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Improving secondary prevention after transient ischaemic attack (TIA) or ischaemic stroke

Marion Boulanger

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Normandie Université

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE

Préparée au sein de l'Université de Caen Normandie

Amélioration de la prévention secondaire après un infarctus cérébral ou un accident ischémique transitoire (AIT).

**Présentée et soutenue par
Marion BOULANGER**

**Thèse soutenue publiquement le 10/12/2019
devant le jury composé de**

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Normandie de Biologie Intégrative,
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PUBLICATIONS AND PRESENTATIONS

The work in this thesis has led to the following publications and presentations:

Publications

Boulanger M, Béjot Y, Rothwell PM, Touzé E. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischaemic attack and ischaemic stroke: systematic review and meta-analysis. *J Am Heart Assoc.* 2018 Jan 18;7:e007267. DOI: 10.1161/JAHA.117.007267

Boulanger M, Li L, Lyons L, Lovett NG, Kubiak MM, Silver L, Touzé E, Rothwell PM on behalf of the Oxford Vascular Study. Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke. *Neurology.* 2019; 93:e1-e13. doi:10.1212/WNL.0000000000007935

Boulanger M, Li L, Lyons L, Lovett NG, Kubiak MM, Silver L, Touzé E, Rothwell PM on behalf of the Oxford Vascular Study. Essen risk score in prediction of myocardial infarction after TIA or ischaemic stroke without prior coronary artery disease. *Stroke* (accepted)

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*equal contribution

Presentations

Boulanger M, Li L, Silver L, Touzé E, Rothwell PM. Subgroups of TIA and ischaemic stroke patients with a high residual risk of coronary events: population-based cohort study Presented for the European Stroke Organisation Conference 2018

Boulanger M, Li L, Lyons L, Lovett NG, Kubiak MM, Silver L, Touzé E, Rothwell PM on behalf of the Oxford Vascular Study. Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke: prospective population-based cohort Presented for the European Stroke Organisation Conference 2019

PUBLICATIONS AND PRESENTATIONS

Boulanger M, Luengo-Fernandez R, Lukha R, Li L, Lyons L, Lovett NG, Kubiak MM, Silver L, Touzé E, Rothwell PM on behalf of the Oxford Vascular Study. Long-term cost of myocardial infarction during follow-up after transient ischaemic attack or ischaemic stroke.

Presented for the European Stroke Organisation Conference 2019

Boulanger M, Li L, Touzé E, Rothwell PM. Risque d'évènement coronarien, récurrence d'infarctus cérébral et saignement majeur après infarctus cérébral ou AIT selon la présence de maladie vasculaire concomitante

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Book chapters

Chapitre sur la prise en charge aiguë d'un infarctus cérébral et d'une hémorragie cérébrale pour l'ouvrage collectif Principes et protocoles en neuro-anesthésie-réanimation, coordonné par C. Gakuba et F. Verdonk (2019) à destination des réanimateurs et urgentistes prenant en charge des patients avec un AVC

Chapitre sur la lecture critique des essais thérapeutiques de phase aiguë et de prévention secondaire pour l'ouvrage collectif Thérapeutique des AVC, coordonné par J.-L. Mas et D. Leys (2018), à destination des neurologues et tous médecins prenant en charge des patients avec un AVC

Chapitre sur la dysplasie musculaire comme causes rares d'AVC pour l'ouvrage collectif Thérapeutique des AVC, coordonné par J.-L. Mas et D. Leys (2018)

GENERAL ABSTRACT

Background.

The current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke is not well known. Previous studies suggest that TIA/ischaemic stroke patients are at substantial risk of long-term recurrent stroke and cardiac events despite secondary prevention management; and that the cause of death after TIA/ischaemic stroke is more often due to coronary events than to recurrent stroke. However, secondary prevention has improved over time and whether absolute risks and high-risk subgroups of patients on current care remain the same as those previously identified is uncertain. Therefore, I aimed to (1) determine the current long-term absolute risks of recurrent stroke and coronary events after TIA or ischaemic stroke and (2) identify individuals who remain at high absolute risk of recurrent ischaemic events despite current secondary prevention management.

Methods and main findings

In a systematic review and meta-analysis of long-term follow-up of studies of TIA or ischaemic stroke patients to determine the risk of myocardial infarction and recurrent stroke after TIA/ischaemic stroke, we showed that the risk of death due to myocardial infarction was not higher than the risk of death due to recurrent ischaemic stroke. The risk of myocardial infarction after TIA/ischaemic stroke has significantly decreased over time since 1970s while the risk of recurrent stroke has not.

In a population-based cohort of consecutive TIA or ischaemic stroke patients in Oxfordshire, UK (Oxford Vascular study, OXVASC) recruited from 2002 to 2014 (n=2,555), the current overall 10-year absolute risk of recurrent ischaemic stroke was 25.3% (95%CI 22.6-27.8) and the 10-year risk of coronary events was 10.6% (95%CI 8.8-12.4). For 2002-2014, the risks of recurrent ischaemic stroke and coronary events have significantly decreased over time. These time trends were independent of any change in vascular risk factors over the study period. TIA/ischaemic stroke patients with co-existing cardiovascular disease, i.e. history of prior coronary or peripheral artery disease, (n=640; 25.0%) were at significantly increased risk of recurrent ischaemic stroke than those without (10-year risk=31.5%, 95%CI 25.1-37.4; versus 23.4%, 20.5-26.3; p=0.0049) and coronary events (10-year risk=22.8%, 17.4-27.9; versus 7.1%, 5.3-8.8; p<0.001).

Then, I determined whether the Essen risk score, which is a simple clinical score to predict the 1-year risk of recurrent ischaemic stroke, identified a subset of patients without prior coronary artery disease who had nevertheless a high risk of myocardial infarction despite current secondary prevention management. The 10-year risk of myocardial infarction in TIA/ischaemic stroke patients without prior coronary artery disease (n=2017; 78.9%) ranged from 0.9% (0-

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1.9) at Essen score ≤ 1 to 29.8% (7.7-46.6) in those with a score ≥ 5 (c-statistic=0.6, 95%CI 0.57-0.71, $p < 0.001$). Among TIA/ischaemic stroke patients without prior coronary artery disease, those with an Essen score of ≥ 4 ($n=294$; 11.5%) were at similarly high 10-year risk of myocardial infarction as patients with prior coronary artery disease (17.2%, 6.9-26.3; versus 16.9%, 11.5-22.0) and of recurrent ischaemic stroke (40.4%, 26.7-51.6; versus 32.4%, 25.2-38.8). Among patients with non-cardioembolic TIA/ischaemic stroke and after exclusion of those on anticoagulants (i.e. on antiplatelet therapy for secondary prevention), the 10-year risk of major extracranial bleeds was high in patients with prior coronary artery disease (12.5%, 6.1-18.4) and in those without prior coronary artery disease and with an Essen score of ≥ 4 (20.7%, 0-37.9).

Eventually, I determined the cost of myocardial infarction after TIA/ischaemic stroke and the likely long-term myocardial infarction-related cost saving from routine co-prescription with new lipid-lowering therapies, PCSK-9 inhibitors, for secondary prevention. The total mean (SD) cost of myocardial infarction was \$9182 (12,757). The 10-year mean cost of myocardial infarction averaged across all patients was \$424 (95%CI 333-525) per patient. The corresponding costs of routine life-long co-prescription of PCSK-9 inhibitors were \$34,767 (33,968-35,679) per patient. Myocardial infarction treatment costs were higher in those with prior coronary (\$787 per patient, 493-1151; versus \$326, 234-434, $p=0.009$) or peripheral artery disease (\$893 per patient, 440-1472; versus \$386, 288-496, $p=0.05$). Cost of routine co-prescription of PCSK9-inhibitors remained over \$24,000 per patient in the subgroups at higher risk of myocardial infarction.

Discussion and perspectives

The overall absolute risks of recurrent ischaemic stroke and coronary events after TIA/ischaemic stroke have decreased over the last decade, and are likely to be explained by the improvement of secondary prevention over time. However, despite current secondary prevention, the subgroups of TIA/ischaemic stroke patients with prior coronary disease and those without prior coronary disease and with an Essen score of ≥ 4 remain at sufficiently high absolute risk of recurrent ischaemic events to justify more intensive treatment.

Compared to current secondary prevention therapies, future secondary prevention therapies would need to achieve a substantial absolute risk reduction to outweigh increased side effects or cost. Thus, in these high-risk subgroups, more intensive lipid-lowering therapies, in addition to statins, might be justified, but the total cost of with PCSK-9 inhibitors seems to exceed the generally accepted cost-effectiveness threshold while benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding.

RESUME GENERAL

Contexte.

Le pronostic à long-terme actuel après un accident ischémique transitoire (AIT) ou un accident vasculaire cérébral ischémique (AVCi, i.e. un infarctus cérébral) reste mal connu. Des études anciennes suggèrent que les patients ayant eu un AIT ou un infarctus cérébral sont exposés à un risque significatif à long-terme de récurrence d'infarctus cérébral et d'évènement coronarien aigu malgré le traitement de prévention secondaire, et que la cause de décès après un AIT/infarctus cérébral serait plus fréquemment due à un évènement coronarien aigu qu'à une récurrence d'infarctus cérébral. Cependant, la prévention secondaire après un AIT ou un infarctus cérébral s'est améliorée au cours du temps et si les risques absolus et les sous-groupes de patients considérés à haut risque de récurrence sous traitement actuel sont les mêmes que ceux identifiés antérieurement reste incertain. Ainsi, j'ai (1) déterminé les risques absolus actuels à long-terme de récurrence d'infarctus cérébral et d'évènement coronarien aigu après un AIT ou un infarctus cérébral et (2) identifié les individus qui restent à haut risque absolu de récurrence ischémique malgré la prévention secondaire actuelle.

Méthodes et principaux résultats

J'ai d'abord réalisé une revue systématique et une méta-analyse des études incluant des patients ayant eu un AIT ou un infarctus cérébral avec un suivi à long-terme pour déterminer le risque d'infarctus du myocarde et de récurrence d'AVC après un AIT/infarctus cérébral. Le risque de décès dû à un infarctus du myocarde n'était pas augmenté par rapport au risque de décès dû à une récurrence d'AVC. Le risque d'infarctus du myocarde après un AIT/infarctus cérébral a significativement diminué au cours du temps depuis les années 1970 tandis que le risque de récurrence d'AVC n'a pas évolué significativement au cours du temps. Cependant, peu d'études ont recruté des patients après les années 2000 et la prévention secondaire après un AIT/infarctus cérébral s'est améliorée dans les dernières décennies, notamment avec l'utilisation de dose plus élevée de statines et un meilleur contrôle de la pression artérielle.

Dans une cohorte populationnelle contemporaine de patients consécutifs ayant eu un AIT ou un infarctus cérébral (Oxford Vascular study, OXVASC) entre 2002 et 2014 (n=2225), le risque absolu à 10ans de récurrence d'infarctus cérébral était de 25.3% (IC95% 22.6-27.8) et le risque à 10ans d'évènement coronarien aigu était de 10.6% (IC95% 8.8-12.4). Entre 2002 et 2014, les risques de récurrence d'infarctus cérébral et d'évènement coronaire aigu ont significativement diminué au cours du temps. La diminution des risques au cours du temps

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n'était pas liée au changement de la prévalence des facteurs de risque vasculaires durant la période d'étude.

Ensuite, j'ai déterminé si les sous-groupes de patients ayant eu un AIT/infarctus cérébral avec une pathologie cardiovasculaire associée (i.e. un antécédent de pathologie coronarienne ou ischémique des membres inférieures) étaient toujours à haut risque résiduel de récurrence d'événements ischémiques malgré la prise en charge actuelle, et pourraient bénéficier d'une prévention secondaire plus intensive. Les patients avec une pathologie cardiovasculaire associée (n=640; 25.0%) avaient un risque significativement plus élevé de récurrence d'infarctus cérébral comparés aux patients sans pathologie cardiovasculaire associée (risque à 10ans=31.5%, IC95% 25.1-37.4; versus 23.4%, 20.5-26.3; p=0.0049) et d'événement coronarien aigu (risque à 10ans =22.8%, 17.4-27.9; versus 7.1%, 5.3-8.8; p<0.001).

Ensuite, j'ai déterminé si le score Essen, qui est un score clinique simple pour prédire le risque de récurrence d'infarctus cérébral à 1an, permettait d'identifier un sous-groupe de patients sans antécédent de pathologie coronarienne qui était néanmoins à haut risque d'infarctus du myocarde malgré la prévention secondaire actuelle. Le risque à 10ans d'infarctus du myocarde chez les patients sans antécédent de pathologie coronarienne (n=2017; 78.9%) variait de 0.9% (0-1.9) pour un score Essen ≤ 1 à 29.8% (7.7-46.6) pour un score ≥ 5 (c-statistic=0.6, IC95% 0.57-0.71, p<0.001). Parmi les patients sans antécédent de pathologie coronarienne, ceux avec un score Essen ≥ 4 (11.5%) avaient un risque absolu à 10ans d'infarctus du myocarde comparable aux patients avec un antécédent de pathologie coronaire (17.2% versus 16.9%) et de récurrence d'infarctus cérébral (40.4% versus 32.4%). Parmi les patients ayant eu un AIT/infarctus cérébral d'étiologie non cardioembolique et après exclusion des patients sous anticoagulants (i.e. sous traitement antiplaquettaire en prévention secondaire), le risque à 10ans d'hémorragie extracrânienne majeure était élevé chez les patients avec un antécédent de pathologie coronaire (12.5%, 6.1-18.4) et chez ceux sans antécédent de pathologie coronaire et avec un score Essen ≥ 4 (20.7%, 0-37.9).

Enfin, j'ai déterminé le coût moyen de la prise en charge d'un infarctus du myocarde à 10ans après un AIT/infarctus cérébral et calculé la potentielle réduction du coût liée à la co-prescription systématique en prévention secondaire d'un nouveau traitement hypocholestérolémiant ayant montré une réduction significative du risque d'infarctus du myocarde, les inhibiteurs de la PCSK-9, en association avec les statines. Le coût moyen de la prise en charge d'un infarctus du myocarde à 10ans après AIT/infarctus cérébral était de 424\$ (IC95% 333-525) par patient. Le coût moyen de la co-prescription systématique d'un inhibiteur de la PCSK-9 à 10ans après un AIT/infarctus cérébral était de 34767\$ (33968-35679) par patient. Le coût moyen de la prise en charge d'un infarctus du myocarde à 10ans était

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significativement plus élevé chez les patients avec un antécédent de cardiopathie ischémique (787\$ par patient, 493-1151; versus 326\$ par patient, 234-434, $p=0.009$) ou une artérite des membres inférieurs (893\$ par patient, 440-1472; versus 386\$ par patient, 288-496, $p=0.05$), du fait de leur risque d'infarctus du myocarde augmenté plutôt que d'un coût de traitement plus élevé. Chez ces sous-groupes de patients à haut risque, le coût moyen de la co-prescription systématique d'un inhibiteur de la PCSK-9 à 10ans restait >24000\$ par patient.

Discussion et perspectives.

Les risques absolus de récurrence d'infarctus cérébral et d'infarctus du myocarde après un AIT/infarctus cérébral ont significativement diminué au cours des dernières décennies, très probablement du fait de l'amélioration de la prévention secondaire avec le temps. Cependant, malgré la prévention secondaire actuelle les sous-groupes de patients ayant eu un AIT/infarctus cérébral avec un antécédent de pathologie coronarienne et ceux sans antécédent coronaire et avec un score Essen ≥ 4 restent à un risque absolu de récurrence d'évènement ischémique suffisamment élevé pour justifier d'une intensification du traitement. Par rapport aux thérapeutiques de prévention secondaire actuelles, les thérapeutiques de prévention secondaire futures nécessitent de permettre d'obtenir une réduction absolue du risque de récurrence d'évènement ischémique suffisante pour compenser un risque augmenté d'effets indésirables ou de surcoût. Chez ces sous-groupes de patients à haut risque de récurrence ischémique, une réduction plus intensive du taux de cholestérol avec les inhibiteurs des PCSK-9, en association avec les statines, paraît tout à fait justifiée, cependant le coût de ces traitements semble excéder la limite du rapport coût-efficacité généralement accepté tandis que le bénéfice d'une majoration du traitement antithrombotique semble contrebalancé par l'augmentation du risque hémorragique extracrânien.

