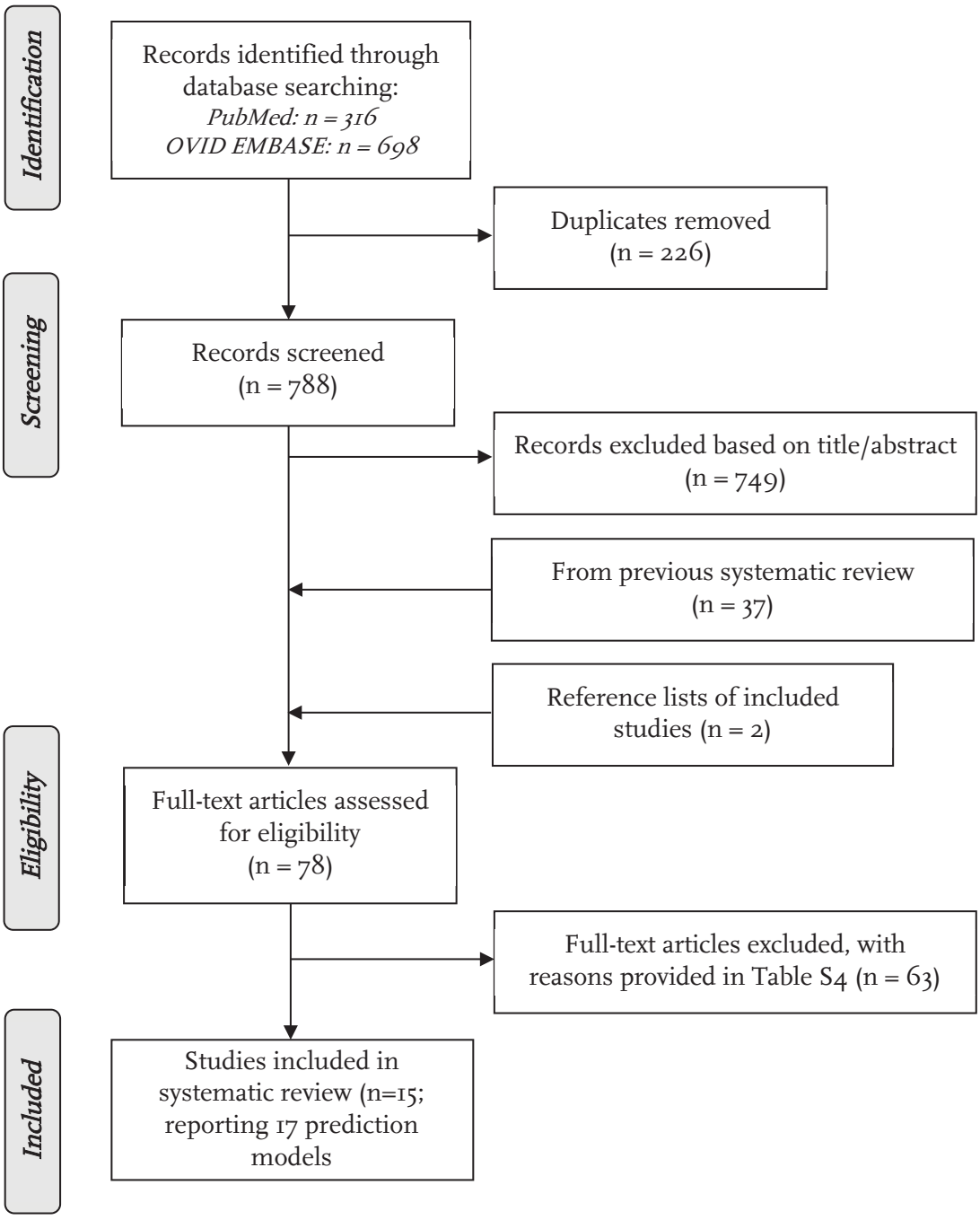
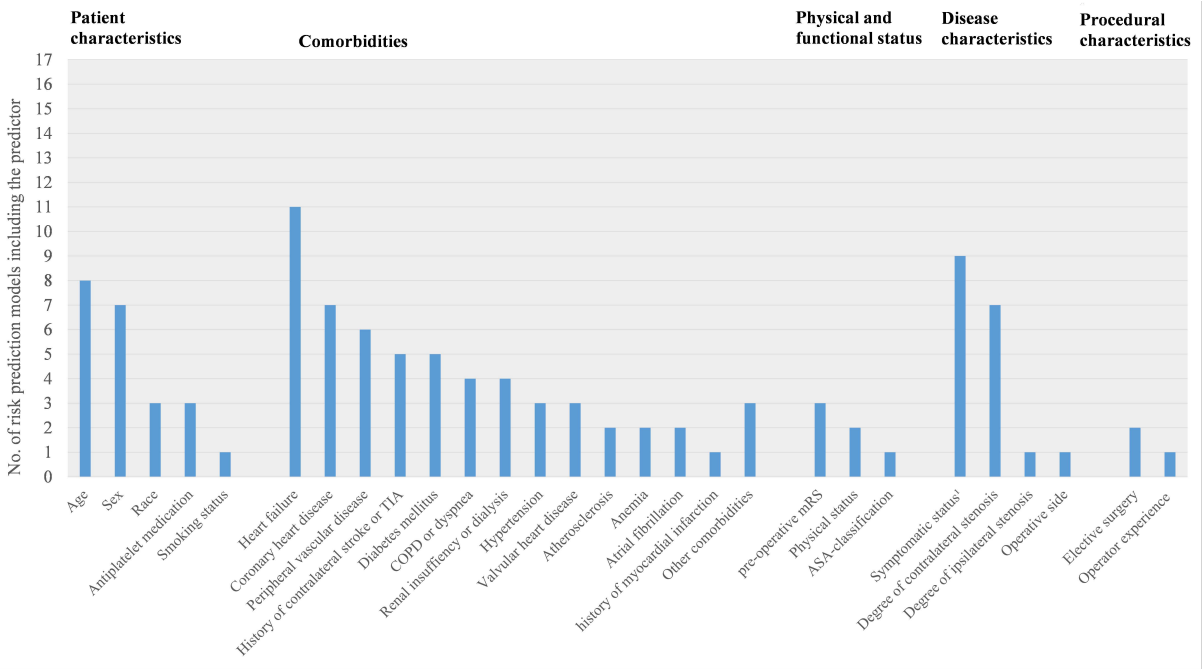


Table 1. Selected characteristics of included prediction models

	First author, year of publication	Symptomatic/ asymptomatic patients	Predicted outcome(s)	N events / N patients (%)	Timeframe of outcome	Number of predictors
1.	Sridharan et al, 2018[25]	Both	Stroke, death, MI	56 / 1496 (3.7)	30-days	7
2.	Eslami et al, 2016[26]	Both	Stroke, MI, death or discharge to rehabilitation facility	389 / 8661 (4.5)	In-hospital	8
3.	Chaudhry et al, 2016[27]	Both	Stroke, cardiac complications or death	1494 / 49,411 (3.0)	In-hospital	7
4.	Wimmer et al, 2014[28]	Both	Stroke or death	213 / 12,889 (1.7)	In-hospital	7
5.	Bekelis et al, 2013[29]	Both	Stroke, MI or death	994 / 35,698 (2.8)	30-days	11
6.	Goodney et al, 2008[30]	Both	Stroke or death	60 / 3092 (1.9)	30-days	6
7.	Tu et al, 2003[31]	Both	Stroke or death	362 / 6038 (5.9)	30-days	5
8.	Kuhan et al, 2001[32]	Both	Major stroke or death	29 / 741 (3.9)	30-days	3
9.	Kucey et al, 1998[33]	Both	Stroke or death	81 / 1280 (6.3)	30-days	7
10.	Stavrinou et al, 2016[34]	Symptomatic	TIA, PRIND, amaurosis fugax or MI	12 / 218 (5.5)	30-days	6
11.	Rothwell et al, 1999[35]	Symptomatic	Major stroke or death	84 / 1203 (6.9)	30-days	3
12.	DeMartino et al, 2017[36]	Asymptomatic	Stroke	287 / 31,939 (0.9)	30-days	11
13.	Gupta et al, 2013[37]	Asymptomatic	Stroke, MI or death	324 / 17,692 (1.8)	30-days	6
14.	Calvillo-King et al, 2010a[38]	Asymptomatic	Stroke or death	200 / 6553 (3.1)	30-days	8
15.	Calvillo-King et al, 2010b[38]	Asymptomatic	Stroke or death	200 / 6553 (3.1)	30-days	7
16.	Calvillo-King et al, 2010c[38]	Asymptomatic	Stroke	165 / 6553 (2.5)	30-days	7
17.	Matsen et al, 2005[39]	NR	Death	125 / 23,237 (0.5)	In-hospital	6

MI, myocardial infarction; N, number; PRIND, prolonged reversible ischemic neurologic deficit; TIA, transient ischemic attack.

Figure 2. Overview of included predictors



Bar chart showing the frequency of the predictors used in the included risk prediction models.

[1] *Symptomatic status was included as predictor in all models that were developed in populations of asymptomatic and symptomatic patients.*

Risk of bias

The overall risk of bias was deemed low in four models,[26,28,36,37] unclear in one model,[29] and high in twelve models.[25,27,30-35,38,39] Concerns with applicability of the models to our population of interest was deemed low in six models,[27,28,30,31,35,36] and high in 11 models.[25,26,29,32-34,37-39] Reasons for high concerns included using a different predicted outcome for development compared with our external validation or using single center data for development, An overview of the risk of bias and applicability of each model is provided in Table S6.

External validations

The validation cohort consisted of 26,293 patients who underwent CEA, of whom 702 (2.7%) developed a stroke or died within 30-days. Some 14,772 (57%) patients underwent CEA for asymptomatic carotid stenosis and 11,035 (43%) for symptomatic carotid stenosis, in whom 5096 (20%) the qualifying event was stroke, 4083 (16%) hemispheric TIA, and 1856 (7%) amaurosis fugax. Characteristics of the external validation cohort in the models are provided in Table 2.