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Background and rationale of this thesis

Stroke corresponds to “rapidly developing clinical signs of focal disturbance of cerebral function of vascular origin”,¹ 85% of strokes are ischaemic and 15% are haemorrhagic. Worldwide, stroke is the second cause of dementia, after Alzheimer’s disease, and the second cause of mortality, after ischaemic heart disease.^{2, 3} Noteworthy, stroke has remained the top two cause of death worldwide since 1990, although the absolute number of deaths due to stroke has increased by 26% between 1990 and 2013.³ Stroke is also the third most common cause of disability in the world, being the first cause of acquired disability in adults,³ and the proportional contribution of stroke-related disability and deaths due to stroke, compared with all diseases, is increasing.³ Worldwide, although the mortality due to stroke has decreased over time, the absolute number of people with a stroke and the stroke-related burden of stroke, is increasing.^{3, 4} The lifetime risk of stroke for adults (25 years of age and older) is substantial and was estimated to be approximately 25% in men and in women in 2016.⁵ Importantly, 90% of the global burden of stroke is attributable to modifiable risk factors, including unhealthy diet, tobacco smoking and metabolic factors (diabetes mellitus, hyperlipidaemia and high body mass index),⁶ highlighting the need to achieve a better control of these risk factors. Despite the decrease in the age-specific incidence of stroke in the high-income countries, the global burden of stroke is projected to increase in the next decades due to the ageing population and the worldwide rise in the prevalence of diabetes mellitus and obesity, especially in young adults.^{7, 8} Improvement of stroke prevention appears therefore essential.

Ischemic stroke and transient ischaemic attack (TIA) represent 85% of all strokes and are caused by an episode of neurologic dysfunction due to focal brain, spinal cord or retinal ischemia.¹ The global burden of ischaemic stroke has increased over time, with a 37% increase in the number of people with incident ischaemic stroke and a 18% increase in the ischaemic stroke-related disability between 1990 and 2010.⁹ The prevalence of ischaemic stroke in 2013, was 18.3 millions cases (8.7 millions in women and 9.6 millions in men), of whom 7.3 millions (40%) were adults aged less than 65 years.³ Conventionally, a TIA is distinguished from an ischaemic stroke on the basis of an arbitrary 24-hour cut-off for resolution of symptoms. Hence, a TIA is defined as an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or hematological disease.¹⁰ The recent definition considers TIA as a transient episode of

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neurological dysfunction caused by focal brain or retinal ischemia without evidence of acute infarction on brain imaging.¹¹ The issue with this latest definition is that distinction between TIA and ischaemic stroke very much depends on the type and the timing of the imaging performed. Computerized tomography (CT) scan has less sensitivity to brain infarction than magnetic resonance imaging (MRI) scan, especially in the first few hours, and small infarcts can be missed even at the later phase.¹² On the other hand, although MR scan can detect brain infarcts in the very acute stage of symptoms onset, the sensitivity may remain limited for small infarction, especially in the brain stem. Also, in some parts of the world (in less developed countries or in more rural part of developed countries), acute imaging is not available in clinical practice, which may well limit the generalizability of this tissue-based definition of TIA. Additionally, previous epidemiological studies reporting incidence, prevalence and prognosis of TIA or ischaemic stroke used the time-based definition of TIA and keeping the same definition over time will ease comparison of estimates between cohorts. In this thesis, I therefore used the conventional definition of TIA based on symptoms or signs lasting less than 24 hours.

The current short-term prognosis after ischaemic stroke remains poor, with 30-day mortality estimated to be 20% worldwide,⁹ while the longer-term outcome is also impaired, even in high income countries. Among TIA or ischaemic stroke survivors treated according to contemporary guidelines in the UK, approximately a third requires some help for daily activities at 3 months and 1 year,¹³ while a quarter developed dementia within 1 year after TIA/ischaemic stroke, with the incidence of dementia being 10 times higher than in non-stroke population.¹⁴ Additionally, patients commonly suffer from psychological disorders after TIA or ischaemic stroke, that also contribute to a reduction in their independence. Stroke-related disabilities have major economic and social impacts for ischaemic stroke patients, as well as for caregivers or patients' family, with less than half of the patients returning to work after the ischaemic stroke,¹⁵ even among young patients.¹⁶ In addition, despite secondary prevention management, patients are exposed to long-term disability and morbidity,¹⁷ even those with less severe stroke. Indeed, the long-term mortality after TIA and minor ischaemic stroke is higher than in people without a stroke.¹⁸ Also, recent data from the TIA registry show that TIA patients are at substantial risk of recurrent ischaemic events, with a risk of recurrent stroke or TIA of 17% and of coronary events of 3% at 5 years.¹⁹ However, this registry only involved patients who were managed in specialized centres with secondary prevention care initiated early after the TIA, that may well have underestimated the absolute risk of recurrent ischaemic events in clinical practice. It should not be surprising, therefore, that stroke represents a significant burden on healthcare systems. In the European Union, the total cost of stroke was estimated to be €45 billion in

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2015, of which €20 billion were due to direct healthcare costs and €25 billion were due to indirect costs related to lost productivity caused by stroke morbidity or death.²⁰ In high-income countries, in addition to the high cost of the initial management of acute TIA or ischaemic stroke, the healthcare cost substantially increases within the year post stroke, with cost being at least doubled.^{21, 22}

Previous follow-up studies of patients with incident ischaemic stroke suggest that although recurrent strokes occur more commonly than cardiac events, cardiac events might account for a greater proportion of death than recurrent stroke, despite patients after ischaemic stroke being on secondary prevention management with antithrombotic therapy that lowers risk of both recurrent ischaemic stroke and myocardial infarction.²³⁻²⁷ Guidelines recommend coronary revascularization for symptomatic coronary artery disease patients to prevent the occurrence of myocardial infarction whereas revascularization for asymptomatic coronary artery disease patients are thought to be less beneficial. However, the prevalence of abnormal myocardial perfusion imaging results in TIA or ischaemic stroke patients with no symptoms suggestive of myocardial ischemia is not uncommon and estimated to be around 30%.²⁸⁻³² Hence, whether selective screening for asymptomatic coronary artery disease could reduce mortality after TIA/ischaemic stroke remains uncertain, mainly because there are few reliable tools to identify TIA/ischaemic stroke patients at high risk of coronary events. Also, long-term estimates on the risk of coronary events or recurrent ischaemic stroke after TIA/ischaemic stroke are scarce and risk factors for myocardial infarction in TIA/ischaemic stroke patients are not well understood. Indeed, whether traditional vascular risk factors, such as history of hypertension or diabetes mellitus, remain good predictors of long-term coronary events after TIA/ischaemic stroke is unclear because such factors are highly prevalent in TIA/ischaemic stroke patients and most of these factors are being controlled with secondary prevention management. There are also no reliable data on coronary risk according to TIA/ischaemic stroke subtype. Unlike coronary disease, TIA or ischaemic stroke is a heterogeneous disease with more than 150 known causes, and the prognosis after TIA or ischaemic stroke varies according to stroke aetiology and presence of vascular risk factors³³ and whether TIA/ischaemic stroke patients at high risk of coronary events are the same as those at high risk of recurrent ischaemic stroke is unknown.

Over the last 15 years, trials of secondary prevention in TIA/ischaemic stroke patients, in particular those of further decrease of blood pressure levels targets³⁴ and of the use of higher dose of statins,¹⁷ have reported significant reduction in the risk of recurrent ischaemic events. However, the impact of these changes on the prognosis of TIA/ischaemic stroke patients

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outside randomised controlled trials remains unclear. Hence, whether the improvement of secondary prevention over the last 15 years, as reported in trials, has led to a decrease in the risk of recurrent ischaemic events at the population-level is uncertain. Also, if the prognosis of TIA/ischaemic stroke has improved over time, whether this improvement remained beyond the first months after the TIA/ischaemic stroke is unknown. Assessing the impact of changes in secondary prevention on the prognosis of TIA/ischaemic stroke patients at the population level is required to allow future strategies in TIA/ischaemic stroke care to be implemented appropriately.

Trials of more intensive secondary prevention with new cholesterol lowering therapies, protein subtilisin-kexin type 9 (PCSK-9) inhibitors, have recently reported significant reduction in the risk of coronary events in patients with stable atherosclerotic disease (80% of whom having history of coronary artery disease) treated with high dose of statin,³⁵⁻³⁷ but relative reduction is modest (between 13% and 27%) and treatment is costly.³⁸ Still in patients with atherosclerotic disease, a recent trial reported a significant reduction in the risk of ischaemic stroke with the combination of an anticoagulant and an antiplatelet therapy compared to an antiplatelet therapy alone.³⁹ However, there was also an increased risk of major bleeding with the combination of treatment.³⁹ These findings show that the improvement of secondary prevention is still achievable, although it also seems necessary to identify individuals at higher absolute risk of recurrent ischaemic events, in whom the potential benefit of these second-line therapies to reduce risk of recurrent ischaemic events might outweigh the risk of side-effects or increased cost. Indeed, a secondary prevention treatment with a large relative risk reduction effect would still have a small overall impact if the absolute risk of recurrent event is low. The subgroup of TIA/ischaemic stroke patients with co-existing stable atherosclerotic cardiovascular disease (coronary or peripheral artery disease) have been shown previously to be at high absolute risk of recurrent stroke and coronary events.⁴⁰⁻⁴² However, whether high-risk subgroups in TIA/ischaemic stroke patients on current management remain the same as those estimated in older studies is uncertain.

Objective of this thesis

In the first part of this thesis, I aimed to determine the long-term prognosis after TIA or ischaemic stroke, in particular the absolute residual risk of recurrent stroke and of coronary events, at the population level. I also aimed to assess the temporal trends in the absolute risk of recurrent stroke and of coronary events in TIA or ischaemic stroke patients and to determine current residual risk on contemporary secondary prevention management. For these aims, I

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firstly undertook a systematic review and a meta-analysis of all published studies and then used data from a contemporary population-based cohort of TIA or ischaemic stroke patients (Oxford Vascular study, OXVASC).

In the second part of the thesis, I aimed to identify individuals who remain at high absolute residual risk of recurrent ischaemic stroke and coronary events despite current secondary prevention management, who might benefit from more intensive secondary prevention. In addition, I determined the long-term cost of myocardial infarction after TIA/ischaemic stroke, overall and in some subgroups of patients, and assessed the likely cost implication of routine prescription of the new lipid-lowering treatment, the PCSK-9 inhibitors, in TIA/ischaemic stroke patients. I used data from the OXVASC study to study these points.

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I.1. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischaemic attack and ischaemic stroke: systematic review and meta-analysis

Boulanger M, Béjot Y, Rothwell PM, Touzé E.
J Am Heart Assoc. 2018 Jan 18;7(2).

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Abstract

Background: Uncertainties remain about the current risk of myocardial infarction after Transient Ischemic Attack (TIA) or ischaemic stroke.

Methods and Results: We undertook a systematic review to estimate the long-term risk of myocardial infarction, compared to recurrent stroke, with temporal trends, in TIA or ischaemic stroke patients. Annual risks and 95% confidence intervals (95%CI) of myocardial infarction and recurrent stroke were estimated using random-effect meta-analyses. We calculated incidence ratios of myocardial infarction /recurrent stroke, for fatal and nonfatal events, using similar analyses. Rate ratios for myocardial infarction in patients with potential risk factors compared to those without were calculated using Poisson regression.

58 studies (131,299 patients) with a mean (range) follow-up of 3.5 (1.0-10.0) years were included. The risk of myocardial infarction was 1.67%/year (95%CI 1.36-1.98, $P_{het}<0.001$ for heterogeneity), and decreased over time ($P_{int}=0.021$). 96% of the heterogeneity between studies was explained by study design, study period, follow-up duration, mean age, proportion of patients on antithrombotic therapy and incident versus combined IS/TIA. The risk of recurrent stroke was 4.26%/year (95%CI 3.43-5.09, $P_{het} <0.001$), with no change over time ($P_{int}=0.63$). The risk of fatal myocardial infarction was half the risk of recurrent fatal stroke (incidence ratio=0.51, 95%CI 0.14-0.89, $P_{het} =0.58$). The risk of nonfatal myocardial infarction was 75% smaller than the risk of recurrent nonfatal stroke (incidence ratio=0.25, 95%CI 0.02-0.50, $P_{het} =0.68$). Male sex, hypertension, coronary and peripheral artery diseases were associated with a doubled risk of myocardial infarction.

Conclusions: After TIA or ischaemic stroke, the risk of myocardial infarction is currently <2%/year and recurrent stroke is a more common cause of death than myocardial infarction.

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Although there is evidence that patients suffering a transient ischaemic attack (TIA) or ischaemic stroke are at high risk of coronary artery disease,^{24-27, 43} current guidelines for prevention of coronary events in high-risk individuals do not include stroke patients.^{44, 45} A writing group committee suggested the inclusion of large atherosclerosis IS while other subtypes of IS are thought to carry a lower risk of coronary artery disease.⁴⁶ In a previous systematic review, the annual risk of myocardial infarction after TIA or IS was shown to be 2.2%.²⁷ However, the current risk of myocardial infarction remains difficult to predict as the improvement of secondary prevention therapies may be counterbalanced by the ageing population. Additionally, long-term estimates were scarce and several cohort studies have been published since this meta-analysis. Moreover, whether coronary events or stroke are the main cause of death in TIA or ischaemic stroke patients remains uncertain. There is also no reliable data on predictors of myocardial infarction among TIA or ischaemic stroke patients.

Therefore, we undertook a systematic review and meta-analysis to determine the long-term risk of myocardial infarction, with temporal trends, along with the risks of recurrent stroke, cardiac and vascular deaths, in TIA or ischaemic stroke patients. Additionally, we compared the risks of myocardial infarction and recurrent stroke, for fatal and nonfatal events, and the risks of cardiac death versus fatal recurrent stroke; and assessed the risk factors for myocardial infarction among TIA or ischaemic stroke patients.

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Methods

Study selection and data collection

We report our study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.⁴⁷ Eligible studies were observational cohort studies or RCTs including ≥ 100 IS or TIA patients with at least one year of follow-up and reporting data on subsequent (fatal or nonfatal) myocardial infarction. In these studies, we also extracted data on recurrent stroke, cardiac and vascular deaths and compared the risks of myocardial infarction and recurrent stroke, as well as the risks of cardiac death and recurrent stroke in the same cohorts. To minimize bias in cardiac and vascular deaths' definitions and increase quality of studies reporting cardiac and vascular deaths, we only selected studies reporting these events if information on myocardial infarction was given separately. When reported in studies, we collected data on risk factors for subsequent myocardial infarction after IS/TIA. We excluded studies with highly selected population (e.g. young age, specific race, patients with a rare cause of stroke). Studies of stroke patients with a small (<15%) proportion of haemorrhagic stroke were not excluded. In cases of multiple publications pertaining to the same population, we included only the publication with the largest amount of data relevant to this review. IS and TIA had to be defined according to the World Health Organization as a minimum.¹ We relied on authors' definitions of myocardial infarction, cardiac and vascular deaths.