Table 2. Selected characteristics of external validation cohort

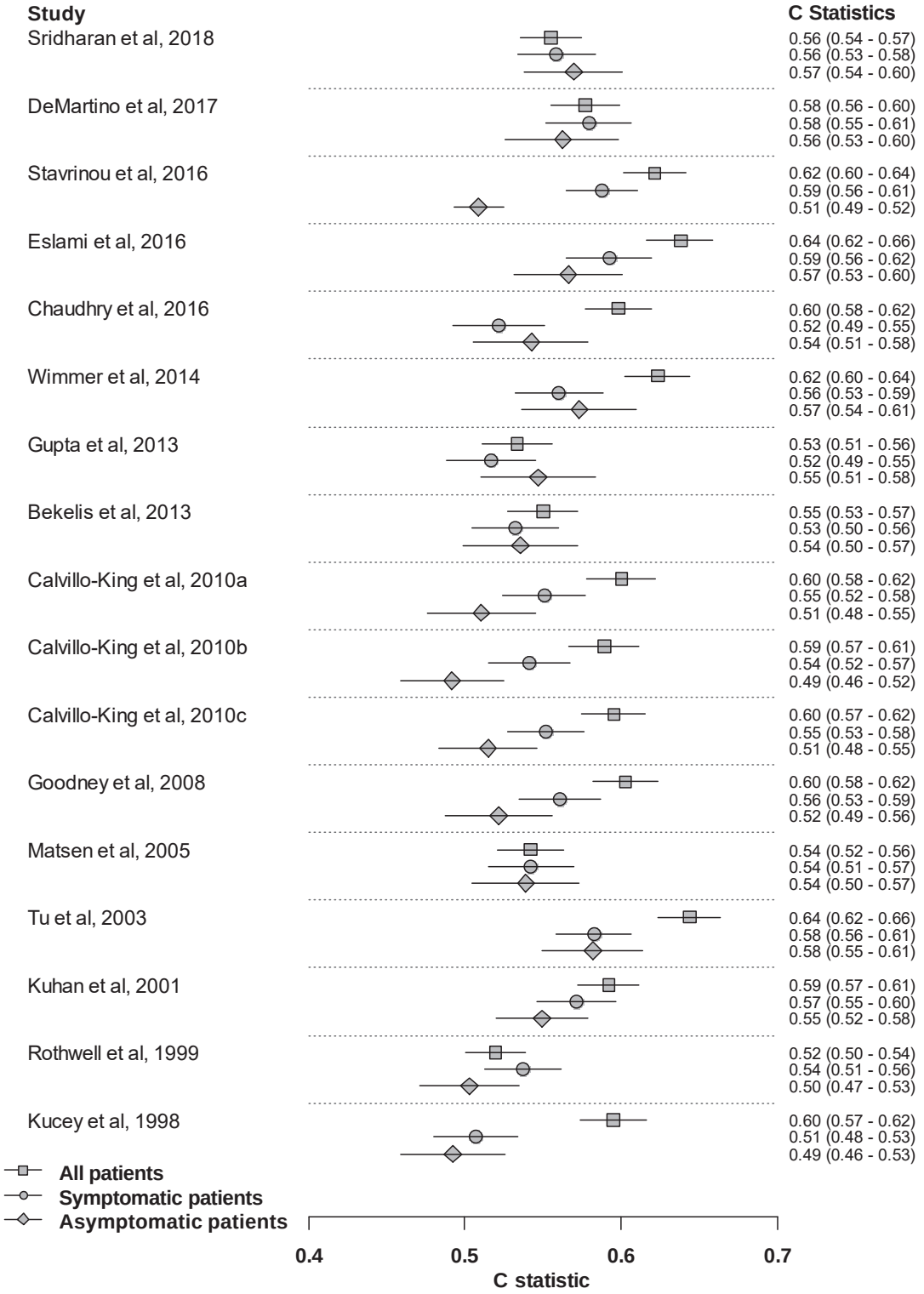
	All patients (n = 26,293)	Patients with procedural stroke or death (n = 702)	Patients without procedural stroke or death (n = 25,591)	Percentage of participants with missing data
Patient characteristics				
Age (years)	71 ± 9.2	72 ± 9.5	71 ± 9.2	0
Male sex	16,136 (61%)	434 (62%)	15702 (61%)	0
Diabetes Mellitus	8082 (31%)	261 (37%)	7821 (31%)	0
Current smoker	7011 (27%)	210 (30%)	6801 (27%)	0
COPD	2650 (10%)	99 (14%)	2551 (10%)	0
Heart failure	380 (2%)	34 (5%)	346 (1%)	0
Nonwhite race	1720 (7%)	56 (9%)	1664 (7%)	9.0
Preoperative hematocrit (%)	39 ± 4.9	39 ± 5.7	40 ± 4.9	3.8
Preoperative creatinine (mg/dL)	1.1 ± 0.72	1.2 ± 0.90	1.1 ± 0.71	3.5
Preprocedural antiplatelet medication	23,426 (89%)	617 (89%)	22,809 (89%)	0.4
Antihypertensive drugs use	21,924 (83%)	606 (86%)	21,318 (83%)	0
ASA Classification				0.1
ASA I-III	20,997 (80%)	461 (65%)	20,536 (80%)	-
ASA IV-V	5262 (20%)	240 (35%)	5022 (20%)	-
Functional status				0.1
Independent	25,541 (97%)	662 (94%)	24,878 (97%)	-
Partially dependent	672 (3%)	34 (5%)	638 (2%)	-
Totally dependent	44 (0%)	5 (1%)	39 (1%)	-
Disease characteristics				
Symptomatic status				1.8
Stroke	5096 (20%)	249 (36%)	4847 (19%)	-
Hemispheric TIA	4083 (16%)	142 (21%)	3941 (16%)	-
Amaurosis fugax	1856 (7%)	32 (5%)	1824 (7%)	-
Asymptomatic	14,772 (57%)	267 (38%)	14,505 (58%)	-
Ipsilateral ICA stenosis[1]				2.1
<50%	316 (1%)	8 (1%)	308 (1%)	-
50-79%	7875 (31%)	218 (32%)	7657 (31%)	-
80-99%	17,245 (67%)	449 (65%)	16,796 (67%)	-
100%	296 (1%)	11 (2%)	285 (1%)	-
Contralateral ICA stenosis[1]				11.8
<50%	13,281 (58%)	290 (46%)	12,991 (58%)	-
50-79%	7169 (31%)	218 (36%)	6951 (31%)	-
80-99%	1725 (7%)	65 (11%)	1660 (7%)	-
100%	1004 (4%)	40 (7%)	964 (4%)	-
Elective surgery	22,194 (82%)	458 (64%)	21,035 (82%)	0.1

Continuous variables are presented as mean ± SD, categorical variables are presented as N (%).
[1] Measured with doppler ultrasound or CT angiography.

All patients

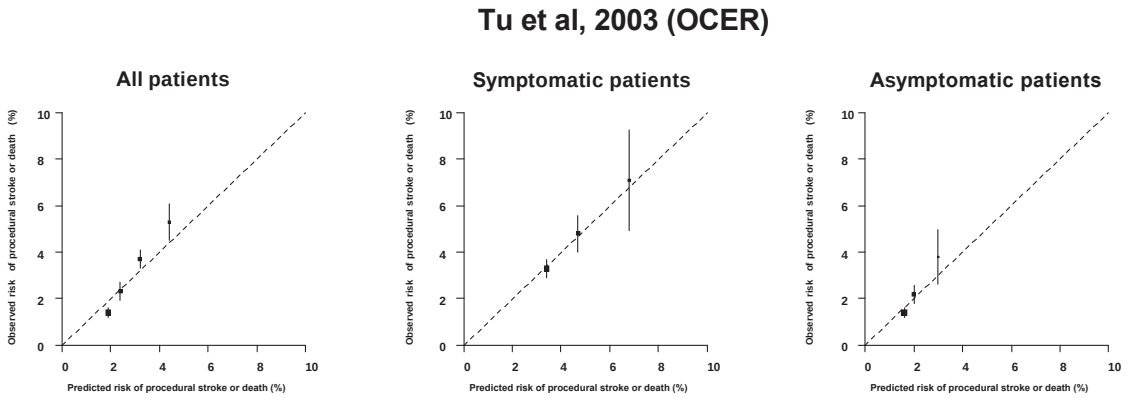
The c-statistics of nine prediction models varied between 0.60 and 0.64[26-28,30,31,33,34,38] and of eight between 0.52 and 0.59[25,29,32,35-39] in the validation population (Figure 3).

Figure 3. Discriminative performance of risk prediction models



The Ontario Carotid Endarterectomy Registry (OCER) model had the highest discrimination value of 0.64 (95% CI 0.62-0.66).[31] The OCER model was developed in a population that consisted of symptomatic and asymptomatic patients and was validated using symptomatic status (stroke or hemispheric TIA vs. amaurosis fugax or retinal infarct vs. asymptomatic), diabetes mellitus, heart failure and contralateral occlusion as predictors. The calibration plot showed good concordance across all risk groups. Most patients (42.9%) were in the lowest risk group with a predicted and observed risk of 1.9% and 1.4%, respectively. The highest risk group of 638 (2.3%) patients showed a predicted and observed risk of 6.0% and 6.7%, respectively (Figure 4). Calibration plots of other validated models are provided in Figure S1.

Figure 4. Calibration plots



Symptomatic patients

External validation in 11,035 patients who underwent CEA for symptomatic carotid stenosis showed c-statistics that varied between 0.51 and 0.59 (Figure 3).[25-39] Two models were developed in populations of symptomatic patients and had c-statistics of 0.59 (95% CI 0.56-0.61; Münster model) and 0.54 (95% CI 0.51-0.56; European Carotid Surgery Trial [ECST] model), but calibration was inaccurate.[34,35]

The Vascular Study Group of New England (VSGNE) model showed the highest discrimination values of 0.59 (95% CI 0.56-0.62)[26] (Figure 3). The calibration plot VSGNE model showed good concordance between predicted and observed risks in lower risk groups, but overestimated risks in the high risk group.[26]

The OCER model showed c-statistic of 0.58 (95% CI 0.56-0.61) and the calibration plot of the OCER model showed good concordance across all risk groups.[31] Most patients (71.7%) were in the lowest risk group with a predicted and observed risk of 3.4% and 3.3%, respectively.

In total, 508 (4.5%) patients had a predicted risk above 6% and 3167 (28.2%) above 4% (Figure 4). Of these 3167 patients, 1211 (38.2%) had ipsilateral stenosis of 50-79% and 1831 (57.8%) had ipsilateral stenosis of 80-99%. Calibration plots are provided in Figure S1-S2.

Asymptomatic patients

External validation in 14,772 patients who underwent CEA for asymptomatic carotid stenosis showed c-statistics that varied between 0.49 and 0.58.[25-39] Models that were developed in populations of asymptomatic patients had c-statistics between 0.49 and 0.56.[36-38] The OCER model had the highest discrimination value of 0.58 (95% CI 0.56-0.59)[31] (Figure 3). The calibration plot showed good concordance across all risk groups. Most patients (64.0%) were in the lowest risk group with a predicted and observed risk of 1.6% and 1.4%, respectively. The highest risk group of 859 (6.2%) patients had a predicted and observed risk of 3.0% and 3.7%, respectively.

In total, 306 (2.1%) patients had a predicted risk of above 3% and 5423 (36.0%) above 2% (Figure 4).

Sensitivity analysis

Complete case analysis showed similar results (Table S7).

Discussion

Our study compared the predictive performance of 17 risk models of procedural stroke or death after CEA in a representative contemporary setting. We found that the Ontario Carotid Endarterectomy Registry (OCER) model that included symptomatic status, diabetes mellitus, heart failure and contralateral occlusion as predictors showed fair discrimination and good concordance between predicted and observed risks of procedural stroke or death after CEA. This model could therefore reliably inform patients and clinicians about expected procedural risks of CEA in symptomatic and asymptomatic patients. The model identified 508 (4.6%) symptomatic and 306 (2.1%) asymptomatic patients with procedural risks exceeding recommended thresholds of 6% and 3% for symptomatic or asymptomatic carotid stenosis, respectively.

We identified a risk prediction model which showed in whom CEA can be performed with acceptable risk. Current procedural risk thresholds to consider CEA are 6% in symptomatic and 3% in asymptomatic patients, but might be reduced in the future since the risk of stroke in medically treated patients has decreased.[40] If the thresholds of procedural stroke or death are to be reduced to 4% in symptomatic and 2% in asymptomatic patients, the proportion of patients with predicted risks based on the OCER model exceeding these thresholds will increase to 28% of symptomatic and 36% of asymptomatic patients.

A previous external validation of the Carotid Stenosis Trialists' Collaboration that compared 19 prediction models with short-term outcome after CEA found poor discriminative performance.[41] Their external validation cohort consisted of 4754 patients from the EVA-3S, SPACE, ICSS, and CREST trials resulting in a more homogenous population as a result of patient selection. This might explain the poorer discriminative performance compared with our study.

Risks of procedural stroke or death also depend on the qualifying symptom and timing of CEA.[42,43] Patients with ischemic strokes have higher risks compared with ocular symptoms, and possibly hemispheric TIAs. Type of symptom was only included as predictor in one of the validated models (NSQIP).[29] Procedural risks are higher when CEA is performed within 48 hours

after ischemic stroke.[44] The risk of stroke recurrence is also high initially and decreases over time, reducing the benefit of CEA. The optimal timing of CEA should therefore balance the risk of recurrent events and procedural risks.

The beneficial effect is clear in symptomatic patients with 70-99% stenosis without near-occlusion and somewhat less clear in patients with 50-69% stenosis.[45] These benefits have become less clear over time since medical therapy for stroke prevention has improved and the absolute gains that individual patients might receive from CEA is smaller. The Carotid Stenosis Risk (CAR) score has been developed to predict the risk of ipsilateral stroke in patients with recently symptomatic carotid stenosis on medical therapy.[46] The currently ongoing ECST-2 re-evaluates the net benefit in symptomatic patients with moderate risk of stroke recurrence, ie. <20% 5-year risk (ISRCTN97744893) calculated with the CAR score. Some predictors of the CAR score overlap with predictors of models for procedural stroke or death, indicating that these predictors identify patient at high risk of stroke rather than selecting patients for the appropriate management strategy.

The absolute risk of a first ipsilateral stroke in patients with asymptomatic carotid stenosis in patients using medical preventive therapy is presumably low but estimates are imprecise due to small sample sizes.[40,47,48] In addition, not all patients are using adequate medical preventive therapy.[49] Stratification tools aiming to identify patients with a higher risk of ipsilateral stroke have been developed but not validated in contemporary cohorts.[50,51] The use of imaging to identify characteristics of plaques vulnerability might improve prediction, but have not been included in established risk prediction models.[52] Validated models of long-term stroke risk in patients with medically treated carotid stenosis showing good predictive performance could be used in conjunction with models of treatment effects to determine who might benefit from carotid interventions.[53]

Strengths and Limitations

The present study has several strengths. We conducted a comprehensive literature search to identify existing prediction models according to a prespecified protocol. A large registry representative of contemporary clinical practice was used for validation. Missing data were limited for most variables and our findings were unaffected by missing data. We also included 30-day outcome events that occurred after discharge to estimate procedural hazards reliably.[54,55] We performed additional analyses by symptomatic status to determine absolute risks of procedural stroke or death in those patients.

The present study also has several limitations. First, though data were collected prospectively, these were not collected primarily for the present analyses. We used proxies when a direct match between the predictors in the models and variables in the external validation cohort was not available, but proxies were not available for some predictors. This might have influenced predictive performance of the validated prediction models. We have therefore provided the linear predictor functions that we used for validation (Table S3). Second, some predictors were not available in the external validation cohort or could not be used due too many missing values (Table S2). Third, some risk prediction models did not allow splitting predicted risks in deciles hampering a direct comparison of calibration plots. However, visual assessment of the calibration plots clearly showed the concordance between predicted and observed risks. Fourth, data on hospital and operator volume, possibly two of the most important determinants of procedural hazards,[56,57] were not available in the external validation cohort and could therefore not be validated in one model that included annual surgeon volume.[33] Fifth, it is unclear whether our findings are generalizable to patients with restenosis, tandem stenosis, or who received previous cervical radiation therapy.[58,59] Sixth, the number of patients who were deemed ineligible for carotid intervention was not collected. Seventh, we were not able to validate some risk prediction models that were developed (partly) in the same dataset.[60-62]

Implications for practice and future research

Risk prediction models help inform patients about procedural hazards and might also contribute to the calculation of the net benefit of CEA in contemporary practice. The OCER model might be further refined by adding additional predictors, such as age, medical history, type of symptom, timing of CEA, and imaging characteristics, as well as by addressing identified shortcomings (in the statistical methods).

Future research will also determine which patients have the greatest reduction in absolute risk by undergoing CEA in contemporary practice weighting short-term procedural hazards against long-term stroke rates in unoperated patients and proportional reduction in non-perioperative stroke following successful CEA. Validation of established risk prediction models and assessment of predictive value of additional imaging characteristics to determine stroke risk in medically managed asymptomatic and (low-risk) symptomatic carotid stenosis is urgently needed.[63] This together with the second Carotid Revascularization versus Stenting Trial (CREST-2; NCT02089217), the ECST-2 (ISRCTN97744893), and the Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher than average Risk of Ipsilateral Stroke (ACTRIS; NCT02841098) will provide reliable evidence to guide clinical decision making.

Conclusion

This external validation study assessed the predictive performance of 17 models for procedural stroke or death after CEA. We found that the Ontario Carotid Endarterectomy Registry (OCER) model that included symptomatic status (symptomatic vs. asymptomatic), diabetes mellitus, heart failure and contralateral occlusion as predictors showed fair discrimination and good concordance between predicted and observed risks in the calibration plot. This model can be applied to symptomatic and asymptomatic patients and can reliably inform patients and clinicians about expected risks of procedural stroke or death of CEA. It might also help focus CEA toward patients who benefit most from it.

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Contributors

MHFP designed the study. MHFP designed the search strategy, performed literature searches and removed duplicates. MHFP and KD screened titles and abstracts and assessed full-text articles and reference lists of included studies. RARH performed the statistical analyses supervised by MHFP, JAAD and JPG. The manuscript was drafted by MHFP. All authors interpreted the data, contributed to revision and editing of the manuscript and approved the final version of the manuscript for submission for publication.

Declaration of interests

MS is a paid consultant for Abbott and Medtronic

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SUPPLEMENTARY MATERIAL

Table S1: Search strategy

Table S2: Matching of predictors with variables in the external validation dataset ACS-NSQIP

Table S3: Linear predictor functions used for external validation

Table S4: Full-text evaluation

Table S5: Characteristics of included prediction models

Table S6: Risk of bias assessment using PROBAST

Table S7: Discrimination values of complete case analysis

Table S8: Predicted and observed risk of procedural stroke or death across risk groups

Figure S1: Calibration plots

Figure S2: Calibration plots of models reporting original intercept (before recalibration)

Supplementary material is attached to this dissertation and can be found here

Part V

Discussion and conclusions

12

General Discussion and Future Perspectives

General Discussion

In this dissertation, we showed ways to improve prevention of ischaemic strokes by early detection and optimising modifiable risk factors. In the first part, we focused on the detection of asymptomatic carotid stenosis, i.e. the estimated diameter reduction of 50% or more, in a screened population and populations of patients with lower-extremity arterial disease. We validated six risk prediction models and developed two novel risk prediction models to detect high-risk cases, thereby enabling targeted screening. We found that the number needed to screen (NNS) to detect a case with asymptomatic carotid stenosis was reduced greatly compared with population-level screening.

In the second part, we investigated the association between adiposity measures and atrial fibrillation (AF) in men and women. We found that both body mass index (BMI) and waist circumference (WC) were associated with AF in men and women. BMI seemed a more informative measure about risk of AF in women and WC seemed more informative in men. In addition, we validated 14 risk prediction models for AF using data from 2.5 million participants who underwent an ECG. We found two models that could reliably detect AF in screened participants and were able to identify a group of participants at high risk of AF. These models outperformed the currently used age criterion for screening of 65 years and older and models for treatment of AF, such as CHA_2DS_2-VASc.

In the third part, we determined the yield and accuracy of screening for AF and carotid stenosis following cardiovascular risk stratification. For this, we stratified participants based on their predicted 10-year risk of CVD using the ASCVD risk prediction model. We found that detection rates of AF and carotid stenosis were higher in people who were a higher predicted CVD risk and the NNS was more than halved. This identified 39.0% of cases with AF and 41.4% of cases with carotid stenosis by screening only 18% of all participants. In addition, we found that additional measurement of height and weight could further refine AF screening. Finally, the estimated risks of AF-related complications, such as ischaemic stroke and systemic thrombo-embolism were higher in participants at high risk of CVD. These cases might therefore benefit most from preventive therapy in terms of absolute CVD risk reduction.

In the fourth part, we focused on the treatment of carotid stenosis by carotid revascularisation. Since carotid revascularisation is a preventive intervention that comes with procedural hazards, the net clinical benefit is crucial. We found that high operator volume and high hospital volume are strongly associated with a decreased risk of procedural stroke or death. For operator speciality, we could not find much reliable evidence for associations. In addition, we investigated the timing of these complications to further reduce the risk of procedural stroke or death. We found that at least of the complications occurred on the day of the operation, but one-third after day 3 when most patient have been discharged. Finally, we investigated the predictive performance of 17 risk

prediction models that were developed to predict procedural hazards of carotid endarterectomy (CEA) and we validated such models in a dataset of 26,293 patients who underwent CEA in the United States. This contemporary dataset showed representative absolute procedural risks of stroke or death after CEA. We found one risk prediction models that showed reliable predictions and could therefore be used to inform patients about procedural hazard and might also help focus CEA toward patients who would benefit most from it.

Targeted screening for asymptomatic carotid stenosis

For a successful targeted screening programme, it needs to fulfil several conditions. First, the condition that is being prevented implies an important health burden. Stroke is the second leading cause of death worldwide and one of the main causes of disability among adults.[1] Fifteen to twenty percent of ischaemic strokes are related to carotid stenosis.[2] Stroke is therefore an important condition to prevent and carotid stenosis might be a target for prevention.

Second, the targeted screening programme needs to reduce the risk of cardiovascular disease, including ischaemic stroke, myocardial infarction and premature vascular death. There is no direct evidence yet that targeted screening reduces these risks. Data from primary prevention trials clearly showed, however, benefit from antihypertensive and lipid-lowering therapy on cardiovascular disease (CVD) incidence (as outlined in *Chapter 1).*[3-5]

Third, the screening test should be valid and reliable. A systematic review and meta-analysis showed a sensitivity of 98% and specificity of 88% when duplex ultrasound was used as diagnostic tool. Reliability was however limited and clinically important variation in measurement properties was found among laboratories.[6]

Fourth, the NNS to detect a case with asymptomatic carotid stenosis should be low. We showed that the NNS can be greatly reduced by identification of a high-risk group. In our population, the NNS of population-level screening was 53 and could be reduced to 13 by screening only cases in the decile at highest predicted risk. This identified around 40% of cases with asymptomatic carotid stenosis of 50% or more. This will also improve the ratio of true-positive to false-positive results that are expected to be brought about with population-level screening.

Fifth, harms of screening and treatment in positive cases should also be considered. Duplex ultrasound is a widely available and non-invasive test and comes without significant harms (except anxiety about the result). Confirmatory test in positive cases might be needed and have potential intrinsic harms, such as small amount of radiation exposure in case of CT angiography or might be difficult in patients with for example severe kidney disease. Harms of treatment include side-effects of medical preventive therapy. When carotid revascularisation is considered as treatment, harms include procedural hazards such as stroke, death, myocardial infarction, nerve injury, haematoma, and other systemic complications. However, because of the

considerable disagreement around the net benefit of carotid revascularisation in patients with asymptomatic carotid stenosis in contemporary practice with effective medical therapy, the current ESVS guidelines concludes that selective screening for asymptomatic carotid stenoses should not be used to identify candidates for invasive carotid interventions.[7]

Finally, screening should also be cost-effective. This depends on the cost of screening and subsequent treatment in positive cases, but presumably most important is the reduction in stroke risk with initiated or improved preventive therapy. In a recent Markov model analysis comparing one-time screening of men aged 65 years with duplex ultrasound and initiation of medical preventive therapy in positive cases concluded that this approach may be cost-effective with €5744 per incremental quality adjusted life year (QALY) gained.[8] Our studies showed that risk prediction models can help to focus screening toward those at high risk of carotid stenosis, thereby reducing costs.

Although the risk reduction by medical therapy might be substantial, there is large variation in risk reduction that can be achieved in patients with asymptomatic carotid stenosis based on available evidence. This hampers a more precise evaluation of targeted screening.

Contemporary stroke risk in patients with medically managed asymptomatic carotid stenosis

Current available evidence

The lack of contemporary data on absolute stroke risks of patients with medically managed asymptomatic carotid stenosis is widely acknowledged.[7] Risks are presumably low and have declined over time,[9] but reported estimates are imprecise due to small sample size and vary between studies due to different selection criteria and regimes of preventive therapy. There is surprising little evidence on subgroups of medically managed patients at high risk of stroke to guide medical decision-making.

The largest study addressing this issue is the Asymptomatic Carotid Stenosis and Risk of Stroke Study (ACSRS).[10] This natural history study recruited 1121 patients with 50-99% stenosis (measured with the ECST method - that might overestimate the degree of stenosis compared with the NASCET method that is now the standard worldwide) between 1998 and 2002. ACSRS included patients in whom surgery was either inadvisable or was not being considered as the physicians did not routinely operate on asymptomatic patients.

During the mean follow-up of 4 years, 59 patients had an ischaemic stroke resulting in an annual stroke risk of 1.3%.[11] Three risk models were developed to stratify patients according to the risk of stroke. One model included the clinical predictors degree of stenosis, pack-years (<10 vs. ≥10 years), history of contralateral TIA or stroke and used ipsilateral cerebral or retinal ischemic events as predicted outcome. Two models included degree of stenosis and duplex-based imaging

predictors, such as grayscale median, plaque area, and discrete white areas for the predicted outcomes ipsilateral cerebral or retinal ischemic events and ipsilateral hemisphere stroke.[11]

Regimes of medical therapy were not prespecified and only 25% of patients used lipid-lowering therapy and 84% antiplatelet therapy at baseline. These percentages increased to 85% and 95% toward the end of the study for lipid-lowering and antiplatelet therapy, respectively.