We extracted data on study design (community-, hospital-based study, randomized controlled trial [RCT]), year of enrollment, duration of follow-up, completeness of follow-up, population characteristics (age, stroke aetiology, proportion of TIA and IS, proportion of patients under antithrombotic therapies at some point during follow-up), potential risk factors for myocardial infarction (sex, history of hypertension, diabetes, current smoking, atrial fibrillation [AF], peripheral artery disease [PAD] and coronary artery disease [CAD], cardiac biomarkers [such as troponin and Brain Natriuretic Peptide] and genetic variants). Assessment of risk of bias was undertaken at the study level based on study design, type of ischaemic event (TIA or ischaemic stroke), incident or combined (incident and recurrent) TIA or ischaemic stroke, methods of ascertainment for TIA or ischaemic stroke and events, completeness of follow-up, delay from stroke onset and definitions of each event. Critical appraisal of the cohort studies is presented in Appendix S1.⁴⁸

Search strategy

We used electronic search strategies (Appendix S2) to identify studies indexed in Medline and

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Embase until December 11, 2016, which reported information on myocardial infarction after TIA or ischaemic stroke. We screened the bibliographies of relevant studies. We screened all titles and abstracts to determine potentially eligible studies and undertook data collection using a pre-specified data extraction file. We did not restrict inclusion by language or date of publication, and study setting or study period.

Statistical methods

The annual absolute risk and their 95% confidence interval (95% CI) of myocardial infarction were calculated using a random-effect model meta-analysis. We explored the time trend of this risk using random effect meta-regressions with the mid-year of the study period as covariate and reported p-values (P_{int}) obtained from random effect meta-regressions analyses. To assess whether the annual risk of myocardial infarction varied with the duration of follow-up, random effect meta-regressions against the duration of follow-up were performed. When possible, stratification of the risk of myocardial infarction by history of coronary artery disease was performed. In additional analyses, we investigated whether the risk of myocardial infarction differs by study design, type of ischaemic event (TIA, ischaemic stroke or stroke), stroke aetiology or incident vs. combined (incident or recurrent) or unspecified TIA or ischaemic stroke using random effect meta-regressions. Furthermore, the proportion of overall heterogeneity in the absolute risk of myocardial infarction across studies that could be accounted for by study design, study period, duration of follow-up, mean age, proportion of antithrombotic and incident vs. combined (incident and recurrent) or unspecified TIA or ischaemic stroke were determined by random-effect meta regression against all above covariates. Sensitivity analyses were undertaken to explore the risk of myocardial infarction in studies with delay from TIA or ischaemic stroke to inclusion < 1 month and in those with completeness of follow-up $\geq 90\%$.

Similar analyses were undertaken to estimate the annual risks of recurrent stroke, cardiac and vascular deaths. Additionally, we explored whether the risks of myocardial infarction and recurrent stroke differ by the presence of an explicit definition of these events reported in studies through metaregressions. We also examined the temporal trends of the main known vascular risk factors: mean age, mean systolic blood pressure at stroke admission and prevalence of current smokers and men.

Then, to compare the risks of myocardial infarction and recurrent stroke, for fatal and nonfatal events separately, we selected studies reporting data on both myocardial infarction and recurrent stroke and calculated annual incidence ratios of myocardial infarction /recurrent stroke for fatal and nonfatal events. We also investigated time trends and variation with

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duration of follow-up. Similar analyses were done for the annual incidence ratio of cardiac death/ fatal recurrent stroke.

Finally, we explored the risk factors for myocardial infarction by selecting the studies reporting the number of patients with and without a potential risk factor and the number of myocardial infarction in each group. The unadjusted rate ratios (RRs) and 95% CI for the risk of myocardial infarction were calculated in patients with a potential risk factor compared to those without using Poisson regression. Heterogeneity of risks across studies was analyzed by χ^2 tests and the p-value (P_{het}) of the test was reported. Statistical analyses were performed in R software version 3.1.3 and STATA version 13..

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Results

Of the 7635 titles identified from searching databases, 686 abstracts were screened leading to the assessment of 180 full texts. Bibliography screening of these eligible full texts resulted in the screening of 45 additional full texts. A total of 167 full texts were finally excluded, leaving 58 studies for inclusion in the meta-analysis (Figure 1). Characteristics of the included studies and definitions of myocardial infarction, recurrent stroke, and cardiac and vascular deaths are reported in Tables 1 to 4. The frequency and the annual risks of each outcome in individual studies are given in Table 5.

There were 7 community-based studies, 25 hospital-based studies and 26 RCTs, involving a total of 131,299 patients with a mean (range) follow-up of 3.5 (1.0-10.0) years. 7 studies included patients with TIA only, 15 with ischaemic stroke only, 30 with TIA or ischaemic stroke and 6 with IS and a small proportion of haemorrhagic stroke. 8 studies were restricted to incident TIA or ischaemic stroke and 50 involved combined or unspecified TIA/ischaemic stroke. Delay from stroke onset to inclusion was <7 days in 9 studies, <1 month in 5, <3 months in 13, <6 months in 11, <12 months in one, <5 years in one study and not reported in 18 studies (Table 1). Mean ages ranged from 59 to 77 years and the prevalence of history of coronary artery disease from 38% to 88%. Active prospective follow-up was undertaken in all except 4 studies, in which administrative follow-up was used. The proportions of patients treated at some point during follow-up with antithrombotic therapy ranged from 50 to 100%, with the lowest prevalence in old RCTs comparing antiplatelet therapy to placebo. The majority of the studies (41 [71%]) had a completeness of follow-up $\geq 90\%$. In the remaining studies, completeness of follow-up ranged from 73% to 88% in 4 studies and was unspecified in 13. 23 (40%) studies provided an explicit definition of myocardial infarction, which was based on clinical parameters, biological markers, ECG changes or International Classification Disease codes (Table 3). An explicit definition of recurrent stroke was given in 15 (38%) studies, a neurologic deficit lasting ≥ 24 hours was the definition used in most of the studies, and only one required a period of neurological stability between index stroke and recurrent stroke (Table 4). Table 6 shows the pooled risks of myocardial infarction, recurrent stroke, cardiac and vascular deaths, overall and in the pre-specified subgroups with difference among subgroups assessed by meta-regressions.

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Table 1 : Characteristics of the included studies in the systematic review

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Achterberg ¹	the Netherlands	1994-2005	IS (55%), H		ND	Prospective (consecutive referrals to a university hospital) with active follow-up	62	68	49	15	8	11		22	ND	97
Agnelli ²	Italy	2005	IS (0%), H		92 (92/ND)	Prospective (hospital admissions) with active follow-up				22	7			25	ND	100
Amarenco ³	France	2005-2008	IS (0%), H		97 (84/28)	Prospective (consecutive ward admissions) with active follow-up	62	75	82	22			15	39	<10 d	99
Appelros ⁴	Sweden	1999-2000	Stroke, C		ND	Prospective (multiple search methods) with active follow-up	76	45	35	18	4	17	24	22	ND	100
Barnett ⁵	Canada, USA, Japan	1985	IS (33%), RCT	Aspirin vs. Aspirin + bybass surgery joining the superficial temporal artery and the middle cerebral artery	100 (100/0)	Prospective with active follow-up	56	82	50	18	12	10			<3 m	100
Bousser ⁶	France	1983	IS (16%), RCT	Placebo, Aspirin or Aspirin+ dypiridamole	66 (66/0)	Prospective with active follow-up	63	70	63	22	7	7		64	<12 m	99
Boysen ⁷	Denmark	1988	IS (49%), RCT	Aspirin vs. placebo after carotid	50 (50/0)	Prospective with active follow-up	59	65	36	7	21	14		77	ND	ND

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endarterectomy

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Boysen (ExSTROKE) ⁸	China, Poland, Estonia	2003- 2005	IS (0%), RCT	Physiotherapist- guided physical activity vs. information on physical activity	ND	Prospective with active follow- up	69	43	54	14	8	8	13	37	<90 d	88
Brown ⁹	USA	2001	IS/TIA, H		ND	Retrospective (screening of administrative database) with administrative follow-up Prospective (consecutive admissions to neurology ward) with active follow-up in patients who survived 1 week after stroke	77	45							ND	100
Busch ¹⁰	Germany	2003- 2004	IS (25%), H		ND	Prospective with active follow- up	64	55	70	32	12	12	18	29	ND	97
Carolei ¹¹	Italy	1992	IS (24%), H		ND	Prospective with active follow- up	56	73	50	15	11	5			< 3 m	100
Chimowitz ¹²	North America	2005	IS (39%), RCT	Warfarin vs. Aspirin	100 (50/50)	Prospective with active follow- up	64	62	84	38		27		21	<3 m	ND
Colantonio ¹³	USA	2003- 2007	IS/TIA, C		ND	Prospective (screening of administrative database and self-reported history of stroke) with active follow-up	65	38		28		0		18	ND	ND
Collins ¹⁴	UK	2004	IS (46%), RCT	Simvastatin vs. placebo	66 (63/3)	Prospective with active follow- up	66	75	50			27		14	<6 m	ND
Culebras ¹⁵	Argentina	2004	IS (19%), RCT	Triflusal vs. Aspirin	100 (100/ND)	Prospective with active follow- up	65	58	71	18	4	6		27	<6 m	100

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Dennis ¹⁶	UK	1990	TIA, C		65 (57/8)	Prospective (multiple search methods) with active follow-up	69	56	34	-	-	-	-		0	99
Diener ¹⁷	Europe	1996	IS (24%), RCT	Aspirine alone, dipyridamole alone, Aspirine + dipyridamole or placebo	100 (100/0)	Prospective with active follow-up	67	58	61	15	22	14	7	24	<3 m	99
Diener (MATCH) ¹⁸	Intern.	2004	IS (21%), RCT	Aspirin + clopidogrel vs. clopidogrel	100 (100/ND)	Prospective with active follow-up	66	63	78	68	10	5			<3 m	99
Falke ¹⁹	Sweden	1994	IS (62%), H		ND	Prospective with administrative follow-up	75	64	21	8	9	9			0	100
Fang ²⁰	China	2003- 2004	IS (0%), H		71 (71/ND)	Prospective (consecutive patients from community-hospitals) with active follow-up	64	51	78	30				25	ND	90
Farrel ²¹	UK	1979- 1985	IS (71%), RCT	2 doses of Aspirin vs. placebo	67 (67/0)	Prospective with active follow-up	60	73	39	4	12	10	2		ND	100
Fields ²²	USA, Canada	1985	TIA, RCT	Aspirin vs. Aspirin + dipyridamole	100 (100/0)	Prospective with active follow-up	63	67	48	15	8	15		58	<3 m	92
Gates ²³	USA, Canada	2002	IS (54%), RCT	Carotid endarterectomy + BMT vs.BMT	97 (97/ND)	Prospective with active follow-up	66	70	61	21	15	18		43	<6 m	ND
Gent (CAPRIE) ²⁴	Intern.	1996	IS (0%), RCT	Clopidogrel vs. aspirin	100 (100/0)	Prospective with active follow-up	65	64	65	25	8	12	4	30	<6 m	99

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Gent (CATS) ²⁵	Canada, USA	1989	IS (22%), RCT	Ticlopidine vs. placebo	50 (50/0)	Prospective with active follow-up	65	62	67	32	11	17	1	7.3	<4 m	99
Goto ²⁶	Japan	2005-2006	Stroke, H		96 (76/20)	Prospective (consecutive outpatients) with active follow-up	68	69	74	22				22	ND	93
Has ²⁷	USA, Canada	1989	IS (50%), RCT	Ticlopidine hydrochloride vs. aspirin	100 (100/0)	Prospective with active follow-up	63	65	53	19	15	17		42	<3 m	97
Helmers ²⁸	Sweden	1987	IS (0%), RCT	Aspirin vs. placebo	50 (50/0)	Prospective with active follow-up	68	62	46	17	9	10	1	10	1-3 w	100
Howard ²⁹	USA	1987-1991	TIA, H		ND	Prospective (screening of admission and discharge records) with active follow-up, using blinded system	64	50	65	15		17		27	ND	ND
Ito ³⁰	Japan	2003	IS (14%), RCT	Ticlopidine vs. ticlopidine + aspirin	100 (100/0)	Prospective with active follow-up	67	65	47	23			3	33	1-6 m (IS) <3 m (TIA)	ND
Kim ³¹	Australia	1996-1999	Stroke, C		ND	Prospective (multiple search methods) with active follow-up in patients who survived 5 years after stroke. Patients with incomplete follow-up were excluded from analyses							19	12	ND	100
Kono ³²	Japan	2006-2007	IS (0%), H		98 (98/ND)	Prospective (consecutive ward admissions) with active follow-up	64	74	74	21				64	<2 w	ND

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Li ³³	Sweden	1991- 1996	Stroke, C		ND	Prospective with administrative follow-up (record linkage)	63	56	79			0		31	ND	ND
Lowenthal ³⁴	Europe	1990	IS (33%), RCT	Aspirin + dipyridamole vs. placebo	50 (50/0)	Prospective with active follow-up	64	58	37	-	-	-	-	43	<3 m	99
MacMahon ³⁵	Intern.	2001	IS (30%), RCT	Perindopril +/- indapamide vs. placebo	ND	Prospective with active follow-up	64	70	48	13				34	<5 y	99
Man ³⁶	Hong Kong	2002- 2004	IS/TIA, H		96 (ND/ND)	Prospective (ward admissions) with active follow-up. Patients with incomplete follow-up were excluded from analyses	73	58	66	33				45	<7 d	100
Manzano ³⁷	Singapour	2003- 2004	IS (0%), H		ND	Prospective (consecutive ward admissions) with active follow-up. Patients with incomplete follow-up were excluded from analyses	65	88	77	40	6	23	9	26	ND	100
Matias-Guiu ³⁸	Portugal, Spain	2003	IS (26%), RCT	Triflusal vs. Aspirin	100 (100/0)	Prospective with active follow-up	65	66	61	24	4	2		31	<6 m	97
Muuronen ³⁹	Finland	1982	TIA, H		ND	Prospective with active follow-up	49	53	27	9	4				0	ND
Norrving ⁴⁰	Sweden	1991	IS (28%), RCT	Aspirin vs. placebo	50 (50/0)	Prospective with active follow-up	67	66	47	13	8	11		27	<3 m	99
Olsson ⁴¹	Sweden	1985	IS (45%), RCT	Warfarin vs. Aspirin +	100 (50/50)	Prospective with active follow-up	66	69	48	12		8			<2 m	81

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

dipyridamole

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Ovbiagele ⁴²	Intern.	1998-2005	Stroke, RCT	Atorvastatin vs. placebo	87 (87/ND)	Prospective with active follow-up	60	62	61	17					<6 m	84
Palnum ⁴³	Denmark	2003-2006	IS (0%), C		ND	Prospective with active follow-up (screening of nationwide database) in patients who survived in hospital or within 30 days after hospital discharge		53	44	13	4	9	15		ND	100
Petty ⁴⁴	USA	2003	IS (18%), C		65 (44/21)	Prospective (medical records linkage system) with active follow-up	75	42	73	17		17			0	ND
Rothwell ⁴⁵	Europe	2000	IS (50%), RCT	Carotid endarterectomy + BMT vs. BMT	85 (78/7)	Prospective with active follow-up	63	72	50	12	17	12		58	<6 m	99
Salgado ⁴⁶	Portugal	1996	IS (0%), H		ND	Prospective (consecutive ED or specialist wards or outpatient clinic attenders) with active follow-up	65	64	72	25	8	5	6	19	<1 w	99
Sander ⁴⁷	Germany	2008	IS (0%), H		ND	Prospective (consecutive admissions to neurologic rehabilitation ward) with active follow-up in patients who survived 3 months after stroke	66	58	79	35			20	18	<3 m	73
Santos-García ⁴⁸	Spain	2005	IS (0%), H		100 (78/22)	Prospective (consecutive patients) with active follow-up. Patients with incomplete	73	58	70	25		7	25		<48 h	100

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

follow-up were excluded from analyses

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Simonsen ⁴⁹	Denmark	1981	TIA, H		ND	Retrospective (screening of hospital records) with administrative follow-up	60	68	16	6	6	7	7		<1 m	100
Sorensen ⁵⁰	Denmark	1983	IS (72%), RCT	Aspirin vs. placebo	50 (50/0)	Prospective with active follow-up	59	73	27		15	9		22	<1 m	100
Toole ⁵¹	USA, Canada, Scotland	2004	IS (0%), RCT	High vs. low dose of folic acid, pyridoxine and cobalamin	ND	Prospective with active follow-up	66	62	74	29		7		17	<4 m	93
Ueno ⁵²	Japan	2008-2014	IS (0%), H		100 (72/29)	Prospective (inpatients registry of the neurology ward) with active follow-up. Patients with incomplete follow-up were excluded from analyses	64	72						31	<7 d	100
Urbaniti ⁵³	Italy	1992	IS (82%), H		100 (100/ND)	Prospective (consecutive admissions to neurosurgical ward) with active follow-up	70	84	61	52	32	15		68	ND	100
Venketasubramanian ⁵⁴	Intern.	2003-2004	IS (28%), H		82 (82/ND)	Prospective (consecutive outpatient/ambulatory clinics attenders) with active follow-up	66	57	80	35	4	30		14	ND	96
Vilanova ⁵⁵	Spain	2006-2013	TIA, H		100 (80/20)	Prospective (consecutive stroke patients) with active follow-up	71	58						14	<48 h	ND

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Von Weitzel-Mudersbac ⁵⁶	Denmark	2007-2008	TIA, H		93 (ND/ND)	Prospective (referrals to neurology clinics) with active follow-up	66	56	70	12	18	11	8	31	ND	100
Whiteley ⁵⁷	UK	2002-2005	Stroke, H		ND	Prospective (consecutive hospital attenders) with active follow-up	71	53	53	12	8	28	20	70	ND	100
Wijnhoud ⁵⁸	the Netherlands	2008	IS (53%), H		ND	Prospective with active follow-up	60	66	53	16		11		29	<6 m	ND

Year: year of enrollment; TIA: transient ischaemic attack; IS: ischaemic stroke (including % of TIA if reported); Stroke: ischaemic or haemorrhagic stroke; Minor: defined as non-disabling or reversible symptoms; H: hospital-based study; C: community-based study; RCT: randomized controlled trial; ED: emergency department; BMT: best medical treatment; AT: antithrombotic therapy; AP: antiplatelet therapy; AC: oral anticoagulant therapy, numbers indicate proportion of patients under antithrombotic therapy at some point during follow-up (when only the proportion of patients under antiplatelet therapy was given, as antiplatelet therapy is the antithrombotic agent mostly used in secondary prevention of stroke, this number was reported as the proportion of patients under antithrombotic drugs ; when the proportions of patients under antiplatelet and anticoagulant drugs were reported without the total proportion of those under antithrombotic drugs, the two proportions were added to calculate the proportion under antithrombotic drugs); AP: antiplatelet therapy; NA: not applicable; ND: not defined; Intern: International; Age: mean age (years); HTN: Hypertension; DM: Diabetes Mellitus; PAD: Peripheral Arterial Disease; CAD: coronary artery disease; FU: follow-up; AF: atrial fibrillation; Smoking: current smoking; Delay: delay from TIA or ischaemic stroke onset to study inclusion; m: month; w: week; d: day

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Table 2 : Definitions of myocardial infarction (MI), recurrent stroke, cardiac and vascular deaths

First author (study name)	MI	Recurrent stroke	Cardiac death	Vascular death
Achterberg ¹	ND	NA	NA	ND
Agnelli ²	1	NA	NA	MI, stroke, SD
Amarenco ³	ND	ND	MI, resuscitation after cardiac arrest, HF	MI, Car, HF, SD, AA
Appelros ⁴	3	NA	NA	NA
Barnett ⁵	ND	ND	NA	MI, SD, other
Bousser ⁶	ND	NA	NA	MI, PAD, PE, SD, CAr, other
Boysen ⁷	2	2	MI, SD	MI, SD
Boysen (EXSTROKE) ⁸	ND	2	NA	Stroke, MI, or other vascular causes, SD
Brown ⁹	3	6	NA	MI, stroke, SD
Busch ¹⁰	ND	7	NA	MI, stroke, SD
Carolei ¹¹	2	NA	NA	MI, HF, SD
Chimowitz ¹²	2	4	MI, SD, HF	NA
Colantonio ¹³	ND	NA	NA	NA
Collins ¹⁴	2	2	NA	NA
Culebras ¹⁵	2	NA	NA	MI, HF, SD, bleeding
Dennis ¹⁶	2	4	MI, SD	MI, Car, HF, SD, AA
Diener (ESPS2) ¹⁷	ND	ND	NA	MI, SD, HF, PE, PAD, haemorrhage
Diener (MATCH) ¹⁸	ND	NA	NA	ND
Falke ¹⁹	2	NA	NA	NA
Fang ²⁰	ND	2	MI, SD	MI, stroke, SD
Farrel ²¹	2	2	MI, SD, other IHD	Stroke, MI, SD, other IHD, AA, PE, gastrointestinal bleeding
Fields ²²	ND	NA	MI, SD	ND

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Gates ²³	2	NA	MI, SD	ND
First author (study name)	MI	Recurrent stroke	Cardiac death	Vascular death
Gent (CAPRIE) ²⁴	2	NA	NA	MI, haemorrhage, others
Gent (CATS) ²⁵	ND	NA	NA	MI, HF, SD
Goto ²⁶	1	5	NA	MI, stroke, SD
Has ²⁷	ND	2	NA	ND
Helmers ²⁸	2	ND	NA	MI, chronic IHD
Howard ²⁹	ND	ND	NA	NA
Ito ³⁰	ND	ND	NA	NA
Kim ³¹	1	ND	NA	MI, stroke
Kono ³²	ND	ND	NA	NA
Li ³³	3	2	NA	NA
Lowenthal ³⁴	ND	NA	NA	MI, SD, other
MacMahon ³⁵	ND	NA	NA	MI, SD, other
Man ³⁶	ND	ND	NA	MI, stroke, AA
Manzano ³⁷	ND	ND	NA	MI, stroke
Matias-Guiu ³⁸	2	NA	NA	ND
Muuronen ³⁹	ND	NA	NA	NA
Norrving ⁴⁰	2	ND	NA	ND
Olsson ⁴¹	ND	NA	NA	NA
Ovbiagele ⁴²	ND	ND	NA	MI, stroke, PAD, revascularization
Palnum ⁴³	ND	ND	NA	NA
Petty ⁴⁴	ND	3	NA	SD, PAD, others
Rothwell ⁴⁵	2	NA	MI, SD	Heart disease, SD, AA
Salgado ⁴⁶	ND	ND	NA	ND

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First author (study name)	MI	Recurrent stroke	Cardiac death	Vascular death
Sander ⁴⁷	ND	NA	NA	MI, stroke
Santos-García ⁴⁸	ND	ND	NA	MI, stroke, other cardiac diseases
Simonsen ⁴⁹	ND	NA	NA	NA
Sorensen ⁵⁰	ND	1	NA	ND
Toole ⁵¹	1	NA	NA	NA
Ueno ⁵²	ND	NA	NA	NA
Urbaniti ⁵³	ND	ND	NA	MI, stroke
Venketasubramanian ⁵⁴	ND	NA	NA	MI, stroke
Vilanova ⁵⁵	2	2	NA	MI, stroke
Weitzel-Mudersbac ⁵⁶	ND	NA	NA	MI, stroke
Whiteley ⁵⁷	ND	ND	NA	MI, stroke, PE
Wijnhoud ⁵⁸	ND	ND	MI, SD	MI, stroke, SD, PAD

MI: definition of myocardial infarction (1: Symptoms suggestive of MI with ECG changes or biological markers elevation [CK-MB or troponin] elevation; 2: Symptoms suggestive of MI and biological markers elevation and ECG changes, 3: ICD codes for MI); Recurrent stroke: definition of recurrent stroke (1: neurologic deficit lasting >72 hours, 2: neurologic deficit lasting >24 hours, 3: new neurological deficit fitting the definition for ischaemic or haemorrhagic stroke occurring after a period of unequivocal neurological stability or improvement, lasting ≥24 hours, 4: neurological deficit lasting >24 hours confirmed on brain imaging, 5: new neurological deficit confirmed on brain imaging, 6: ICD codes, 7: acute new deficit lasting >24 hours or new lesion demonstrated on brain imaging); Card.death: definition of cardiac death; Vasc.death : definition of vascular death ; HF: heart failure; SD, sudden death; CAr, cardiac arrhythmia; PE, pulmonary embolism; AA, ruptured aortic aneurysm; TE: thrombo-embolic diseases; IHD: ischaemic heart disease, CD: cardiac disease, S: stroke.

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Table 3 : Numbers and proportions of studies with definitions of myocardial infarction (MI)

Definitions of MI used in study	N studies; N patients (%)
Symptoms suggestive of MI with ECG changes or biological markers elevation	4; 8425 (6)
Symptoms suggestive of MI with ECG changes and biological markers elevation	16; 23,053 (27)
International Classification Diseases (ICD) codes	3; 2694 (5)
No explicit definition	35; 97,127 (62)

Table 4 : Numbers and proportions of studies with definitions of recurrent stroke

Definitions of recurrent stroke used in study	N studies; N patients (%)
Neurologic deficit lasting >72 hours	1; 203 (3)
Neurologic deficit lasting >24 hours	8; 11,131 (20)
Neurological deficit lasting >24 hours confirmed on brain imaging	2; 753 (5)
Acute new deficit lasting >24 hours or new lesion demonstrated on brain imaging	1; 204 (3)
New neurological deficit fitting the definition for ischaemic or haemorrhagic stroke occurring after a period of unequivocal neurological stability or improvement, lasting \geq 24 hours	1; 1111 (3)
New neurological deficit confirmed on brain imaging	1; 3351 (3)
International Classification Diseases (ICD) codes	1; 1923 (3)
No explicit definition	24; 78,848 (60)

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Table 5 : Risks of myocardial infarction (MI), recurrent stroke, cardiac and vascular deaths in the included studies

First author (study name)	n patients	Mean follow- up (years)	Total MI, n (%/year)	Fatal MI, n (%/year)	Nonfatal MI, n (%/year)	Total recurrent stroke, n (%/year)	Recurrent fatal stroke, n (%/year)	Recurrent nonfatal stroke, n (%/year)	Incidence ratio nonfatal MI / recurrent nonfatal stroke	Incidence ratio fatal MI / recurrent fatal stroke	Cardiac death, n (%/year)	Incidence ratio cardiac death / recurrent fatal stroke	Vascular Death, n (%/year)
Achterberg ¹	971	6.3	72 (1.2)										113 (1.8)
Agnelli ²	755	1							0.2				24 (3.1)
Amarenco ³	377	2.6			3 (0.3)				0.2		5 (0.5)		7 (0.7)
Appelros ⁴	377	10	49 (1.3)	30 (0.8)	19 (0.5)								
Barnett ⁵	1377	4.7		83 (1.3)		410 (6.3)				1.28			244 (3.8)
Bousser ⁶	604	3	18 (1)	4 (0.2)	14 (0.8)								
Boysen ⁷	301	2.1	2 (0.3)			20 (3.2)							18 (2.8)
Boysen (EXSTROKE) ⁸	314	2	4 (0.6)			25 (4.0)							7 (1.1)
Brown ⁹	1923	2	108 (2.8)			239 (6.2)							2 (0.6)
Busch ¹⁰	204	2.3	4 (0.9)	2 (0.4)		23 (4.9)							2 (0.4)
Carolei ¹¹	712	4			19 (0.7)								
Chimowitz ¹²	569	1.8	19 (1.9)	3 (0.3)	16 (1.6)	109 (10.6)					5 (0.5)		26 (2.5)
Colantonio ¹³	3432	5.8	145 (0.7)	53 (0.3)									
Collins ¹⁴	3280	4.8	389 (2.5)			339 (2.2)							
Culebras ¹⁵	429	1.6			9 (1.3)								13 (1.9)
Dennis ¹⁶	184	3.7	17 (2.5)			45 (6.6)					17 (2.5)	1.13	34 (5)
Diener (ESPS2) ¹⁷	6602	2	167 (1.3)	70 (0.5)	97 (0.7)	830 (6.3)			0.13	0.73			
Diener (MATCH) ¹⁸	7599	1.5	141 (1.2)										245 (2.1)
Falke ¹⁹	209	6	52 (4.1)	36 (2.9)	16 (1.3)				1.33				
Fang ²⁰	710	5	25 (0.7)	9 (0.3)		75 (2.1)			0.29	0.47	14 (0.4)	0.74	33 (0.9)
Farrel ²¹	2435	4	117 (1.2)	45 (0.5)	72 (0.7)	320 (3.3)	55 (0.6)	265 (2.7)	0.27	0.82	173 (1.8)	0.65	253 (2.6)

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First author (study name)	n patients	Mean follow- up (years)	Total MI, n (%/year)	Fatal MI, n (%/year)	Nonfatal MI, n (%/year)	Total recurrent stroke, n (%/year)	Recurrent fatal stroke, n (%/year)	Recurrent nonfatal stroke, n (%/year)	Incidence ratio nonfatal MI / recurrent nonfatal stroke	Incidence ratio fatal MI / recurrent fatal stroke	Cardiac death, n (%/year)	Incidence ratio cardiac death / recurrent fatal stroke	Vascular Death, n (%/year)
Fields ²²	890	2.1	48 (2.6)	26 (1.4)	22 (1.2)						41 (2.2)		59 (3.2)
Gates ²³	2815	5	533 (3.8)		238 (1.7)						295 (2.1)		
Gent (CAPRIE) ²⁴	6431	1.9	95 (0.8)	25 (0.2)	70 (0.6)								204 (1.7)
Gent (CATS) ²⁵	1053	2	25 (1.2)										
Goto ²⁶	3351	1	14 (0.4)	1 (0.03)		106 (3.2)			0.13	0.14			30 (0.9)
Has ²⁷	3069	3		35 (0.4)		39 (0.4)				0.9	167 (1.8)	4.28	236 (2.6)
Helmers ²⁸	505	2	44 (4.4)	12 (1.2)	32 (3.2)	64 (6.3)			0.7	0.67	17 (1.7)	0.94	52 (5.1)
Howard ²⁹	280	3	30 (3.6)			22 (2.6)							
Ito ³⁰	270	1.6	2 (0.5)			23 (5.3)							
Kim ³¹	639	5	62 (1.9)			30 (0.9)							
Kono ³²	102	3	4 (1.3)			25 (8.2)							
Li ³³	394	7.5	37 (1.3)			32 (1.1)							
Lowenthal ³⁴	2500	2	103 (2.1)	44 (0.9)	56 (1.1)								169 (3.4)
MacMahon ³⁵	6105	3.9	276 (1.2)	120 (0.5)	156 (0.7)				0.24	1.3			379 (1.6)
Man ³⁶	428	5.4	32 (1.4)	10 (0.4)	22 (1)	91 (3.9)							32 (1.4)
Manzano ³⁷	1311	1	29 (2.2)			136 (10.4)							51 (3.9)
Matias-Guiu ³⁸	2107	2.5	35 (0.7)	6 (0.1)	29 (0.6)								68 (1.3)
Muuronen ³⁹	314	7.8	40 (1.6)	24 (1)	16 (0.7)								
Norrving ⁴⁰	1360	2.7	122 (3.3)	46 (1.3)	76 (2.1)	205 (5.6)							
Olsson ⁴¹	135	1		5 (3.7)									
Ovbiagele ⁴²	3969	4.9	141 (0.7)			446 (2.3)							110 (0.6)
Palnum ⁴³	28612	2.5	837 (1.2)			2658 (3.7)							