Discrimination of these models varied between an AUROC of 0.66 (95% CI 0.62-0.72) for the model with clinical predictors and 0.82 (95% CI 0.78-0.86) for the model that included duplex-based imaging predictors. Calibration showed that most patients (58%) were in the low-risk group (defined as a 5-year predicted ipsilateral stroke risk of <5%) with an observed risk of 1% (95% CI 0.2%-2%). In the high-risk group (defined as a 5-year predicted ipsilateral stroke risk of ≥20%) of 86 (7.7%) patients, an observed risk of 29% (95% CI 14%-33%) was found. Interestingly, 84 (98%) of these 86 patients had ≥70% asymptomatic carotid stenosis.

Attempts to pool the results of the ACSRS with other study-level results have been published.[9,12,13] The overall pooled annual risk of ipsilateral stroke was 1.68% (95% CI 1.45%-2.11%) in 26 studies in patients with asymptomatic carotid stenosis of 50% or more.[12] A similar ipsilateral stroke rate of 1.6% (95% CI 1.3%-1.9%) was found in 10 studies reporting risks in patients with asymptomatic carotid stenosis of 70% or more.[13] It was also found that the risk of stroke declined over time, presumably as a result of improved medical preventive therapy.[9,12]

The current literature has important shortcomings. The most important shortcoming is that outcomes are only provided on study-level and not stratified by usage of medical therapy and regimes for medical therapy are not prespecified, for example target level of blood cholesterol. This hampers the disclosure of the full potential of current medical therapy. Different grading systems have been used to determine the degree of stenosis.[14] Some patients underwent carotid interventions during follow-up and are not always censored properly. Selection of patients and outcome ascertainment bias should also be considered.

Imaging characteristics of plaque vulnerability

The ACSRS study used duplex-based imaging predictors in addition to patient and disease characteristics and showed improved prediction of ipsilateral cerebrovascular or retinal ischaemia by using plaque echodensity (by measuring grayscale median), plaque heterogeneity (by measuring discrete white areas) and plaque area.

Plaque echolucency has histopathological correlates of lipid-rich necrotic core and intraplaque haemorrhage.[15,16] The risk of ipsilateral stroke was increased in patients with asymptomatic carotid stenosis of 50% or more with predominantly echolucent plaques compared with predominantly echogenic plaques in a meta-analysis of five studies, with a relative risk (RR) of 2.61 (95% CI 1.47-4.63).[17]

Other findings from the ACSRS study include the identification of stenosis progression as risk factor for ischaemic stroke, with an RR of 1.92 (95% CI 1.14-3.25),[18] juxtaluminal black (hypoechoic) area on computerised plaque analysis, with a hazard ratio (HR) of 2.34 (95% CI 1.89-2.91),[19] silent brain infarction on CT, with a HR of 3.0 (95% CI 1.46-6.29).[20]

Another study that has contributed to this field is the Asymptomatic Carotid Emboli Study (ACES). This was a prospective multinational observational study that included 482 patients with asymptomatic carotid stenosis of 70% or higher. Included patients underwent transcranial Doppler ultrasound. Transcranial Doppler ultrasound can be used to measure asymptomatic embolisation. These are circulating emboli that are captured during recording of the ipsilateral middle cerebral artery. The presence of embolic signals was associated with a higher risk of ipsilateral stroke, with an odds ratio (OR) of 5.35 (95% CI 1.51-18.94).[21] When pooled with data from five other studies, the pooled OR was 6.63 (95% CI 2.85-15.44).[22-26]

Transcranial Doppler ultrasound was used in the ACES study to measure cerebral reactivity.[27] This reactivity is a response of the blood flow in the middle cerebral artery to vasodilatory stimuli, such as increased inspired carbon dioxide or an intravenous injection of the carbonic anhydrase inhibitor acetazolamide. Impaired cerebrovascular reactivity was associated with an increased risk of ipsilateral stroke when combined in a meta-analysis of four studies, with an OR of 6.14 (95% CI 1.27-29.75).[27-30] The findings should be interpreted with caution, because the wide confidence intervals due to the low number of patients and events indicate considerable uncertainty about the effect size.

Predictors of high stroke risk using MRI were identified, such as intraplaque haemorrhage (HR 4.59 [95% CI 2.91-7.24]; 7 studies), lipid-rich necrotic core (HR 3.00 [95% CI 1.51-5.95]; 4 studies), and thinning/rupture of the fibrous cap (HR 5.93 [95% CI 2.65-13.20]; 4 studies).[31]

Apart from the duplex-based imaging predictors included in the ACSRS risk model, imaging characteristics have not been included in risk prediction models to identify patients at high risk of stroke. The current ESVS guidelines concluded that CEA should be considered in patients with ≥60% asymptomatic carotid stenosis in the presence of one or more imaging characteristics that may be associated with a higher risk of ipsilateral stroke.[7] It has been suggested that these criteria are expected to lack enough discriminative ability to identify patients at higher risk of ipsilateral stroke to justify CEA.[32] This is also recognised in the ESVS guidelines and a validated risk prediction model to identify patients at high risk of ipsilateral stroke is needed, because at this moment it is unclear how these imaging characteristics translate into long-term absolute risks of ipsilateral stroke in patients using effective medical therapy and it is also unclear how much predictive value is added by including imaging in risk prediction models compared with models that use patient and disease predictors.

United Kingdom Carotid Cohort Study

We designed a large prospective observation study to fill this evidence gap. For this, we designed the United Kingdom Carotid Cohort Study (UKCCS) with the aim to assess contemporary stroke risks among patients with carotid stenosis who are managed medically. This is a pilot study of 1000 eligible participants from Oxfordshire and Gloucestershire NHS vascular laboratories who underwent a duplex ultrasound of the carotid arteries.

The main outcome is the long-term risk of stroke over 5 and 10 years, among people with and without significant carotid artery stenosis (defined a maximum diameter reduction of the carotid artery of 50% or more).

The inclusion criteria for this study were:

1) Male or female participants aged 18 years or above;
2) Carotid duplex or non-invasive carotid imaging at an NHS hospital with either
    a) visible unilateral or bilateral carotid artery stenosis of the common carotid artery or internal carotid artery (≥50%; "cases") or
    b) No clinically significant carotid artery stenosis (<50%; "controls")
3) Willing and able to give written informed consent for participation in the study.

Exclusion criteria for this study were:

1) Lacks capacity
2) Does not have an NHS number (eg. From Guernsey, Jersey or the Isle of Man). This is required for follow-up data-linkage and ascertainment of outcome events.
3) Recent carotid revascularisation (ie, 6 week post-operative duplex scan)

The duplex ultrasound of the carotid arteries is performed as part of routine clinical care. Vascular scientists use locally available duplex equipment and quantify the degree of carotid stenosis using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. We recorded the peak systolic velocity (PSV) and end diastolic velocity (EDV) of the internal and common carotid arteries. We used the standard conversion table published by the joint working group from the Vascular Society of Great Britain and Ireland and the Society for Vascular Technology of Great Britain to estimate the degree of stenosis.[14] If both sides showed asymptomatic carotid stenosis, patients were classified according to the greatest percent non-occlusive diameter reduction.

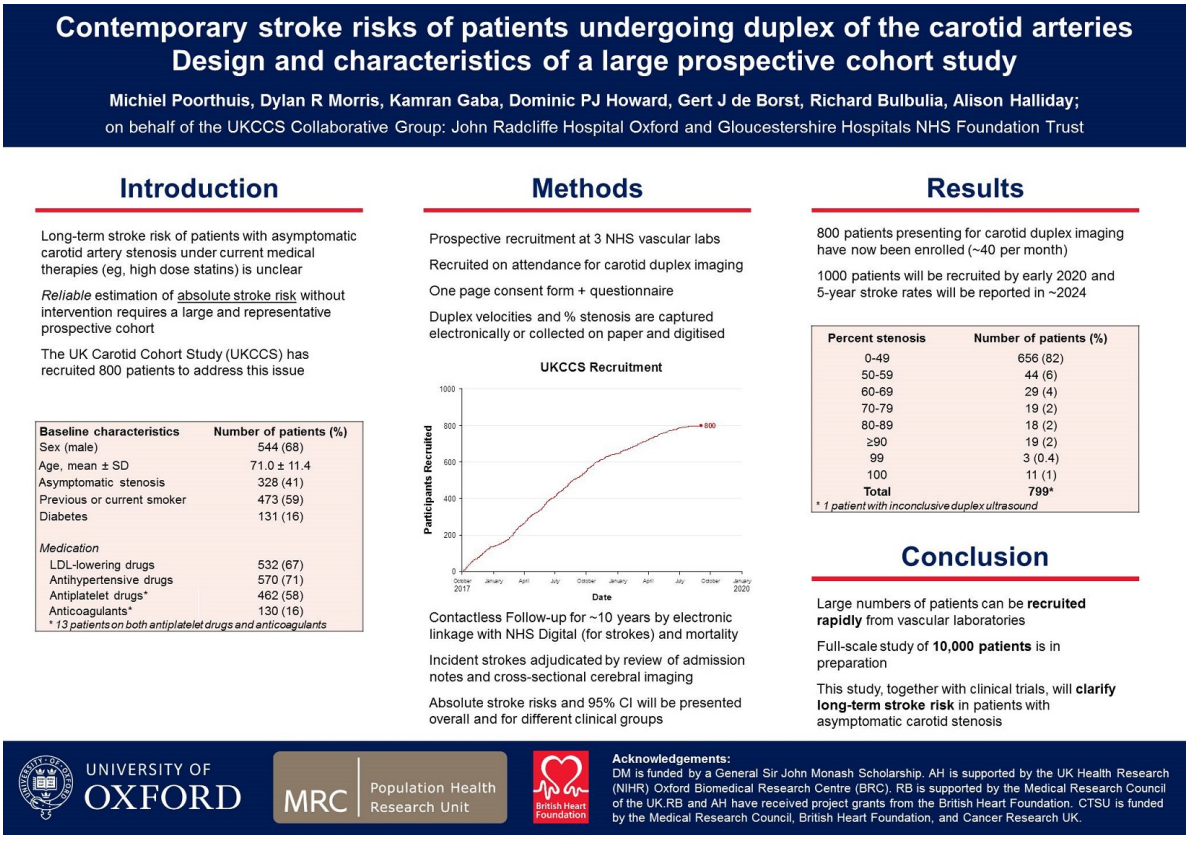
Baseline characteristics including past medical history, current medications and vascular risk factors were collected with a medical questionnaire. Tracking of outcome events during follow-up is planned through electronic data-linkage with central registries (NHS Digital for hospital

episode statistics and Office of National Statistics for mortality data). This approach has shown to have good validity for major outcome events, such as strokes.[33]

We recruited 882 patients between August 2018 and January 2020, but recruitment was suspended early 2020 due to COVID-19. The manuscript was intended to be part of this dissertation but could not be included due to these unprecedented circumstances.

We performed interim analysis of the first 800 patients in September 2019. These preliminary results are shown in Figure 1. Results of the follow-up are expected in 2025 and 2030. This pilot study will inform the design of a large-scale study that is planned after UKCCS pilot study. This will provide reliable and precise estimates of long-term stroke risk in patients with medically managed asymptomatic carotid stenosis and might help disclose the optimal prevention strategy for relevant subgroups of such patients.

Figure 1.



Plasma biomarkers

Markers of excessive endothelial and coagulation system activation might also improve risk prediction, but these have not been used as predictors in published risk modelling studies.