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

First author (study name)	n patients	Mean follow- up (years)	Total MI, n (%/year)	Fatal MI, n (%/year)	Nonfatal MI, n (%/year)	Total recurrent stroke, n (%/year)	Recurrent fatal stroke, n (%/year)	Recurrent nonfatal stroke, n (%/year)	Incidence ratio nonfatal MI / recurrent nonfatal stroke	Incidence ratio fatal MI / recurrent fatal stroke	Cardiac death, n (%/year)	Incidence ratio cardiac death / recurrent fatal stroke	Vascular Death, n (%/year)
Petty ⁴⁴	1111	10	77 (0.7)			110 (1.0)							
Rothwell ⁴⁵	3007	6	91 (0.5)							0.87	206 (1.1)	1.96	472 (2.6)
Salgado ⁴⁶	145	3.3	4 (0.8)	0 (0)	4 (0.8)	30 (6.4)			0.14				8 (1.7)
Sander ⁴⁷	1167	1.1	11 (0.9)			35 (2.8)							30 (2.4)
Santos-García ⁴⁸	120	4	5 (1)			21 (4.4)							5 (1)
Simonsen ⁴⁹	243	6		22 (1.5)									55 (3.8)
Sorensen ⁵⁰	203	2.1	20 (4.7)			28 (6.6)							12 (2.8)
Toole ⁵¹	3680	1.7	237 (3.8)										
Ueno ⁵²	177	3.5	5 (0.8)										
Urbaniti ⁵³	150	6.2	16 (1.7)	11 (1.2)	5 (0.5)	11 (1.2)			0.63	2.75			13 (1.4)
Venketasubramanian ⁵⁴	18992	2			399 (1.1)				0.37				855 (2.3)
Vilanova ⁵⁵	628	2.6	28 (1.7)	1 (0.1)		71 (4.3)			0.4	0.33			4 (0.2)
Weitzel-Mudersbac ⁵⁶	306	1			0 (0)								5 (1.6)
Whiteley ⁵⁷	877	2.1	69 (3.7)	35 (1.9)		106 (5.8)			0.79	0.56			113 (6.1)
Wijnhoud ⁵⁸	489	2.1	8 (0.8)	2 (0.2)		39 (3.8)			0.18	0.25	12 (1.2)	1.5	21 (2)

N: number, MI: myocardial infarction, TIA: transient ischaemic attack; IS: ischaemic stroke

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

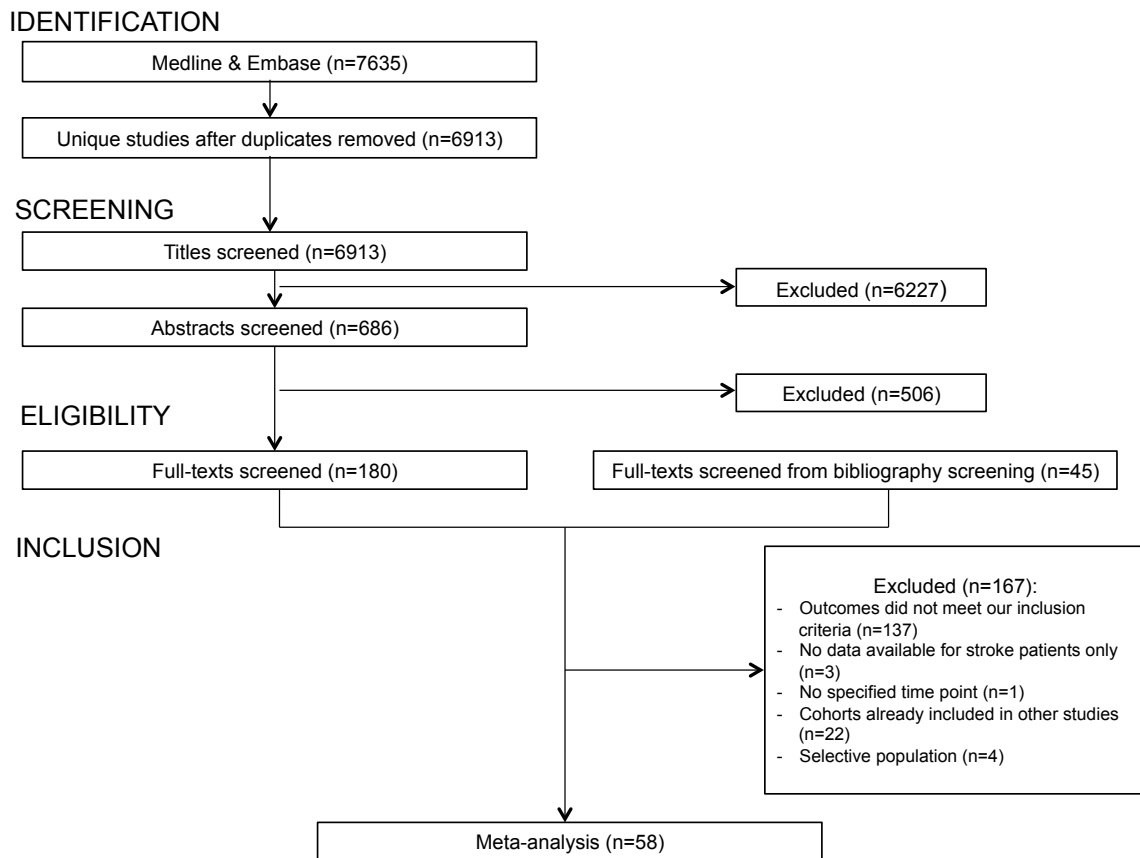


Figure 1 : PRISMA Flow diagram describing identification, screening, eligibility, and inclusion of studies in the systematic review

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Table 6 : Annual risks of myocardial infarction (MI), recurrent stroke, cardiac and vascular deaths in subgroups analyses

Population	N; n	Annual risk, % (95% CI)	<i>P</i> _{int}	N; n	Annual risk, % (95% CI)	<i>P</i> _{int}
		Total MI			Recurrent total stroke	
All	46; 101,786	1.67 (1.36-1.98)		34; 73,184	4.26 (3.43-5.09)	
Study design			0.48			0.18
RCT	21; 53,592	1.80 (1.26-2.34)		14; 30,359	4.58 (3.26-5.91)	
Community-based studies	6; 33,638	1.35 (0.93-1.76)		5; 30,940	2.55 (0.50-4.60)	
Hospital-based studies	19; 13,556	1.62 (1.14-2.09)		15; 11,885	4.54 (3.35-5.72)	
Type of ischaemic event			0.42			0.35
TIA	5; 2296	2.26 (1.62-2.89)*		3; 1092	4.42 (2.24-6.59)	
IS	12; 43,274	1.50 (0.82-2.18)		9; 32,986	5.21 (3.46-6.97)	
Mixed TIA and IS	23; 45,609	1.67 (1.22-2.12)		17; 29,876	4.26 (3.06-5.46)	
Stroke	6, 9607	1.51 (0.61-2.41)		5, 9230	2.60 (0.93-4.27)	
Stroke aetiology			0.91			
Large artery atherosclerosis	11; 16,214	1.46 (0.85-2.08)		-	-	
Small vessel disease	3; 307	1.49 (0.57-2.42)†		-	-	
Cardio-embolism	2; 260	1.50 (0.81-2.19)‡		-	-	
Incident IS/TIA			0.62			0.95
Incident	8; 32,699	1.47 (0.95-2.00)		7, 32,322	4.68 (3.41-5.94)	

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Combined or unspecified		38; 69,087	2.06 (1.29-2.82)	27, 40,862	4.15 (3.15-5.15)
			Fatal MI	Recurrent fatal stroke	
All		30; 50,364	0.66 (0.46-0.86)	18; 34,445	0.77 (0.45-1.10)
Study design				0.96	0.36
	RCT	15; 37,696	0.63 (0.41-0.85)	9; 27,272	0.63 (0.40-0.86)
	Community-based studies	3; 4920	0.57 (0.24-0.89)	2; 823	1.44 (0.19-2.69)§
	Hospital-based studies	12; 7748	0.76 (0.30-1.22)	7; 6350	0.78 (0.02-1.57)
Type of ischaemic event				0.88	0.87
	TIA	4; 2075	0.94 (0.27-1.62)	2; 812	1.12 (0.86-3.09)
	IS	4; 7791	0.35 (0.04-0.75)	3; 1360	0.78 (0.09-1.65)‡
	Mixed TIA and IS	19; 35,893	0.64 (0.40-0.87)	9; 23,437	0.60 (0.46-0.73)
	Stroke	3, 4605	0.87 (0.01-1.92)	4, 8836	1.15 (0.26-2.59)
Incident IS/TIA				0.95	
	Incident	4, 1860	0.29 (0.03-0.61)	4, 1667	0.65 (0.11-1.42)
	Combined or unspecified	26, 48,504	0.73 (0.51-0.96)	14, 32,778	0.81 (0.44-1.19)
			Nonfatal MI	Recurrent nonfatal stroke	
All		31; 65,808	0.88 (0.70-1.07)	20; 51,568	2.92 (2.22-3.62)
Study design				0.020	0.51
	RCT	13; 33,352	1.15 (0.81-1.49)	7; 24,062	3.73 (2.70-4.77)
	Community-based studies	2; 3809	0.47 (0.38-0.56)#	2; 823	2.15 (0.19-6.43)

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

		Cardiac death		Vascular death	
Hospital-based studies		16; 28,647	0.73 (0.52-0.95)	11; 26,683	2.49 (1.73-3.26)
Type of ischaemic event			0.84		0.092
	TIA	4; 2138	0.88 (0.27-1.50)	2; 812	4.23 (3.41-5.05)†
	IS	6; 8923	0.88 (0.14-1.62)	5; 2492	3.11 (1.46-4.76)
	Mixed TIA and IS	18; 50,141	0.92 (0.71-1.13)	9; 39,428	3.06 (2.00-4.12)
	Stroke	3, 4605	0.87 (0.01-1.75)	4, 8836	1.84 (0.57-3.10)
Incident IS/TIA			0.67		0.83
	Incident	4, 1860	0.80 (0.27-1.34)	4, 1667	3.90 (2.04-5.76)
	Combined or unspecified	27, 63,948	0.90 (0.69-1.10)	16, 19,901	2.71 (1.96-3.47)
All		11; 15,050	1.38 (0.96-1.81)	38; 76,501	2.17 (1.75-2.59)
Study design			0.60		0.62
	RCT	7; 13,290	1.59 (1.14-2.03)	18; 43,170	2.38 (1.92-2.85)
	Community-based studies	1; 184	2.50 (1.32-3.67)	1; 184	4.99 (3.36-6.63)
	Hospital-based studies	3; 1576	0.60 (0.20-1.01)#	19; 33,147	1.83 (1.18-2.49)
Type of ischaemic event			0.51		0.65
	TIA	2; 1074	2.27 (1.69-2.84)	5; 2251	2.69 (1.05-4.32)
	IS	3; 1592	0.78 (0.05-1.52)	10; 11,835	2.09 (1.23-2.96)
	Mixed TIA and IS	6; 12,834	1.44 (0.96-1.91)	20; 54,218	2.06 (1.65-2.48)
	Stroke	-	-	3, 8197	2.49 (1.00-5.99)

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Incident IS/TIA		0.71		0.91	
Incident	2, 894	1.36 (0.69-3.42)	6, 3710	1.36 (0.05-2.66)	
Combined or unspecified	9, 14,156	0.56 (0.27-0.86)	32, 72, 791	2.32 (1.90-2.74)	

Numbers are percentage, otherwise indicated; N: number of studies, n: number of patients, RCT: randomized controlled trial; TIA: Transient Ischemic Attacks; IS: ischaemic stroke; Stroke: ischaemic and haemorrhagic stroke

P_{int}: P interaction against study design (RCT, community-based, hospital-based studies); type of ischaemic event (TIA, ischaemic stroke or mixed TIA and ischaemic stroke), TIA/ischaemic stroke aetiology (large artery atherosclerosis, small vessel disease or cardio-embolism), or incident TIA or ischaemic stroke (incident vs. combined (incident and recurrent) or unspecified TIA/IS). There was a significant heterogeneity across studies in all analyses with $p < 0.001$, except * $p=0.0179$, † $p=0.79$, ‡ $p=0.14$, § $p=0.0274$, || $p=0.0301$, # $p=0.74$

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

Risk of myocardial infarction

The annual risk of myocardial infarction was 1.67% (95%CI 1.36-1.98, 46 studies, 100,786 patients, with significant heterogeneity across studies, $P_{het} < 0.001$). 96% of the heterogeneity across studies was explained by study design, study period, duration of follow-up, mean age, prevalence of antithrombotic therapy and incident vs. combined IS/TIA. The annual risk of myocardial infarction significantly decreased over time ($P_{int}=0.021$, Figure 2). This time trend did not differ between community-based studies (7 studies, 34,749 patients) versus hospital-based studies and RCTs (51 studies, 96,550 patients, $P_{int}=0.58$). The risk of myocardial infarction was lower in studies that enrolled patients after 2005 (0.90%, 95%CI 0.49-1.32, 6 studies, 5914 patients) than in those that enrolled patients between 1990 and 2005 (1.53%, 95%CI 1.14-1.91, 26 studies, 83,884 patients), and before 1990 (2.32%, 95%CI 1.63-3.00, 14 studies, 10,988 patients, $P_{int}=0.015$). The mean systolic blood pressure at stroke admission ($P_{int}=0.02$) and the prevalence of current smokers ($P_{int}=0.04$) have decreased over time, whereas the mean age ($P_{int}=0.81$) and the proportion of men ($P_{int}=0.65$) have not. The risk of myocardial infarction did not significantly vary with the duration of follow-up (range 1.0-10.0 years, $P_{int}=0.88$, Figure 3). The annual risk of myocardial infarction was higher in studies restricted to patients with history of coronary artery disease (1.91%, 95%CI 1.45-2.37, 5 studies, 2309 patients) than in those without (0.85%, 95%CI 0.56-1.14, 3 studies, 7795 patients, $P_{int}=0.036$). When restricting to studies with a mid-year period ≥ 2000 , the annual risk of myocardial infarction was 1.02% (95%CI 0.68-1.36, 3 studies, 3351 patients) in patients with no history of coronary artery disease and 3.64% (1.59-5.69, 3 studies, 1163 patients) in those with coronary artery disease ($P_{int}<0.001$).

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

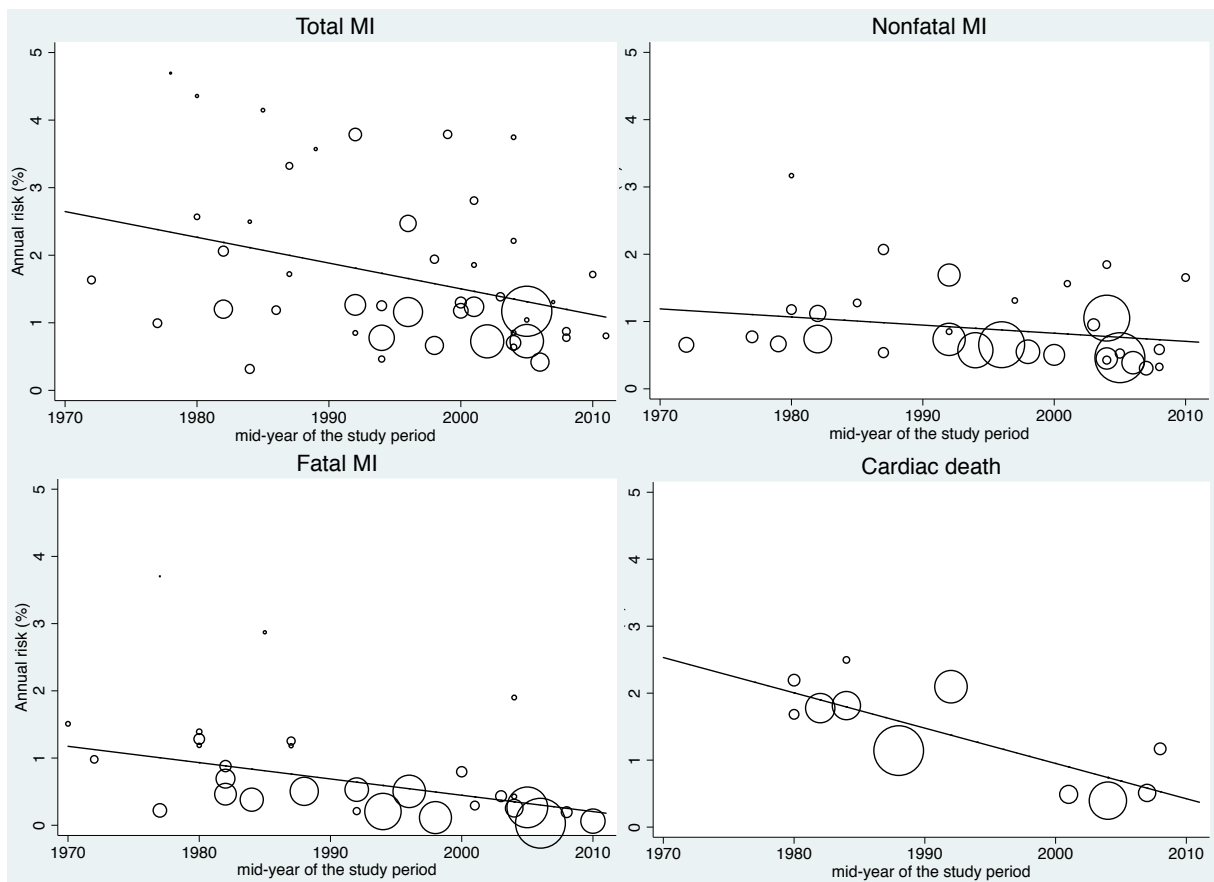


Figure 2 : Evolution of the annual risks of myocardial infarction (MI) and cardiac death in TIA or ischaemic stroke patients over time

The size of the plot is inversely proportional to the within study variance.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

There was no significant difference in the risk of myocardial infarction between study designs ($P_{int}=0.48$), types of ischaemic event ($P_{int}=0.42$) and incident versus combined or unspecified TIA or ischaemic stroke ($P_{int}=0.62$, Table 6). Although number of studies reporting the risk of myocardial infarction by stroke aetiology was small, the risk did not seem to differ between large artery atherosclerosis, small vessel disease and cardio-embolism ($P_{int}=0.91$, Table 6). The annual risk of myocardial infarction did not differ according to whether an explicit definition of myocardial infarction was reported or not ($P_{int}=0.54$, Tables 2 and 3). The sensitivity analysis restricted to studies with recruitment delay < 1 month from stroke onset (2.10%, 95%CI 1.30-2.90, 11 studies, 3015 patients, $P_{het} < 0.001$) and those with completeness of follow-up ≥ 90 % (1.78%, 95%CI 1.39-2.17, 41 studies, 111,729 patients, $P_{het} < 0.001$) found a similar risk of myocardial infarction to the overall risk.

The annual risk of fatal myocardial infarction was 0.66% (95%CI 0.46-0.86, 30 studies, 50,364 patients, $P_{het} < 0.001$). There was a significant decrease in the annual risk of fatal myocardial infarction over time ($P_{int}=0.002$, Figure 2), with no variation with the duration of follow-up (range 1.0-10.0 years, $P_{int}=0.25$, Figure 3). There was no significant difference in the risk between study designs ($P_{int}=0.96$), types of ischaemic event ($P_{int}=0.88$) and incident versus combined or unspecified TIA/ischaemic stroke ($P_{int}=0.95$, Table 6).

The annual risk of nonfatal myocardial infarction was 0.88% (95%CI 0.70-1.07, 31 studies, 65,808 patients, $P_{het} < 0.001$). The risk of nonfatal myocardial infarction was higher in RCTs (1.15%, 95%CI 0.81-1.49, 13 studies, 33,352 patients) than in community- (0.47%, 95%CI 0.38-0.56, 2 studies, 3809 patients) and hospital-based studies (0.73%, 95%CI 0.52-0.95, 16 studies, 28,647 patients, $P_{int}=0.020$). There was no evidence for a variation over time ($P_{int}=0.14$, Figure 2) or with the duration of follow-up (range 1.0-10.0 years, $P_{int}=0.45$, Figure 3). There was no difference in the risk between types of ischaemic event ($P_{int}=0.84$) and incident versus combined or unspecified TIA/ischaemic stroke ($P_{int}=0.67$, Table 6).

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

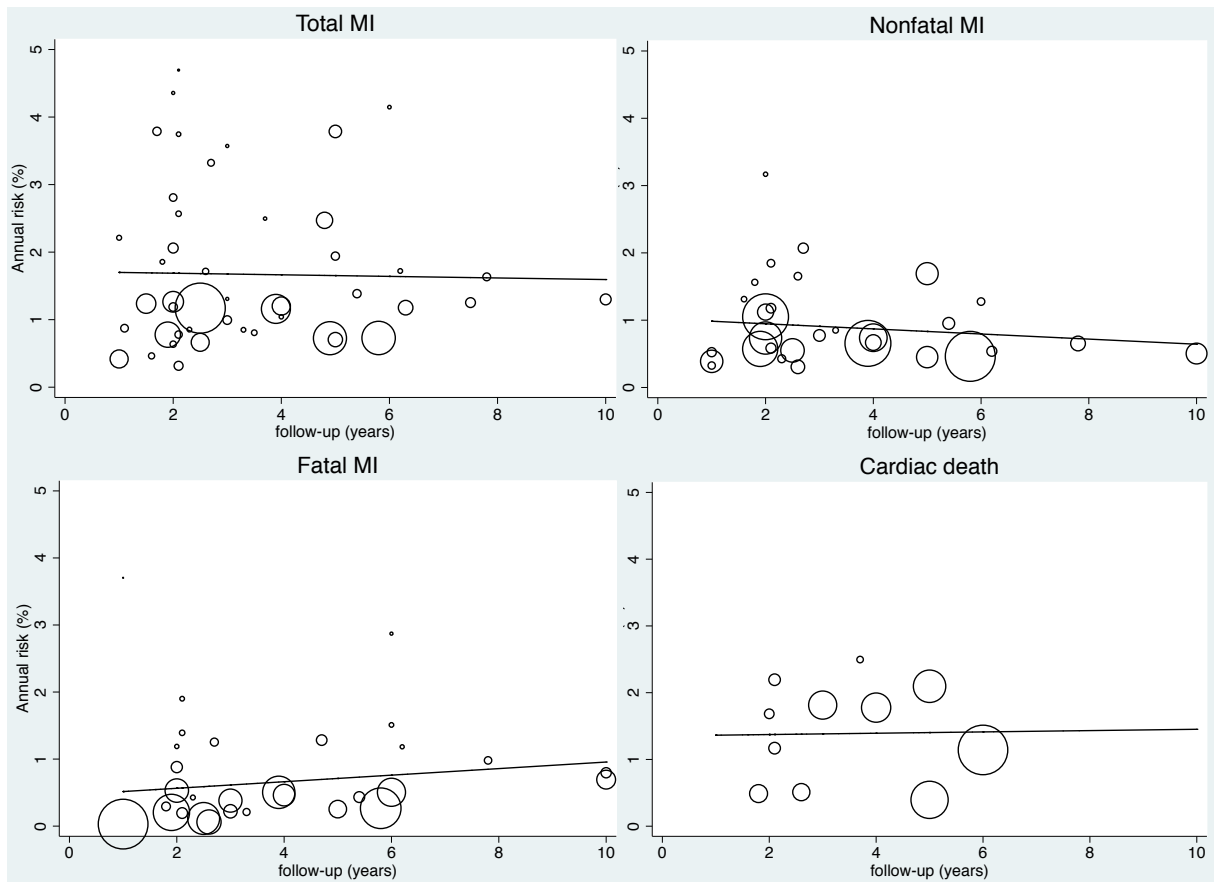


Figure 3 : Evolution of the annual risks of myocardial infarction (MI) and cardiac death in TIA or ischaemic stroke patients with the duration of study's follow-up

The size of the plot is inversely proportional to the within study variance.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

Risk of recurrent stroke

The annual risk of recurrent stroke was 4.26% (95%CI 3.43-5.09, 34 studies, 73,184 patients, $P_{het}<0.001$). 60% of the heterogeneity across studies was explained by study design, study period, duration of follow-up, mean age, proportion of patients on antithrombotic therapy and incident vs. combined IS/TIA. The risk of recurrent stroke did not markedly vary over time ($P_{int}=0.63$, Figure 4) and significantly decreased with the duration of follow-up (range 1.0-10.0 years, $P_{int}<0.001$, Figure 5).

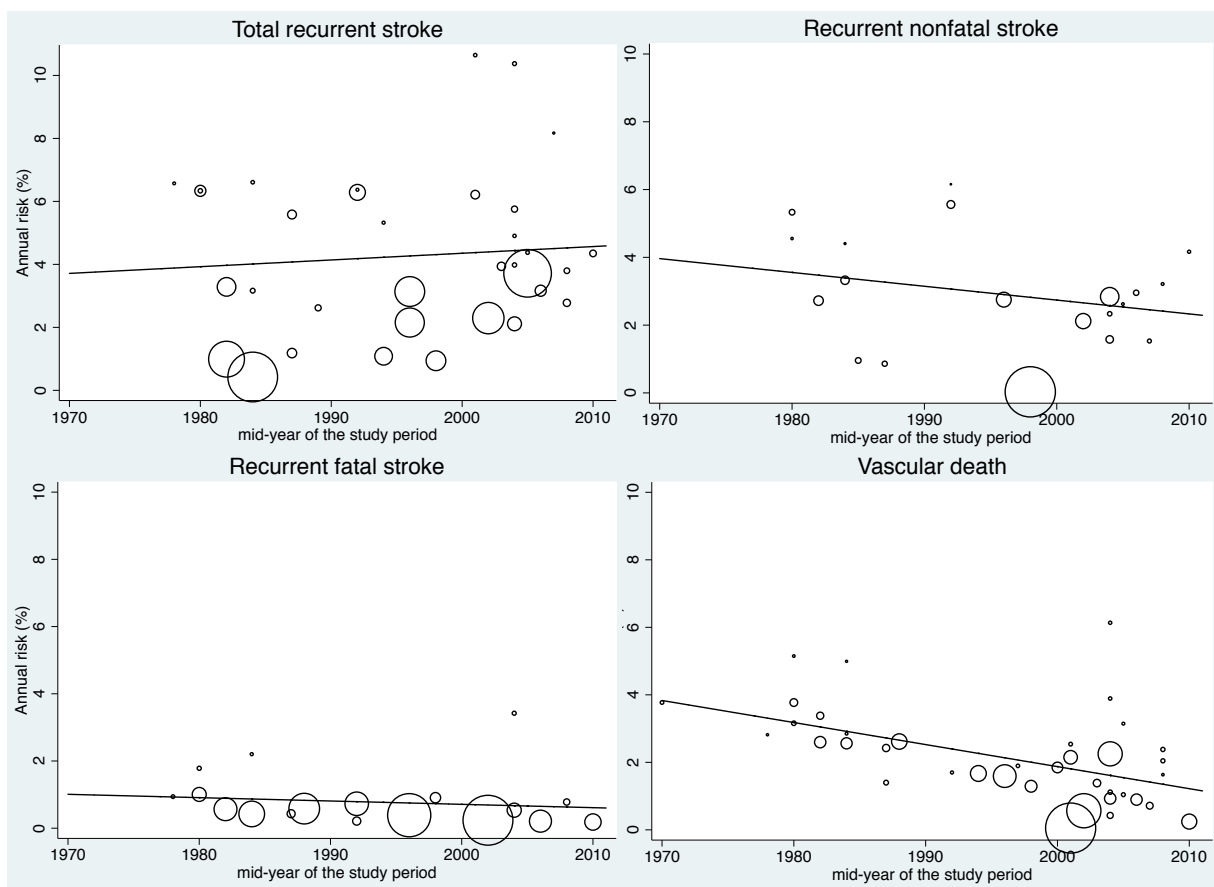


Figure 4 : Evolution of the annual risks of recurrent stroke and vascular death in TIA or ischaemic stroke patients over time

The size of the plot is inversely proportional to the within study variance.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

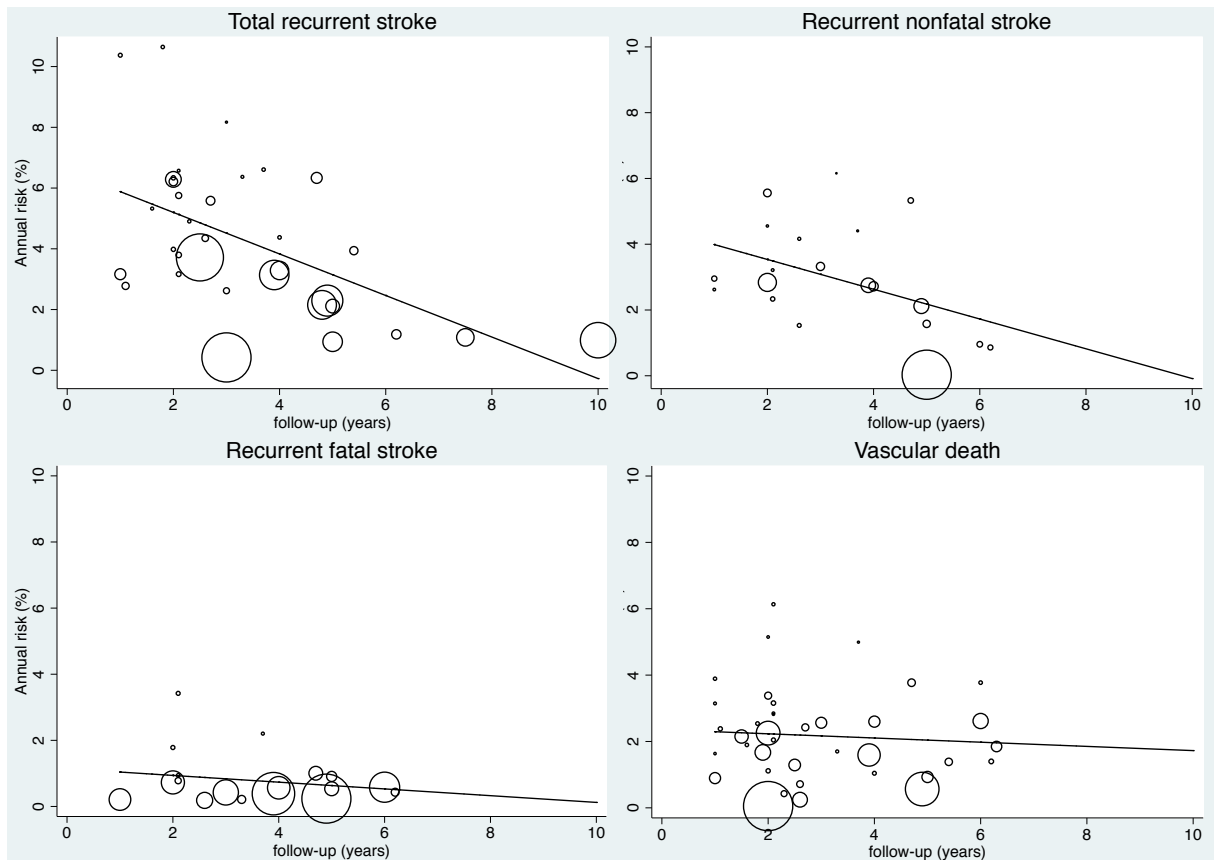


Figure 5 : Evolution of the annual risks of recurrent stroke and vascular death in TIA or ischaemic stroke patients with the duration of study's follow-up

The size of the plot is inversely proportional to the within study variance.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

The risk of recurrent stroke tended to be higher in RCTs (4.58%, 95%CI 3.26-5.91, 14 studies, 30,359 patients) and hospital-based studies (4.54%, 95%CI 3.35-5.72, 15 studies, 11,885 patients) as compared to community-based studies (2.55%, 95%CI 0.50-4.60, 5 studies, 30,940 patients, $P_{int}=0.18$, Table 6). No significant difference in the risk of recurrent stroke was observed between incident versus combined or unspecified TIA/ischaemic stroke ($P_{int}=0.95$) and types of ischaemic event ($P_{int}=0.35$), although the risk in studies reporting ischaemic stroke as well as a small proportion of haemorrhagic stroke was estimated to be lower than the one in TIA or ischaemic stroke studies (Table 6). The risk of recurrent stroke stratified by presence of coronary artery disease was reported in only one study.⁴⁹ The sensitivity analysis restricted to studies with inclusion delay < 1 month from stroke onset (5.07%, 95%CI 3.63-6.51, 14 studies, 4746 patients, $P_{het}<0.001$) and those with completeness of follow-up ≥ 90 % (4.56%, 95%CI 3.53-5.58, 21 studies, 60,310 patients, $P_{het}<0.001$) found a similar risk of recurrent stroke to the overall risk. The risk of recurrent stroke did not differ according to whether an explicit definition of recurrent stroke was reported or not ($P_{int}=0.28$, Tables 2 and 4).