Optimizing strategies to prevent carotid-related ischaemic stroke

Targeted screening in Sweden

The most recent study on screening for carotid stenosis was performed in Uppsala between 2007-2009, of which the cost-effectiveness have been discussed above.[34,35] In total, 4,657 men aged 65 years who attended screening for abdominal aortic aneurysm were invited for duplex ultrasound of the carotid arteries to detect carotid stenosis (measured with the ECST method – as stated above, this method might overestimate the degree of stenosis compared with the NASCET method).[34]

Carotid stenoses of 50-99% were detect in 94 (2.0%) men and carotid occlusion in 15 (0.3%) men. Antiplatelet and lipid-lowering therapy were used in only 42% and 41% of patients with stenoses, respectively. Participants were invited after five years for a re-screening.[35] In total, 3,057 were re-screened at age 70, and 61 (2.0%) new 50-99% stenoses were detected in patients <50% stenosis at first screening.[35] Progression of stenosis was seen in four (13%) patients with known stenosis of 50-79%, of whom two developed symptoms and an additional five (42%) of twelve patients with known stenosis of 80-99% developed symptoms. These symptoms included TIA, amaurosis fugax and ischaemic stroke.

These findings provoked concerns, since rates were expected to be much lower in these patients with asymptomatic carotid stenosis of 50-99% detected at age 65 years and despite prescription of statins and antiplatelet therapy.[34,36,37] However, compliance of medical therapy after 5 years in patients with 50-99% carotid stenosis at 65 years was rather low and might have contributed to these findings.[35,38] Nevertheless, despite these shortcomings in compliance, the rate of major strokes was very low since "most were transient in nature".[38] Unfortunately, actual annual (ipsilateral) stroke rates were not provided. It nevertheless stresses the importance of careful implementation of targeted screening for asymptomatic carotid stenosis with close follow-up in detected cases to maintain compliance.

Offering screening for asymptomatic carotid stenosis together with AAA ultrasound screening facilitates and decreases costs of implementation. In this dissertation, we suggested targeted screening can also be offered following cardiovascular risk stratification *(Chapter 7)*. This has several advantages: Cardiovascular risk stratification is commonly used in clinical practice. Several predictors that are also associated with increased risk of carotid stenosis are included in the risk stratification. Using this stratification of people might be more accurate in identifying people who should be tested for asymptomatic carotid stenosis. It might also be more cost-effective because of the higher prevalence (and lower NNS) in high risk groups. Compliance might be improved because screening is part of cardiovascular risk management that aims to optimise multiple modifiable risk factors and implies close follow-up.

Antithrombotic therapy and the COMPASS trial

A new landmark trial is the COMPASS trial that included 27,395 patients with stable atherosclerotic vascular disease of whom 1919 patients were recruited because of previous stable carotid disease (defined as carotid revascularisation or carotid stenosis of at least 50%).[39,40] The overall trial result showed that low-dose rivaroxaban twice a day plus aspirin once a day reduced major adverse cardiovascular events compared with aspirin alone. The effects were clear in subgroups of patients with stable peripheral arterial disease and stable coronary artery disease, but the effect was not seen in patients with stable carotid disease.[40,41] However, this RCT was not designed to detect treatment effects in this specific subgroup of patients with carotid stenosis and subgroups should always be interpreted with caution.[42] In addition, while the confidence intervals were wider due the relative low number of patients with carotid disease included, the point estimates were comparable between subgroups.[40]

It raised the possibility of long-term prevention by dual pathway inhibition in patients with asymptomatic carotid stenosis or after carotid revascularisation but presumably needs additional confirmation.

Net clinical benefit of carotid revascularisation

In patients in whom it is thought that carotid revascularisation is needed, the net benefit of prevention does also on procedural hazards. In this dissertation, we showed that high operator volume and high hospital volume are possibly two of the most important determinants of procedural hazards after CEA *(Chapter 8)*. Although the current available evidence did not allow to provide a quantified volume threshold, it indicates that centralisation of operative care will lead to better outcomes after CEA. Some RCTs, such as the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST),[43,44] Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S),[45] the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE),[46] and the International Carotid Stenting Study (ICSS),[47] also used volume threshold for their credentialing processes. This is important because it diminishes an operator effect when determining the efficacy of carotid revascularisation.

We also showed when procedural complications occur *(Chapter 10)*. We showed that one-third of procedural complications occurred after day 3 when most patients have been discharged. This was also seen after carotid revascularisation in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).[48,49] This stressed the importance of reporting 30-days outcomes after discharge to estimate true risks after carotid revascularisation, but also the need for methods to reduce procedural complications after discharge.

Finally, we showed how risk prediction models can be used for patient selection and inform patients about procedural hazards of CEA *(Chapter 11)*. We were able to show how the risk

prediction model of the Ontario Carotid Endarterectomy Registry (OCER) can predict the risk of stroke or death reliably.[50] This risk prediction model included symptomatic status, diabetes mellitus, heart failure, and contralateral occlusion as predictors and showed fair discrimination and good concordance between predicted and observed risks. This model identified 508 (4.6%) symptomatic and 306 (2.1%) asymptomatic patients with predicted procedural risks above the recommended threshold of 6% and 3% procedural stroke or death for CEA in symptomatic and asymptomatic patients, respectively.[7] To determine the net clinical benefit of CEA in contemporary practice, long-term stroke rates in unoperated patients and the proportional reduction in non-perioperative strokes following successful CEA also need to be considered.

Other considerations to determine and optimise the net clinical benefit of carotid revascularisation, such as the optimal anti-thrombotic therapy in early secondary prevention, are beyond the scope of this dissertation and can be found in relevant section of current guidelines.[7,51]

Targeted screening for AF

Current recommendations for targeted screening of AF include pulse palpation or ECG rhythm strip in patients aged 65 years and older or considering systematic screening in people aged 75 years and older.[52] These recommendations are based on the SAFE study that showed a 60% improvement over 12 months in detection of AF by opportunistic and systematic screening compared with routine care.[53,54]

In the recent pragmatic, cluster RCT from the Netherlands, opportunistic screening for AF using a single-lead ECG *(MyDiagnostick)* in GP practices did not result in a higher yield of AF cases compared with usual care.[55] The participation rate was low with 10.7% of the potentially eligible patients. In the opportunistic screening group, 123 (1.43%) new AF cases were detected. Of these, 95 patients were detected with usual care and 28 with screening. In the usual care group, 117 AF cases were detected (1.37%). The rate was not statistically significant, with P=0.73. It should be noted that the rate of detected AF cases in the usual care group was considerably higher compared with the 1.04% in the SAFE study. This might indicate that detection rates by usual care have improved compared with a decade ago.

Undetected AF and screen tests

Undetected AF is common and was found in 1.4% adults aged 65 years and older in the general population using a single time-point screening.[56,57] A single time-point screening is however likely to underestimate the true burden of AF since it is often paroxysmal and asymptomatic. The Swedish STROKESTOP study screened 7173 participants from the general population who were 75 or 76 years old with a single ECG and found undetected AF in 0.5% of participants. This increased to 3.0% with intermittent ECG recordings over two weeks.[58]

The assessment of Remote Heart Rhythm Sampling Using the *AliveCor* Heart Monitor to Screen for Atrial Fibrillation (REHEARSE-AF) used the CHA_2DS_2-VASc for selection of patients.[59] Using this enriched population identifies patients in whom anticoagulation should be considered if AF is found. In total, 1001 participants were included and were randomised between twice-weekly ECG screening using a single handheld lead for 30 seconds over a period of 12 months or no screening. All AF diagnoses were confirmed by cardiologists. More AF cases were detected in the screening group than in the no screening group (19 vs 5 cases), resulting in a HR of 3.9 (95% CI 1.4-10.4). It should be noted that eight (42%) cases in the screening group were asymptomatic and none in the no screening group. In addition, 12 (63%) cases had paroxysmal AF compared with none in the no screening group. Finally, although this study was not powered to detect difference in stroke outcomes, a similar number of strokes and TIAs were found in both groups.

The detection rate of AF is likely to increase with a range of new wearable devices to continuously monitor cardiac rhythm that have become available, for example the *AppleWatch* (using photoplathysmography).[60] In the Apple Heart Study, 419,297 self-enrolled participants over 8 months and if irregular pulse was detected by the *AppleWatch*, participants were notified to contact the study doctor to discuss wearing a one week ECG patch. Only 2161 (0.5%) of participants received a notification of irregular pulse and 450 (21%) of them eventually wore the ECG patch. AF was ultimately detected in 153 (34%) of these 450, resulting in a positive predictive value of 84%.

The use of modern technology will certainly contribute to more self-monitoring of health and might be used to earlier detect conditions such as AF. It tends, however, to attract more young participants. This was also seen in the Apple Heart Study in which the mean age was 41 (SD: 13) years.[60] This might, however, also lead to more false-positive cases. We described the use of risk prediction models to detect AF in high risk groups. The prevalence in these high-risk groups is higher compared with the prevalence in the population and leads to lower number of false-positive cases.

During continuous monitoring of heart rhythm, brief episodes of AF or atrial arrhythmia are also detected. These brief episodes are called atrial high rate episodes (AHRE) and their clinical significance in terms of stroke risk is currently uncertain.

Harms of AF screening

The US Preventive Services Task Force (USPSTF) found no evidence whether harms were associated with AF screening.[61] A subset of patients included the SAFE study reported no difference in anxiety scores between systematic and opportunistic screening.[54]

The high number of false-positive cases, especially in screening low-risk populations is a potential harm. These patients might be exposed to unnecessary investigations and an increased risk of haemorrhage if anticoagulant therapy is initiated.

Risk of AF-related complications

It is clear that patients with AF are at higher risk of stroke and other cardiovascular disease outcomes.[62] Anticoagulation with either a vitamin K antagonist such as warfarin or a Direct Oral Anticoagulant (DOAC) can reduce their stroke risk by around 65% in high risk patients. The CHA_2DS_2-VASc is recommended to determine which patients with non-valvular AF are at high risk of ischaemic stroke and systemic thrombo-embolism.[63] Anticoagulants are, however, associated with an increased risk of haemorrhage and individualised risk predictions to predict the risk of major haemorrhage can be done with the HAS-BLED score.[64]

Frequency of duration of AF episodes are not included in these risk prediction models. Some found that thrombo-embolic risks of AF are not influenced by symptomatic status of AF,[65,66] but generalisability of the risk scores to patients from the general population with screen detected AF or AHRE is unclear. The net clinical benefit of anticoagulant treatment in this specific group of patients therefore needs further refinement.

This was also the greatest concern of the USPSTF to recommend against routine screening with ECG to detect AF.[61] There was insufficient evidence that treatment of screen detected asymptomatic AF resulted in better outcomes than treatment after detection by usual care or after symptoms develop.

Cost-effectiveness of AF screening

Several studies have been published on the cost-effectiveness of AF screening, assessing different screening approaches and screening tests. Costs of AF screening depend on the screening tests, selection criteria for screening, the duration and frequency of screening, the number of patients treated with antithrombotic therapy (and adherence), and the number of prevented strokes.

A systematic review evaluated different economic evaluations of screening strategies for AF.[67] This study compared nine studies and it was concluded that both opportunistic and systematic population-level screening are cost-effective compared with no screening. Opportunistic was more cost-effective compared with systematic population-level screening. This recommendation was mainly based on the economic evaluation of the SAFE-study where opportunistic screening of 65-year-old individuals from the UK was found to be cost-effective, with estimated costs of £363 compared with no screening.[54] Importantly, the detection rate of the SAFE study, as described above, should be realised and should be higher than routine care.[67] We have seen that the detection rate of AF by routine care improved since the recruitment of the SAFE study.[55]

Different approaches, such as nurse pulse palpation, photoplethysmography, or modified blood pressure monitors with confirmation of findings with a 12-lead ECG are probably more cost-effective. Screening approaches that use a single screen at a given age are more cost-effective when people at higher ages were screened, but repeat screening was more cost-effective than single screenings if compliance to antithrombotic therapy remained adequate.[67]

Another study simulated and compared over two billion different AF screening designs and found cost-effective seven designs. In addition, it was shown that repeat screening is beneficial at reasonable costs.[68] Targeted screening for AF using our validated risk prediction models *(Chapter 6)* have not been evaluated for cost-effectiveness. Recently, however, the cost-effectiveness of targeted screening using a machine learning risk prediction algorithm was determined and showed that the costs per QALY decreased with this approach compared with opportunistic and systematic screening.[69,70]

Risk prediction modelling as replacement or surrogate for randomised clinical trials? A critical note

The availability of large amounts of data, often called 'big data', has had an enormous impact on the development of risk prediction modelling research. This type of statistical modelling often requires large amounts of data to obtain precise estimates. Such large datasets also formed the basis of the research presented in this dissertation.