The annual risk of recurrent fatal stroke was 0.77% (95%CI 0.45-1.10, 18 studies, 34,445 patients, $P_{het}<0.001$). The risk did not markedly vary over time ($P_{int}=0.55$, Figure 4) or with the duration of follow-up (range 1.0-6.2 years, $P_{int}=0.36$, Figure 5). There was no difference in the risk of recurrent fatal stroke between types of ischaemic event ($P_{int}=0.87$), and incident versus combined or unspecified TIA/ischaemic stroke ($P_{int}=0.58$), but the risk tended to be lower in RCTs (0.63%, 95%CI 0.40-0.86, 9 studies, 27,272 patients) and hospital-based studies (0.78%, 95%CI 0.02-1.57, 7 studies, 6350 patients) as compared to community-based studies (1.44%, 95%CI 0.19-2.69, 2 studies, 823 patients, $P_{int}=0.36$, Table 6).

The annual risk of recurrent nonfatal stroke was 2.92% (95%CI 2.22-3.62, 20 studies, 51,568 patients, $P_{het}<0.001$). The risk did not markedly vary over time ($P_{int}=0.24$, Figure 4) and significantly decreased with the duration of follow-up (range 1.0-6.2 years, $P_{int}=0.031$, figure 5). There was no difference in the risk between study designs ($P_{int}=0.51$) and incident versus combined or unspecified TIA/ischaemic stroke ($P_{int}=0.83$, Table 6).

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

Risk of vascular death

The annual risk of cardiac death was 1.38% (95%CI 0.96-1.81, 11 studies, 15,050 patients, $P_{\text{het}} < 0.001$). 68% of the heterogeneity between studies was explained by study design, study period, duration of follow-up, mean age, and proportion of patients on antithrombotic therapy. We could not explore the influence of incident vs. combined TIA/ischaemic stroke on the heterogeneity across studies due to insufficient data. The risk of cardiac death significantly decreased over time ($P_{\text{int}} < 0.001$, Figure 2) and was estimated to be 0.54% (95%CI 0.28-0.80, 4 studies, 2145 patients, $P_{\text{het}} < 0.18$) in studies which enrolled patients from 2000. That risk did not markedly vary with the duration of follow-up (range 1.0-10.0 years, $P_{\text{int}} = 0.95$, Figure 3). There was no significant difference in the risk of cardiac death between study designs ($P_{\text{int}} = 0.60$), types of ischaemic event ($P_{\text{int}} = 0.51$) and incident versus combined or unspecified TIA/ischaemic stroke ($P_{\text{int}} = 0.71$, Table 6). None of the studies reported data on the risk of cardiac death stratified by presence of coronary artery disease. The sensitivity analysis restricted to studies with recruitment delay < 1 month from stroke onset (1.47%, 95%CI 0.33-2.60, 3 studies, 1066 patients, $P_{\text{het}} < 0.01$) and those with completeness of follow-up ≥ 90 % (1.43%, 95%CI 0.92-1.94, 8 studies, 11,177 patients, $P_{\text{het}} < 0.001$) found similar risk of cardiac death to the overall risk.

The annual risk of vascular death was 2.17% (95%CI 1.75-2.59, 38 studies, 76,501 patients, $P_{\text{het}} < 0.001$). 80% of the heterogeneity between studies was explained by study design, study period, duration of follow-up, mean age, proportion of patients on antithrombotic therapy and incident vs. combined TIA/ischaemic stroke. The risk of vascular death significantly decreased over time ($P_{\text{int}} < 0.001$, Figure 4) and was estimated to be 1.71% (95%CI 1.11-2.32, 20 studies, 45,060 patients, $P_{\text{het}} < 0.001$) in studies that enrolled patients from 2000. This risk did not markedly vary with the duration of follow-up (range 1.0-10.0 years, $P_{\text{int}} = 0.64$, Figure 5). There was no significant difference in the risk of vascular death between study designs ($P_{\text{int}} = 0.62$), types of ischaemic event ($P_{\text{int}} = 0.65$) and incident versus combined or unspecified TIA/ischaemic stroke ($P_{\text{int}} = 0.91$, Table 6). The annual risk of vascular death was significantly higher in patients with history of coronary artery disease (3.10%, 95%CI 2.78-3.43, 3 studies, 7513 patients, $P_{\text{het}} = 0.23$), than in those without (1.41%, 95%CI 0.95-1.88, 3 studies, 15160 patients, $P_{\text{het}} = 0.001$, $P_{\text{int}} < 0.0001$). The sensitivity analysis restricted to studies with recruitment delay < 1 month from stroke onset (2.33%, 95%CI 1.14-3.51, 9 studies, 2833 patients, $P_{\text{het}} < 0.001$) and those with completeness of follow-up ≥ 90 % (2.30%, 95%CI 1.82-2.78, 31 studies, 69,064 patients), $P_{\text{het}} < 0.001$) found similar risk of vascular death to the overall risk.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

Comparison of the risk of myocardial infarction and recurrent stroke

Numbers of fatal and nonfatal myocardial infarction and recurrent stroke along with respective incidence ratios are reported for each study in Table 2. In studies reporting both the numbers of fatal myocardial infarction and recurrent fatal stroke, the risk of fatal myocardial infarction was half the risk of recurrent fatal stroke (incidence ratio=0.51, 95%CI 0.14-0.89, 14 studies, 29,451 patients, $P_{het}=0.58$), with a decreasing trend over time ($P_{int}=0.14$, Figure 6). That ratio did not markedly vary with the duration of follow-up ($P_{int}=0.16$). TIA/ischaemic stroke patients were 75% less likely to develop a nonfatal myocardial infarction than a recurrent nonfatal stroke in studies reporting both the numbers of nonfatal myocardial infarction and recurrent nonfatal stroke (incidence ratio=0.25, 95%CI 0.02-0.50, 15 studies, 42,330 patients, $P_{het}=0.68$), with no change over time ($P_{int}=0.73$) or with the duration of follow-up ($P_{int}=0.55$, Figure 6).

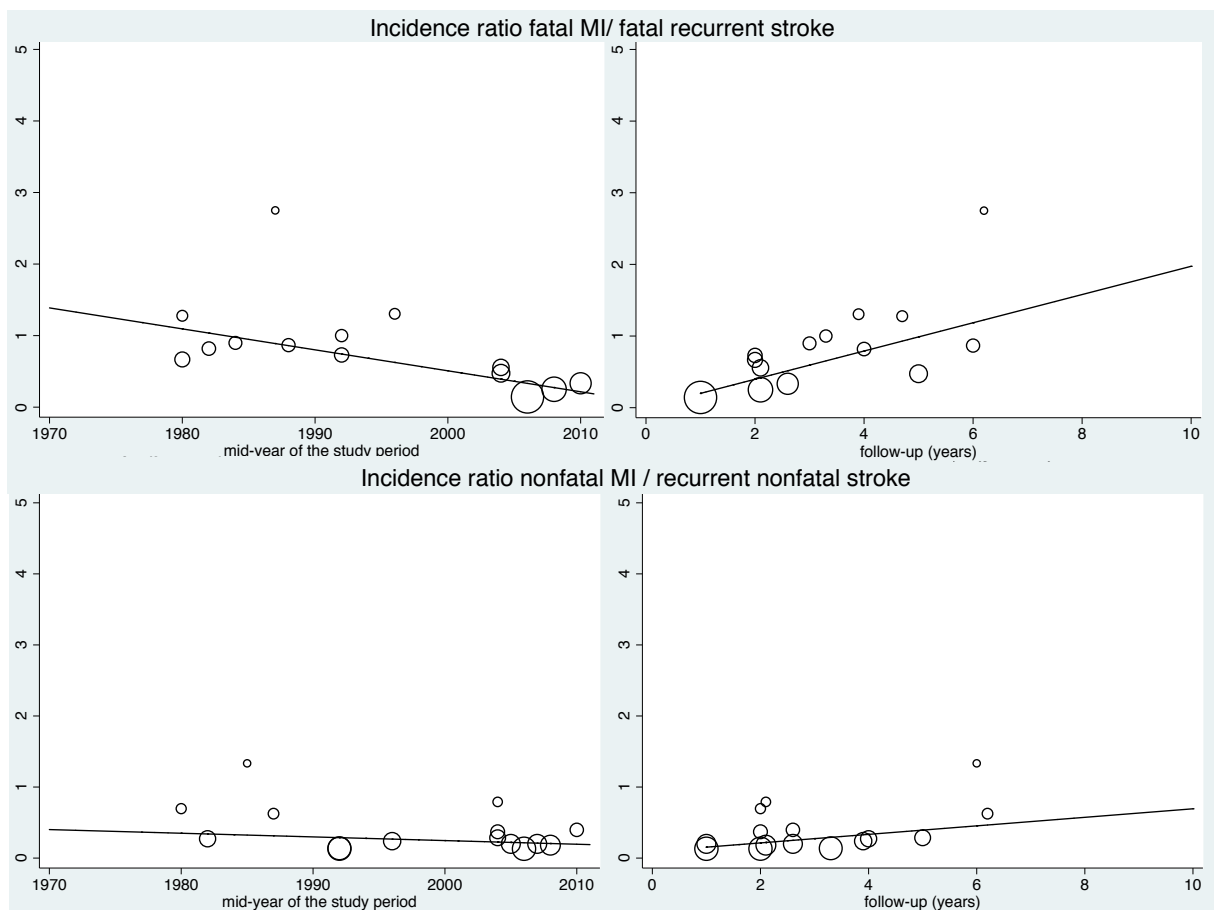


Figure 6 : Evolution of the incidence ratio of fatal and nonfatal myocardial infarction (MI) / recurrent stroke over time and with the duration of study's follow-up

The size of the plot is inversely proportional to the within study variance.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

Numbers of cardiac death and the incidence ratio of cardiac death / recurrent fatal stroke are given for each study in Table 2. There was a non-significant higher risk of cardiac death than recurrent fatal stroke in studies reporting both the numbers of cardiac death and recurrent fatal stroke (incidence ratio=1.39, 95%CI 0.52-2.27, 7 studies, 10,399 patients, $P_{het}=0.68$), with no change over time ($P_{int}=0.60$) or with the duration of follow-up ($P_{int}=0.97$, Figure 7).

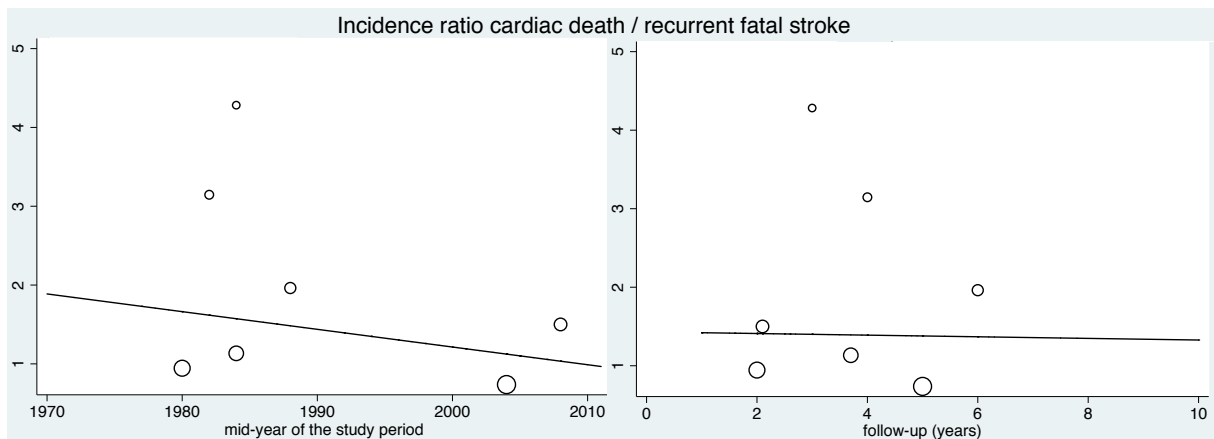


Figure 7 : Evolution of the incidence ratio of cardiac death / recurrent fatal stroke against study's duration follow-up and over time

The size of the plot is inversely proportional to the within study variance.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
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Risk factors for myocardial infarction

Pooled rate ratios for myocardial infarction, when calculable, are presented in figure 8. Male sex ($p < 0.001$), history of hypertension ($p = 0.022$), coronary ($p < 0.001$) and peripheral artery diseases ($p = 0.0043$) were associated with a doubled risk of myocardial infarction. There was no significant difference in the risk of myocardial infarction in patients with a history of atrial fibrillation ($RR = 0.87$, $95\%CI = 0.47-1.50$), diabetes ($RR = 1.14$, $95\%CI = 0.71-1.76$), and current smoking ($RR = 1.21$, $95\%CI = 0.83-1.73$) compared to those without. Only one study investigated dyslipidemia as a potential risk factor for myocardial infarction and found a significant increased likelihood of myocardial infarction in patients with dyslipidemia than in those without, in univariate but not in multivariate analysis.⁵⁰ We could not assess the influence of biomarkers and genetic variants on the risk of myocardial infarction because no study reported this information.