Risk prediction models are a powerful way to guide clinical decision making by taking multiple predictors into account and obtain more individualised predictions of risks. The stratification of patients might help to focus health resources to those who benefit most from it and to refrain from those who do not benefit (although identification of a clinically relevant threshold is sometimes difficult). Prediction research is increasingly promoted as alternative to RCTs to determine the effects of treatment using "real-world evidence" and providing a more personalized approach. In contrast, trials are expensive and use strict inclusion criteria to make the sample of patients homogeneous, but not representative for the whole patient population, it is claimed.

It is true that in some circumstances, the relation between a treatment and its effect is so strong that bias can be ruled out as an explanation. This type of relationship is coined a "dramatic effect", and defined as "*(a)* that the conventionally calculated probability of the two groups of observations coming from the same population should be less than 0.01 and *(b)* that the estimate of the treatment effect (rate ratio) should be large."[71] Example of such dramatic effects include insulin for diabetes or neostigmine for myasthenia gravis.

When treatment effects are moderate, it is however important to note that potential biases are inherent to observational data (and the same holds true for risk prediction modelling using trial

data) underlying the risk prediction modelling. These potential biases are important if they lead to false conclusions that a treatment produces benefit or harm, even after application of strategies capable of adjusting with certainty for bias. In those circumstances, RCTs are generally required to obtain reliable evidence about treatment effects.

In a recent article, the importance of RCTs is clearly summarized: "The "magic" of randomization is that it is guaranteed to result in groups of patients that are balanced (give or take the play of chance) with respect to both known and unknown risk factors (regardless of whether those risk factors have been assessed and, hence, with respect to their risks of any type of health outcome."[72] The observed effect can be attributed as causal to the allocated treatment.

Risk prediction modelling can complement evidence form RCTs in some instances. As stated above, there is strong need for a risk prediction model to predict the long-term stroke risk in medically managed patients with asymptomatic carotid stenosis. Reliable predictions will help to determine the absolute gains that individual patients might receive from CEA in addition to medical therapy, but potential biases cannot be fully ruled out.

It is for this reason that researchers are commended for the tremendous efforts to undertake RCTs, such as the ACST-2, CREST-2, and ACTRIS. It is disappointing that SPACE-2 and ECST-2 had to be stopped because of recruitment rates that were slower than anticipated.[73,74] Collaborations to combine data of RCTs, such as the Carotid Stenosis Trialists' Collaboration, are of crucial importance to guide patient care appropriately.[75-77]

FUTURE PERSPECTIVES

Carotid stenosis: beyond the controversy and the formulation of a research agenda for contemporary practice

There is perhaps no other field in cerebrovascular neurology that has caused so much controversy as asymptomatic carotid stenosis. The excessive number of published reviews, opinions, comments or positions statement largely outweighs the original data studies. In this paragraph, I hope to formulate a research agenda that will inform contemporary practice.

Targeted screening for asymptomatic carotid stenosis

For a targeted screening programme to be worthwhile, it should be clear what the aim of screening is, i.e. initiation or improvement of medical preventive therapy. Taking this as a starting point, it is necessary to determine the optimal threshold for targeted screening. For this, risks of strokes and other cardiovascular events in patients with medically managed asymptomatic carotid stenosis should be determined and how many events can be prevented by improved cardiovascular risk management in those in whom asymptomatic carotid stenosis is detected. Finally, the cost-effectiveness of a targeted screening programme should be determined and will depend on the latter findings but also on how the targeted screening programme is implemented in clinical practice.

Previous reports investigated whether common carotid intima-media thickness improved risk prediction of CVD and found that there was only a small improve that was possibly not clinical meaningful.[78] However, whether asymptomatic carotid stenosis can in turn improve the prognostic accuracy of cardiovascular risk prediction using traditional predictors needs further research.

Antithrombotic therapy in patients with carotid stenosis

As highlighted in the general introduction of this dissertation, the evidence underlying recommendations for antiplatelet therapy in patients with asymptomatic carotid stenosis is scarce and generalisability of the COMPASS trial that included a subgroup of patients who underwent carotid revascularisation or with asymptomatic carotid stenosis of at least 50% to patients with carotid disease presumably needs further confirmation.[40]

A complementary approach might be to determine in which patients with carotid stenosis (both asymptomatic and symptomatic) currently recommended antithrombotic therapy is not sufficient to prevent long-term stroke and other manifestations of CVD. These patients might benefit from additional antithrombotic therapy, but this should be weighed against the risk of haemorrhage. Risk prediction models like CHA_2DS_2-VASc might help identifying such patients.

Antithrombotic therapy in the acute phase after ischaemic stroke or TIA related to carotid stenosis is beyond the scope of this dissertation and current recommendations can be found in relevant guidelines.[7,51]

Carotid interventions

It is necessary to determine the net clinical benefit of prevention in contemporary practice to determine the role of carotid intervention. As outlined above, contemporary practice is characterised by more effective medical therapy that reduced the risk of stroke and with that the absolute gains patients might receive from an additional CEA.[79]

Possible approaches to obtain more reliable estimates and predictions of stroke risk in medically managed patients with asymptomatic carotid stenosis would be an individual patient data (IPD) meta-analysis or an extension of the UKCCS in order to obtain precise estimates of stroke risk and disclose optimal prevention strategies for relevant subgroups of patients. In addition, validated risk stratification tools in contemporary populations using medical preventive therapy are needed.[11,80]

These risk prediction models should ideally include predictors that are routinely collected in clinical practice but might also consider imaging characteristics or plasma biomarkers as predictors, if that would improve the predictive performance.

In addition, to reduce the risk of procedural stroke and death, optimal volume thresholds balancing a minimum adverse event rate and practical feasibility need to be established. Other measures of quality of care should be identified and implemented. There is also a need for methods to reduce procedural complications after discharge.

This will be complemented by evidence from ongoing RCTs:

- CREST-2 randomises asymptomatic patients between medical therapy plus CEA vs. medical therapy alone and medical therapy plus CAS vs. medical therapy alone;
- ACTRIS will randomise asymptomatic patients at higher risk of ipsilateral stroke between BMT vs. BMT plus CEA/CAS.

These RCTs will re-assess the efficacy and safety of additional carotid revascularisation in contemporary practice.

In asymptomatic patients in whom the absolute gain of carotid revascularisation are found to be worthwhile, the ACST-2 will explore whether CEA or CAS is better, especially in a pooled analyses with ACT-1, SPACE-2, CREST-1, CREST-2 and ECST-2. Transcarotid artery revascularization with flow reversal is a new approach for carotid stenting and showed promising results.[81,82] A trial with randomised treatment allocation is needed to determine the role of this new technique.

Atrial fibrillation: determining the clinically relevant burden

Future research should determine what the optimal approach for targeted AF screening is in terms of the screening test, selection criteria for screening, and duration and frequency of screening. It is also necessary to determine how many strokes can be prevented by improved preventive therapy in patients with screen detected AF or AHRE. Validated risk prediction models could guide decisions about antithrombotic therapy in such populations. New RCTs also started to address these issues.

Current ongoing RCTs in AF screening

Recently, four studies on AF screening were initiated to determine whether screening is cost-effective and improves outcomes of patients with AF:

- The Screening for Atrial Fibrillation with ECG to Reduce stroke (SAFER; ISRCTN16939438) study is a feasibility study to include 9600 participants of whom some will be invited to be screened with a handheld single-lead ECG recorder to record their heart rhythm at home over a period of 2-4 weeks.
- VITAL-AF (NCT03515057) is a pragmatic cluster-trial to include 35,308 participants with eight primary care practice randomised to AF screening using a single-lead ECG device and eight primary care practices to usual care.[83]
- The Active monitoring for atrial fibrillation (AMALFI; ISRCTN15544176) aims to randomise 2500 participants with CHA_2DS_2-VASc of 3 or more in men or 4 or more in women in the UK between a self-applied ECG monitor that is worn for two weeks to detect undiagnosed AF and usual care.
- Detecting and Diagnosing Atrial Fibrillation (D_2AF; NTR4914) is a cluster randomised trial to compare different case-finding approaches with usual care in 19,200 participants aged 65 or older and compare detection rates after 1 year.

The SAFER study is powered to detect differences in long-term AF-related complications, such as ischaemic stroke rates, major haemorrhage, and mortality. This will help determine the risks and benefits of anticoagulant therapy in patients with screen detected AF compared with patients with symptomatic AF. The yield and accuracy of screening targeted to high-risk patients is examined in the VITAL-AF and the Silence Study (NCT02893215). AMALFI, together with SCREEN-AF (NCT02392754), will determine which device is most accurate and cost-effective.

Use of innovative technology, such smartwatches, will increase the detection rate of silent AF. Future research should determine what burden of screen detected AF is significant and which of these patients benefit from anti-thrombotic treatment weighing long-term risk of stroke and systemic thromboembolism against haemorrhagic complications. Two studies have been registered to address the optimal treatment in patients with AHRE: NOAH (NCT02618577) and ARTESiA (NCT01938248).[84,85]

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Summary

Stroke is the second leading cause of death and a major cause of disability worldwide. Around 12 million people suffer a stroke annually and over 100 million people live with the consequences of a stroke resulting in stroke-related disability-adjusted life years. Stroke has two broad causes that both result in disruption of the cerebral blood flow that is necessary to deliver oxygen and nutrients to the brain: ischaemia and haemorrhage.

Ischaemic strokes are caused by a lack of blood flow and haemorrhage is caused by excess of blood outside the blood vessels leading to compression of surrounding tissue. In approximately 80% of stroke the cause is ischaemic in nature and the resulting 20% is haemorrhagic. In this dissertation, we focused on (the prevention of) ischaemic strokes.

Some fifteen to twenty percent of ischaemic strokes are related to carotid stenosis and another fifteen to twenty percent to atrial fibrillation (AF), the most common cardiac arrhythmia. In both cases, blood clots are formed that block access to particular regions of the brain. Strokes related to carotid stenosis and AF tend to be more disabling and fatal compared with other ischaemic stroke subtypes. The risk of stroke recurrence is also higher with these stroke subtypes.

Prevention strategies to reduce the stroke risk in patients with carotid stenosis or AF are well established, but many people with these conditions go undetected. Ischaemic stroke might even be the first manifestation of these conditions. This led to an interest in screening to detect carotid stenosis and AF. Early detection. This allows the initiation or intensification of prevention strategies to optimise modifiable risk factors.

The most rigour and simple approach to screening is systematic screening of the population. This will identify all people with the conditions, but it will also bring about many false-positive and false-negative cases. In addition, the costs of systematic screening are high, and it is presumably not the most efficient way to use available health resources. This is the reason that screening for carotid stenosis is currently not recommended. The yield is screening is too low due to the low prevalence of carotid stenosis in the population. Screening for atrial fibrillation is recommended in people aged 65 and older by pulse palpation following by an electrocardiogram if an irregular pulse is found. This is a type of targeted screening where age is used as selection criterion.

In the **first part** of this dissertation, we have assessed published risk prediction models and developed novel risk prediction models to detect carotid stenosis. These risk prediction models use multiple predictors, such as age and sex, but also medical history, physical and blood measurements, to estimate the risk of carotid stenosis. This risk estimation can be used to target screening to people at high risk. A targeted screening is more efficient, more cost-effective, and will bring about less false-positive and false-negative cases.

It is important that the predictions are accurate. The risk prediction model should be able to discriminate between with and without carotid stenosis and the predicted risks should concord the observed risks. If for example, the risk prediction model overestimates the risks, the yield of screening will be lower than anticipated if applied in practice. Accurate predictions are a necessary condition for targeted screening.

In **Chapter 2**, we have searched the literature for published risk prediction models to detect asymptomatic carotid stenosis in the population and we validated them in a contemporary large population of 600,000 people who underwent screening. We identified six models of which two showed accurate predictive performance and could be used to identify individuals at high risk reliably. In **Chapter 3**, we developed a novel risk prediction model by adding new predictors and we were able to improve the yield of targeted screening. If this novel risk prediction model were to be used for a targeted screening programme to screen individuals in the highest decile of risk only, the number of people that need to be screened to detect one individual with carotid stenosis was decreased a fourfold compared with systematic screening of the population. Such a targeted screening would identify around 40% of all cases with carotid stenosis.

It is known that certain patients have a higher risk of carotid stenosis, for example patients with peripheral arterial disease. Their overall risk of carotid stenosis is higher compared with the general population. In **Chapter 4**, we developed a novel risk prediction model to detect asymptomatic carotid stenosis in patients with peripheral arterial disease. We found that the risk of asymptomatic carotid stenosis could be predicted reliably, and the yield of screening would be higher compared with targeted screening of patients without peripheral arterial disease.

In the **second part** of this dissertation, we shifted our attention to AF. Individuals who are overweight or obese are at higher of AF. A commonly used measure of adiposity is body mass index (BMI), but other measures are also available. One of them is waist circumference, a measure of central or abdominal adiposity. This measure has received less attention than BMI yet may provide additional information on the risk of AF. It is currenly unclear whether the risk of AF varies across different measures of adiposity and between sexes.

In **Chapter 5**, we found a positive association between BMI and AF (above 20 kg/m^2), and between WC and AF in both men and women. When performing analyses by sex, we found that BMI seems a more informative measure about risk of AF in women and WC seems more informative in men.

In **Chapter 6**, we search the literature for risk prediction models to detect AF and assessed their predictive performance in a population of 2.5 million people who underwent screening and in whom 10,464 AF was found. We found 14 risk prediction models to detect AF, all of which outperformed an age threshold of 65 years. The risk prediction models that were originally developed to detect AF performed better than model originally developed for the treatment of AF (such as $CHADS_2$ and CHA_2DS_2-VASc). We assessed whether $CHADS_2$ and CHA_2DS_2-VASc could also be used to detect AF, because that offers the possibility of using a single score for prediction of AF diagnosis and risk stratification of outcomes, such as stroke or systemic thromboembolism.

Two risk prediction models showed reliable predictions of the risk of AF. If these models were to be used to targeted screening programme to screen individuals in the highest decile of risk only, the number of people that need to be screened to detect one individual with AF was decreased a fourfold compared with systematic screening of the population. Such a targeted screening would identify 39% of all cases with AF.

In the **third part**, we determined the yield and accuracy of targeted screening for AF and carotid stenosis following cardiovascular risk stratification. Cardiovascular risk stratification aims to reduce the incidence of cardiovascular disease (CVD) in individuals without manifestations of CVD by optimizing modifiable risk factors. These prevention strategies overlap partly with prevention

strategies in patients with AF or carotid stenosis, but these latter patients are by definition at high risk of CVD and additional disease-specific preventive interventions.

In **Chapter 7**, we showed that targeted screening of AF and carotid stenosis following cardiovascular risk stratification showed a higher prevalence of AF and carotid stenosis in those at higher risk of CVD. In addition, the risk of AF-related complications, such as ischaemic stroke and thrombo-embolism, in was higher cases at high risk of CVD, suggesting that those in whom AF is detected by targeted screening might achieve the highest reduction in absolute CVD risk by improving primary prevention strategies.

A carotid intervention to remove the stenosis might further reduce the risk of stroke in some patients with carotid stenosis, but the net benefit of prevention in part depends on procedural hazards. In the **fourth part**, we investigated ways to reduce the risk of procedural complications after carotid revascularisation.

In **Chapter 8**, we pooled the results of 87 studies on the association between operator and hospital volume on outcomes after carotid endarterectomy (CEA) and carotid artery stenting (CAS). We showed that high operator volume and high hospital volume are possibly two of the most important determinants of procedural hazards after CEA. Although the current available evidence did not allow to provide a quantified volume threshold, it indicates that centralisation of operative care will lead to better outcomes after CEA.

In **Chapter 9**, we determined whether operator speciality was also associated with outcomes after CEA and CAS. We found 35 studies, but most studies did not assess the relationship reliably and were at high risk of bias hampering to restricted CEA or CAS to specific specialities.

To further reduce the risk of procedural stroke or death, it is necessary to analyse when and how procedural complications might be prevented. In **Chapter 10**, we assessed the frequency and timing of procedural complications after CEA for asymptomatic carotid stenosis. At least half of the procedural strokes in this study were ischaemic and ipsilateral to the treated artery. Half of all procedural complications occurred on the day of CEA, but one-third after day 3 when most patients have been discharged. It stresses the need for methods to reduce procedural complications after discharge and clear instructions to patients when they experience a procedural complication.

In **Chapter 11**, we searched the literature for risk prediction models to select patients for CEA based on the predicted risk of procedural stroke or death. To determine the predictive performance of such models, we validate the models in a dataset of 26,293 patients who underwent CEA in the United States. We assessed 17 models and found that most models were not able to predict the risk of procedural stroke or death reliably. One model, however, developed in the Ontario Carotid Endarterectomy Registry (OCER) showed reasonable predictive performance. This model used symptomatic status, diabetes mellitus, heart failure and contralateral occlusion as predictors.

When we restricted the analyses to 11,035 symptomatic and 14,772 asymptomatic patients, we found that the OCER model was again most reliable. This model identified 508 (4.6%) symptomatic and 306 (2.1%) asymptomatic patients who had a predicted risk of procedural stroke or death that exceeded currently recommended thresholds. The OCER risk model can therefore inform patients about procedural hazards and help focus CEA toward patients who would benefit most from it.

The studies in this dissertation aimed to reduce stroke incidence by improving primary and secondary prevention strategies for AF and carotid stenosis-related ischaemic stroke. To enable primary prevention strategies, we assessed targeted screening approach for early detection of AF and carotid stenosis. In patients in whom carotid stenosis (that has caused a stroke or that has not yet caused a stroke) is detected, we showed ways to improve the net clinical benefit of carotid revascularisation.

Samenvatting in Nederlands

Elk jaar krijgen in Nederland 50,000 patiënten een beroerte, ook wel een cerebrovasculair accident (CVA) genoemd. Een ingrijpende gebeurtenis in het leven van mensen. Op dit moment zijn er 300,000 mensen in Nederland die leven met de gevolgen van een CVA. Er bestaan verschillende typen CVA. De belangrijkste zijn: een herseninfarct (in ongeveer 80% van de gevallen) en een hersenbloeding (in ongeveer 20% van de gevallen). Deze dissertatie richt zich op herseninfarcten.

Een herseninfarct is een afsluiting van een belangrijk bloedvat dat de hersenen van bloed voorziet. Hierdoor krijgt het gedeelte van het hersenweefsel dat achter de afsluiting ligt onvoldoende bloedtoevoer. Dit heeft tot gevolg dat er tekort is aan zuurstof optreedt in de hersenen.

Deze afsluiting van het bloedvat naar de hersenen is meestal het gevolg van een bloedpropje. Dit propje wordt veelal elders in de bloedvaten gevormd en wordt met de bloedstroom vervoerd naar de hersenen. De vorming van dit propje kan komen door een afwijkend hartritme (boezemfibrilleren) of door langzame vernauwing van de halsslagaderen (aderverkalking). We hebben ons gericht op patiënten met herseninfarcten die veroorzaakt worden door vernauwing van de voorste halsslagaders of door een afwijkend hartritme. Patiënten met deze condities hebben een verhoogd risico op het krijgen van een herseninfarct.

Het is mogelijk bij patiënten met boezemfibrilleren of halsslagadervernauwing het risico op een herseninfarct te verlagen. Dit wordt preventie genoemd. Om tot preventie over te gaan moet eerst vastgesteld worden dat mensen een van deze twee aandoeningen hebben, want veelal geven ze geen klachten voordat ze een herseninfarct veroorzaken. Dit kan door middel van screening.

De meest eenvoudige en grondige vorm van screening is het screening van de volledige populatie. Het voordeel is dat alle gevallen worden gedetecteerd, maar het nadeel is dat veel patiënten onterecht als negatief (vals negatief) en positief (vals positief) worden aangemerkt. Daarnaast brengt het hoge kosten en veel gebruik van beschikbare middelen met zich mee. Op dit moment wordt screening op halsslagadervernauwing daarom niet aanbevolen. De opbrengt van een dergelijke screening is te laag omdat te weinig mensen de aandoening hebben. Screening op boezemfibrilleren wordt wel aangeraden bij patiënten boven de 65 jaar door de pols te nemen en indien het ritme onregelmatig is wordt een hartfilmpje (ECG) gemaakt om vast te stellen of er daadwerkelijk boezemfibrilleren is. Dit is een vorm van selectieve screening, waarbij de leeftijd als criterium wordt genomen.

In het **eerste deel** van deze dissertatie hebben we gezocht naar voorspelmodellen die voorspellen of mensen een halsslagadervernauwing hebben. Deze voorspelmodellen gebruiken meerdere karakteristieken van patiënten zoals leeftijd en geslacht, maar ook informatie uit de medische voorgeschiedenis en bloedonderzoek en geven op basis van deze informatie een personaliseerde risicoschatting. Deze risicoschatting kan gebruikt worden om selectief patiënten te screening waarvan het voorspelmodel aangeeft dat het om een hoog risicopatiënt gaat. Een selectieve screening heeft als voordeel dat het effectiever en daarmee goedkoper is en er minder mensen een vals positieve of vals negatieve uitslag krijgen.

Belangrijk is uiteraard wel dat het voorspelmodel accuraat is. Het moet goed onderscheid kunnen maken met mensen met en mensen zonder een halsslagadervernauwing en het voorspelde risico moet overeenkomen met het risico in de te screenen populatie. Als het voorspelmodel de risico

bijvoorbeeld overschat, zal de opbrengst van screening lager uitvallen dan verwacht en vice versa. Accurate voorspellingen zijn dus een noodzakelijke voorwaarde voor een selectieve screening.

In **hoofdstuk 2** van deze dissertatie hebben we gezocht naar eerder gepubliceerde voorspelmodellen om halsslagadervernauwing te detecteren en gekeken hoe goed de voorspellingen uitpakten in een grote hedendaagse populatie van 600,000 patiënten die een screening hebben ondergaan. We vonden zes modellen waarvan er twee accurate voorspellingen deden. Toch bleef de opbrengst van selectieve screening van hoog risicopatiënten beperkt. In **hoofdstuk 3** hebben we daarom een nieuw voorspelmodel ontwikkeld en hebben we extra voorspellers toegevoegd. De opbrengst van selectieve screening op halsslagadervernauwing konden we daarmee verbeteren. Wanneer met behulp van dit nieuwe voorspelmodel een selectief screeningprogramma wordt opgezet waarbij enkel de 10% hoogste risicopatiënten wordt gescreend, zal het aantal patiënten dat gescreend moet worden om één nieuwe patiënt met halsslagadervernauwing te detecteren een viervoud lager liggen ten opzichte van een systematische screening van de gehele populatie. Bij een dergelijk selectief screeningsprogramma zal ongeveer 40% van alle patiënten met halsslagadervernauwing worden gevonden.

Het is bekend dat er bepaalde patiënten zijn die een extra hoog risico hebben op halsslagadervernauwing. Een bekende groep zijn patiënten met slagadervernauwing van de benen (perifeer arterieel vaatlijden). In deze groep ligt het risico een stuk hoger dan in de populatie. Toch heeft ook niet iedere patiënt met perifeer arterieel vaatlijden hetzelfde risico op een halsslagadervernauwing. In **hoofdstuk 4** beschrijven we daarom de ontwikkeling van een voorspelmodel om te kijken welke patiënten met perifeer arterieel vaatlijden een hoog risico hebben op een halsslagadervernauwing. De opbrengst van selectieve screening in deze specifieke groep patiënten bleek nog hoger te zijn dan selectieve screening van patiënten zonder perifeer arterieel vaatlijden.

In het **tweede deel** van deze dissertatie richten we ons op boezemfibrilleren. Het is bekend dat boezemfibrilleren vaker voorkomt bij patiënten met overgewicht. Om overgewicht vast te stellen, wordt vaak body mass index (BMI) of Quetelet index gebruikt. Dit wordt berekend door het gewicht in kilogrammen te delen door het kwadraat van de lengte in meters. Er zijn echter ook andere methoden om overgewicht vast te stellen. Een daarvan is het meten van de buikomvang. Eerder onderzoek heeft laten zien dat buikomvang vooral schadelijk is bij mannen en in mindere mate bij vrouwen. Het is echter onduidelijk welke van de twee methoden het best het risico op boezemfibrilleren kan voorspellen en of deze man-vrouw verschillen ook belangrijk zijn wanneer het gaat om het risico op boezemfibrilleren.

In **hoofdstuk 5** hebben we laten zien dat zowel BMI als buikomvang voorspellers zijn voor het risico op boezemfibrilleren. Dit effect was iets meer uitgesproken voor buikomvang dan voor BMI wanneer we alle patiënten samen analyseerden. Wanneer mannen en vrouwen echter apart geanalyseerd werden, zagen we dat buikomvang bij mannen en BMI bij vrouwen een betere risico-inschatting gaf.

Daarna hebben we **in hoofdstuk 6** gekeken of er ook voorspelmodellen voor boezemfibrilleren gepubliceerd zijn en hebben we bepaald hoe accuraat de voorspellen zijn door deze modellen toe te passen op een populatie van 2,5 miljoen mensen die een screening ondergingen waarvan er 10,464 (0.41%) boezemfibrilleren hadden. We vonden 14 gepubliceerde voorspelmodellen die allemaal betere voorspellingen deden dat het aanbevolen leeftijdscriterium. De voorspelmodellen die specifiek voor de detectie van boezemfibrilleren waren ontwikkeld, voorspelden beter dan voorspelmodellen die ontwikkeld waren voor de behandeling van boezemfibrilleren (zoals de $CHADS_2$ en CHA_2DS_2-VASc). Dat laatste werd onderzocht om te kijken of een selectieve

screening op boezemfibrilleren toegepast kon worden op patiënten die vervolgens ook behandeld dienen te worden met bloedverdunners.

We vonden dat de twee beste voorspelmodellen accuraat konden voorspellen wie er een hoog risico heeft op boezemfibrilleren. Wanneer met behulp van deze voorspelmodellen een selectief screeningsprogramma wordt opgezet waarbij enkel de 10% hoogste risicopatiënten wordt gescreend, zal het aantal patiënten dat gescreend moet worden om één nieuwe patiënt met boezemfibrilleren te detecteren een viervoud lager liggen ten opzichte van een systematische screening van de gehele populatie. Bij een dergelijk selectief screeningsprogramma zal 39% van alle patiënten met aanwezige boezemfibrilleren worden gevonden.

In het **derde deel** hebben we onderzocht of screening op halsslagadervernauwing en boezemfibrilleren gecombineerd kan worden met het cardiovasculair risicomanagement dat doorgaans door huisartsen wordt gedaan. Cardiovasculair risicomanagement heeft als doel het opsporen van patiënten met een hoog risico op het ontwikkelen van hart- en vaatziekten om preventieve maatregelen te kunnen nemen. Deze preventieve maatregelen overlappen voor een deel met de maatregelen bij halsslagadervernauwing en boezemfibrilleren, maar patiënten met deze laatste twee aandoeningen hebben per definitie een hoog risico op hart- en vaatziekten en aanvullende preventieve maatregelen zijn doorgaans nodig.

In **hoofdstuk 7** bleek dat patiënten met een hoog risico op hart- en vaatzieken ook een hoog risico hadden op halsslagadervernauwing of boezemfibrilleren. De opbrengst van selectieve screening op basis van het vastgestelde risico op hart- en vaatzieken bleek hoger dan screening van de gehele populatie. Tevens bleek dat het voorspelde risico op een herseninfarct hoger was bij patiënten die tevens een hoog risico op hart- en vaatziekten hadden. Dit betekent dat screening van deze patiënten ook de meeste potentie biedt om door middel van preventie risico's te verlagen.

De preventieve maatregelen bij patiënten met halsslagadervernauwing en boezemfibrilleren bestaan uit levensstijladviezen (stoppen met roken, afvallen, gezond dieet), medicamenteuze behandeling (cholesterolverlagende medicatie, bloeddrukverlagende medicatie en bloedverdunners). In sommige gevallen wordt er een aanvullende interventie gedaan om de halsslagadervernauwing op te heffen (carotis desobstructie). Bij alle preventieve maatregelen moet een afweging gemaakt worden tussen het beoogde effect en mogelijke bijwerkingen. Het beoogde doel is het voorkomen van een herseninfarct, maar de behandeling met bloedverdunner brengt het risico van een bloeding met zich mee en een interventie de risico's van de operatie. Tijdens de operatie kan men een herseninfarct ontwikkelen of zelfs overlijden. In het **vierde deel** hebben we onderzocht hoe complicaties van de operatie zo laag mogelijk gehouden kunnen worden.

In **hoofdstuk 8** hebben we onderzocht of operatieve risico's lager zijn wanneer patiënten door chirurgen worden geopereerd die veel van dergelijke operaties doen of in ziekenhuizen worden behandeld die deze operaties vaak uitvoeren. Hiervoor hebben we resultaten van 87 gepubliceerde studies samengevoegd om het gemeenschappelijke effect te kunnen bepalen. We vonden dat zowel de hoeveelheid operaties van de chirurg als de hoeveelheid operaties dat in het ziekenhuis wordt verricht van zeer groot belang is om de operatieve risico's te verminderen. Het bleken zelfs twee van de sterkste voorspellers.

In **hoofdstuk 9** werd gekeken of de specialisatie van de chirurg eveneens een belangrijke rol speelt. Hier konden we in de 35 gepubliceerde studies geen aanwijzingen voor vinden, maar werd ook niet duidelijk dat er geen verband was. Er waren simpelweg te weinig betrouwbare gegevens beschikbaar om dit met zekerheid vast te kunnen stellen.

Om het risico op een operatieve beroerte of overlijden te kunnen verlagen, is het belangrijk inzicht te hebben wanneer deze operatieve complicaties optreden. Dit is ook belangrijk om patiënten na de operatie veilig met ontslag te kunnen laten gaan. In **hoofdstuk 10** hebben we gekeken wanneer complicaties optraden en van wat voor type beroertes er sprake was. We zagen dat de meeste beroertes herseninfarcten waren die optraden aan de kant waar de operatie had plaatsgevonden. Ongeveer de helft vond plaats op de dag van de operatie, maar een derde vond plaats na dag 3 wanneer de meeste met ontslag zijn. Deze analyse benadrukt het belang van het instellen van patiënten op de juiste medicatie en heldere instructies aan patiënten bij ontslag hoe te handelen bij tekenen van een beroerte.

In **hoofdstuk 11** hebben we gezocht naar gepubliceerde voorspelmodellen die het risico op operatieve complicaties voorspellen bij patiënten die een carotis desobstructie ondergingen. We hebben gekeken hoe accuraat de voorspellingen waren in een hedendaagse dataset van 26,293 patiënten die in Amerika behandeld waren. We hebben in totaal 17 voorspelmodellen vergeleken en vonden dat de bruikbaarheid veelal beperkt was. Wel was er één model (ontwikkeld in de Ontario Carotid Endarterectomy Registry [OCER]) dat betrouwbaar kon voorspellen welke patiënten een laag en welke patiënten een hoog risico op operatieve complicaties hebben. Dit model gebruikte symptomatische status (dat is of de halsslagadervernauwing de afgelopen zes maanden een TIA of herseninfarct veroorzaakt heeft), suikerziekte (diabetes mellitus), hartfalen en volledige afsluiting van de niet geopereerde halsslagader als voorspellers.

Ook wanneer we aparte analyses uitvoerden voor 11,035 symptomatische en 14,772 asymptomatische patiënten kwam hetzelfde model als beste naar voren. Deze laatste analyses lieten zien dat het model betrouwbaar 508 (4.6%) symptomatische en 306 (2.1%) asymptomatische patiënten kon identificeren die een voorspeld operatief risico hadden boven de aanbevolen drempelwaarde in hedendaagse richtlijnen van 6% bij symptomatische en 4% bij asymptomatische patiënten.

De studies die ten grondslag liggen aan deze dissertatie hebben als doel het voorkómen van herseninfarcten die veroorzaakt worden door halsslagadervernauwing of boezemfibrilleren door het optimaliseren van primaire en secundaire preventiestrategieën. Om primaire preventie te kunnen verbeteren hebben we de mogelijkheid van selectieve screening op halsslagadervernauwing en boezemfibrilleren onderzocht om zo deze condities in een vroeg stadium te detecteren. In patiënten bij wie een halsslagadervernauwing (die een herseninfarct veroorzaakt heeft of dat nog niet gedaan heeft) is gedetecteerd, hebben we gekeken naar manieren waarop we de effectiviteit van operatieve behandeling konden verbeteren.

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Michiel

List of publications

This thesis:

1. **Poorthuis MHF**, Halliday A, Massa MS, Sherliker P, Clack R, Morris DR, Clarke R, de Borst GJ, Bulbulia R, Lewington S. Validation of Risk Prediction Models to Detect Asymptomatic Carotid Stenosis. *Journal of the American Heart Association.* 2020;9(8):e014766.
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Other publications:

11. Harris, L, **Poorthuis MHF**, Grover P, Kitchen N, Al-Shahi Salman R. Surgery for cerebral cavernous malformations: A systematic review and meta-analysis.
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1. Högberg D. Asymptomatic Carotid Stenosis: The Silent Threat. *European Journal of Vascular and Endovascular Surgery.*

2. Guerra F, Stronati G. Risk prediction models in atrial fibrillation: from theory to practice. *European Journal of Preventive Cardiology.*

3. Wee IJY. Comment on "Problems With Investigating the Association Between Operator Volume, Hospital Volume, and Outcomes of Carotid Revascularization" *Ann Surg*. 2019;270(2):e50.

   Reply: Poorthuis MHF, Brand EC, Bulbulia R, Halliday A, Bots ML, de Borst GJ. Response to Comment on "High Operator and Hospital Volume are Associated With a Decreased Risk of Death and Stroke Following Carotid Revascularization: A Systematic Review and Meta-analysis: Authors' Reply" *Ann Surg*. 2019;270(2):e50-e51.

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5. Lynch TG. All politics is local. *J Vasc Surg* 2020;72(1):344-345.

Curriculum vitae

Michiel Poorthuis was born in Hilversum, the Netherlands. He graduated from the secondary school Comenius College in Hilversum (Gymnasium, *cum laude)* in 2008 and started medical school at Utrecht University. From his second year onward, he started a second study, philosophy, at Utrecht University. To pursue his interest in contemporary continental philosophy, he continued his studies in philosophy at the Institute of Philosophy of the University of Leuven, Belgium, where he obtained his B.A., M.A., and M.Phil. (all *magna cum laude)*.

Michiel gained interest in medical research early during his medical studies. He worked as a student-researcher at the department of neurology (supervisors: prof. Rinkel, prof. Klijn and prof. Kappelle) and vascular surgery (supervisor: prof. de Borst) of the University Medical Center Utrecht. His first research project was a collaborative work with the University of Edinburgh (prof. Al-Shahi Salman) and focused on cerebral cavernous malformations. For this research project, Michiel was visiting researcher in Edinburgh twice and this work was awarded the Investigator Award of the European Stroke Conference for excellent research in cerebrovascular disease in 2014.

After graduating from medical school, Michiel started as resident not in training (ANIOS) at the department of neurology of the Tergooi Ziekenhuizen in Blaricum (supervisor: dr. de Kruijk). After one and a half year of clinical work, he started to work as a Ph.D. student at Utrecht University (supervisors prof. de Borst) in collaboration with the Nuffield Department of Population Health of the University of Oxford, United Kingdom (supervisors: prof. Halliday and mr. Bulbulia) focussing on the detection of carotid stenosis and atrial fibrillation and the treatment of carotid stenosis to prevent ischaemic strokes. The results of this scrutiny of optimising primary and secondary prevention strategies of ischaemic strokes are presented in the present dissertation. His work was awarded the best e-Poster presentation at the 33rd conference of the European Society of Vascular Surgery and the best poster / short communication award at the 9th Munich Vascular Conference.

Michiel started as a resident not in training (ANIOS) at the department of neurology of the University Medical Center Utrecht after he finished his Ph.D. He hopes to combine clinical work and research in (cerebrovascular) neurology in the future.