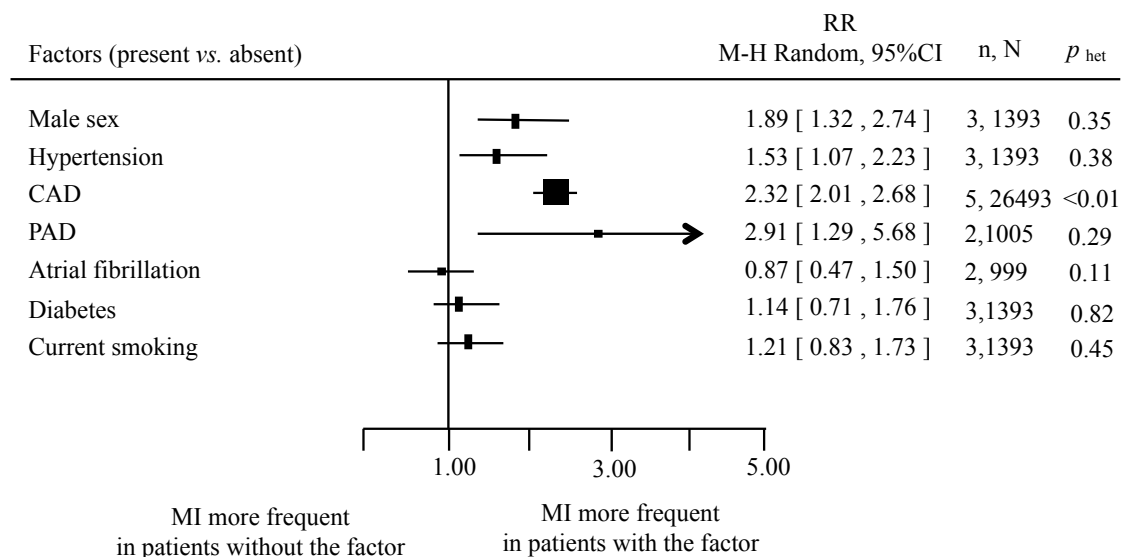


Figure 8 : Forest plots of the meta-analyses of potential risk factors for myocardial infarction (MI) in TIA or ischaemic stroke patients

RR: rate ratio, M-H: Mantel-Haenszel, CI: confidence interval, n: number of studies, N: number of patients, p_{het} : p value for heterogeneity, CAD: coronary artery disease, PAD: peripheral artery disease.

The size of the square is proportional to the sample size of the study.

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Discussion

In this meta-analysis of TIA/ischaemic stroke patients, the risks of myocardial infarction, cardiac and vascular deaths significantly decreased over time. The risk of subsequent myocardial infarction was estimated to range between 0.49%/year and 1.32%/year since 2005. On the opposite, the risk of recurrent stroke did not markedly vary over time. TIA/ischaemic stroke patients were found to be more likely to have a recurrent fatal stroke than a fatal myocardial infarction. Unlike the risk of recurrent stroke that seemed to decrease with time after the index stroke, the risks of myocardial infarction, cardiac and vascular deaths after TIA/ischaemic stroke remained stable. Male sex, history of hypertension, coronary and peripheral artery disease were associated with a doubled risk of myocardial infarction.

Our review shows that, overall, the current risk of myocardial infarction after TIA/ischaemic stroke is below 1.3%/year, *i.e.* less than the usual threshold considered to classify high risk patients ($\geq 20\%$ at 10 years).⁵¹ Observed decrease in the risks of total myocardial infarction, fatal myocardial infarction and cardiac death over time may be partly explained by a better management of acute myocardial infarction. However, in such case, an increase in the risk of nonfatal myocardial infarction over time would have been expected. As that risk has not markedly varied over time, the variation in the risk of myocardial infarction is likely to be due to the reduction in the prevalence of vascular risk factors. In particular, the substantial reduction in the rate of current smoking observed over time and the improvement of secondary prevention (the decrease in blood pressure levels observed over time as well as the use of high dose of statin drugs since 2006¹⁷) might well have contributed to this decrease. Additionally, a fall in the incidence of myocardial infarction over time in the general population (not restricted to stroke patients) has been reported previously in population-based studies,^{52,53} and is likely to be attributable to the treatment of modifiable risk factors.

By contrast, despite improvement in secondary prevention of stroke,^{54,55, 56} the risk of recurrent stroke did not seem to have significantly varied over time. Unlike myocardial infarction in which the only underlying mechanism is large artery atherosclerosis, the heterogeneity in stroke aetiology may partly explain this lack of reduction in the risk of recurrent stroke over time. Findings from a nation-wide register of stroke patients suggest that the reduction in the risk of stroke recurrence observed over time was mainly due to the decrease in the early risk of stroke recurrence. On the contrary, temporal trends of the long-term risk of recurrence showed no significant variation over time.⁵⁷ However, this study was subjected to selection bias as only young patients were included. Another population-based study reporting temporal trends of

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recurrent stroke separately at various time-points after the index stroke has not identified any significant decrease over time in the risk of stroke recurrence in patients of all age ranges.⁵⁸ Our review updates the general assumption that cardiac events remained the main cause of death after stroke.²³⁻²⁶ The significant decrease observed over time in the risks of fatal myocardial infarction and cardiac death but the relative stability of the risk of recurrent fatal stroke over time are likely to explain previous findings. In our review of studies reporting the number of myocardial infarctions as long as of cardiac death and recurrent fatal stroke, the risks of cardiac death and recurrent fatal stroke were comparable. Additionally, TIA/ischaemic stroke patients were found to be more likely to have a recurrent fatal stroke than a fatal myocardial infarction. Uncertainties remain about the other causes of cardiac death not classified as attributable to myocardial infarction and how to prevent them, most of these cardiac deaths being classified as sudden deaths.

Our findings have several implications for further research on secondary prevention of TIA/ischaemic stroke. First, the current relatively low absolute risk of fatal myocardial infarction after TIA/ischaemic stroke, especially in patients without history of coronary artery disease, suggests that a RCT aiming to assess effect on mortality of screening for asymptomatic coronary artery disease in TIA/ischaemic stroke patients would require thousands of patients to show a benefit. For instance, in a trial of TIA/ischaemic stroke patients aiming to show a relative risk reduction of 30% on mortality from myocardial infarction between those who would benefit from a screening for asymptomatic coronary artery disease and those who would not, with a 80% power and a 0.05 two-sided p value, and assuming an annual risk of fatal myocardial infarction of 0.65%, a total of 45,000 patients would be needed. Second, although the sample size of studies reporting the risk of myocardial infarction by stroke subtype was small, the risk did not seem to differ across stroke aetiology, suggesting that similar intensive preventive strategies should be implemented in patients with any subtype of stroke. Additionally, the risks of myocardial infarction, recurrent stroke and cardiac and vascular deaths did not significantly differ between TIA and ischaemic stroke, suggesting that ischaemic stroke and TIA patients should benefit from equal therapy to lower these risks. Third, male sex, history of hypertension, coronary and peripheral artery disease were associated with a doubled risk of myocardial infarction after TIA/ischaemic stroke. However, these factors are not so helpful in clinical practice as they are highly prevalent in stroke patients and patients after stroke receive antithrombotic and antihypertensive therapies that lower their risk. Clinically useful scores are required to risk stratify patients at high risk of myocardial infarction after stroke.

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Our study has some limitations. First, although we only included studies with ≥ 100 patients to minimize the risk of chance finding due to small sample size and used a random-effect meta-analysis model, there was substantial heterogeneity across studies in the absolute risks. Substantial heterogeneity across studies, *i.e.* the variability in the estimates due to clinical and/or methodological differences between studies, is not uncommon in meta-analyses of absolute risks. Because of this heterogeneity between studies, the interpretation of our pooled estimates of absolute operative risks might not be seen as straightforward. However, the 95%CI obtained through a random effect meta-analysis well describes uncertainty in the average risk. For instance, looking at all studies, the risk of myocardial infarction was 1.67%/year, with 95%CI interval, at least equal to 1.36%/year and as high as 1.98%/year. As suggested for meta-analyses in the presence of heterogeneity within studies, the use of funnel plot and test for small-effect study are not appropriate.²⁴⁻²⁷ Heterogeneity can cause asymmetric funnel plots, even in the absence of publication bias, and may therefore lead to false-positive claims for publication bias. Therefore, we did not report funnel plots. However, we examined potential sources of heterogeneity in the overall risk of each event. This revealed that at least 60% of the heterogeneity across studies in the absolute risks was explained by the following studies 'characteristics: study design, study period, duration of follow-up, incident versus combined or unspecified TIA/ischaemic stroke, mean age, and proportion of patients on antithrombotic therapy. However, these potential sources need to be interpreted with caution as these analyses are exposed to ecological biases.²⁸ On the opposite, there was no significant heterogeneity in the incidence ratios of myocardial infarction / recurrent stroke and of cardiac death/ recurrent fatal stroke. Second, the majority of studies did not report a definition of myocardial infarction or recurrent stroke. However, there was no significant difference in the risks of myocardial infarction and recurrent stroke between studies which reported a specified definition and those which did not. Among studies reporting a definition of recurrent stroke, only one required a period of neurological stability and the likelihood of an underestimated risk of early recurrent stroke was therefore low. Third, the average follow-up duration of studies was 2 to 4 years and scarce information was available on the very long-term risk of myocardial infarction. Ageing, which is likely to increase the risk of myocardial infarction, rises with the duration of follow-up and we cannot exclude that the risk of myocardial infarction rises later on. Delay from stroke onset to inclusion was several weeks or months, precluding us to assess the early risk of myocardial infarction and cardiac death and higher early risks after stroke cannot be ruled out. However, the sensitivity analyses restricted to studies with recruitment delay < 1 month from stroke onset found similar results to the overall findings.

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I.2. Time trends (2002-2014) in the risk of coronary events and of recurrent ischaemic stroke after TIA or ischaemic stroke at the population-level

Boulanger M, Li L, Lyons L, Lovett NG, Kubiak MM, Silver L, Touzé E, Rothwell PM on behalf of the Oxford Vascular Study.

Preamble

Data used for these analyses are those collected from patients recruited from 2002 to 2014 in the Oxford Vascular Study (OXVASC). However, in order to study the temporal trends in the risk of coronary events and recurrent ischaemic stroke in TIA or ischaemic stroke patients over three 5-year study periods (2002-2017), I planned to complete the analyses with data on patients recruited from 2002 to 2017, with follow-up extended up to April 2020. This part of the thesis has therefore not been submitted for publication at the time of the redaction of the thesis.

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Abstract

Background and Purpose: Whether the improvement of the prognosis of TIA or ischaemic stroke over the last 15 years, as reported in trials, remained at the population level is uncertain. In a population-based cohort of TIA or ischaemic stroke patients, we determined temporal trends in the risk of follow-up coronary events and recurrent ischaemic stroke from 2002 to 2014.

Methods: In a population-based cohort of consecutive patients with TIA or ischaemic stroke (OXVASC), we determined the temporal trends in the risk of coronary events and of recurrent ischaemic stroke for 3 different study periods (2002-2007; 2007-2012; and 2012-2014), based on changes in secondary prevention management. Additionally, we assessed whether any change in the risk was independent of vascular risk factors (i.e. age, sex, prior hypertension, diabetes mellitus, hyperlipidaemia, history of smoking, previous TIA or ischaemic stroke, history of coronary or peripheral artery disease) and presence of large artery disease TIA/ischaemic stroke subtype, that have been shown to be associated with higher risk of recurrent ischaemic events, using multivariable Cox analysis.

Results: Over the three study periods, TIA/ischaemic stroke patients (n total=2555) were younger and were less likely to have had a previous TIA or ischaemic stroke, prior peripheral artery disease and prior hypertension. The risk of follow-up coronary events significantly decreased over time ($p < 0.001$), with 1-year risk decreasing from 3.3% (95%CI 2.2-4.5) in 2002-2007 to 1.0% (95%CI 0.1-2.0; $p = 0.0057$) in 2012-2014. The risk of recurrent ischaemic stroke also significantly decreased over time (1-year risk=13.9%, 95%CI 11.6-16.0 versus 6.1%, 95%CI 3.7-8.5; $p < 0.001$). These trends were independent of any change in vascular risk factors and presence of large artery disease TIA/ischaemic stroke subtype with a multivariable adjusted hazard ratio of 0.56 (95% CI 0.39-0.79, $p = 0.0011$) for the risk of coronary events and of 0.72 (95% CI 0.58-0.89, $p = 0.0023$) for risk of recurrent ischaemic stroke in the 2nd study period and of 0.47 (0.31-0.72, $p < 0.0001$) and 0.69 (0.57-0.85, $p < 0.0001$) in the 3rd study period, compared to the 1st study period.

Conclusion: The risk of coronary events and of recurrent ischaemic stroke after TIA/ischaemic stroke has significantly decreased since 2002 at the population level, most likely due to the improvement of secondary prevention. These time trends highlight the need of implementing further strategies to continue to improve the prognosis of TIA/ischaemic stroke patients.

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Introduction

Previous studies showed that the risk of coronary events after TIA or ischaemic stroke has decreased between the 1970s and the early 2000s while the risk of recurrent stroke has not markedly varied over the same period of time.⁵⁹ Since then, secondary prevention of TIA/ischaemic stroke has improved further in the last 15 years and guidelines for management of TIA/ischaemic stroke patients have been updated.⁶⁰⁻⁶² In particular, trial of further decrease of blood pressure levels targets³⁴ and of the use of higher dose of statins¹⁷ in TIA/ischaemic stroke patients have reported significant reduction in the risk of recurrent ischaemic events. However, the real impact of these recent changes in secondary prevention on the prognosis of TIA/ischaemic stroke patients at the population-level, outside randomized controlled trials, remains uncertain. Also, if the prognosis of TIA/ischaemic stroke has improved over time, whether this improvement remained beyond the first months after the TIA/ischaemic stroke (*i.e.*, the relatively short period as evaluated in randomised clinical trials) is unknown. Assessing the impact of changes in secondary prevention on the prognosis of TIA/ischaemic stroke patients at the population level is required to allow future strategies in TIA/ischaemic stroke care to be implemented appropriately, particularly with trials of new lipids lowering therapies reporting significant reduction in the risk of coronary events in patients with cardiovascular diseases.

In a population-based study of consecutive TIA or ischaemic stroke patients, we aimed to determine temporal trends in the risk of follow-up coronary events and recurrent ischaemic stroke from 2002 to 2014.

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Methods

The Oxford Vascular study (OXVASC) is an ongoing population-based study of the incidence and outcome of all acute vascular events (myocardial infarction, stroke, peripheral artery disease).⁶³ The study population comprised all 92,728 individuals, irrespective of age, registered with 100 family physicians in nine general practices in Oxfordshire, UK. The analysis reported here included consecutive cases, irrespective of age, with a first TIA or ischaemic stroke from April 1, 2002, to March 31, 2014, with follow-up until September 30, 2014. The OXVASC study design has been described in detail previously.⁶³ Briefly, multiple overlapping methods of hot and cold pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke.^{64, 65} These include: 1) a daily, rapid access “TIA and stroke clinic” to which participating general practitioners and the local emergency department refer individuals with suspected TIA or minor stroke; 2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; 3) daily searches of the local emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner’s reports for out of hospital deaths; 6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals. Patients gave written informed consent after an event or assent was obtained from a relative for patients who were unable to provide consent. OXVASC was approved by our local research ethics committee.

Demographic data, prior comorbidities and medication were collected from face-to-face interviews and cross-referenced with primary care records. All cases were investigated and treated according to contemporary guidelines. Patients were classified as having a prior coronary artery disease if they had at least one of the following: previous myocardial infarction; unstable angina; angina; previous percutaneous coronary intervention or coronary artery bypass graft surgery. Prior peripheral artery disease was defined as having at least one of the following: previous acute limb ischemia; critical limb ischemia; intermittent claudication; previous angioplasty or stenting; peripheral arterial bypass graft or amputation. For intermittent claudication, the diagnosis was based on the judgement of the study clinician based on both prior medical records and symptoms. Written informed consent or assent from relatives was obtained in all patients. OXVASC was approved by our local research ethics committee.

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Standard definitions were used for TIA and stroke, which have been reported previously.^{63, 64} All cases were reviewed by a senior neurologist (PMR) and TIA/ischaemic stroke aetiology was categorised according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Appendix I).⁶⁶ All patients were followed up face to face at 1, 6, 12, 60 and 120 months by a study nurse or physician and subsequent vascular events identified. For patients who had moved out of the study area, telephone follow-up was done, and patients with dementia were followed-up via a carer or by assessment in a nursing home. All recurrent events that presented to medical attention would also be identified by ongoing daily case-ascertainment of all acute vascular events in the study population. All study patients were also notified to the UK Office of National Statistics such that all deaths were reported back to the study with causes. Deaths were also identified by regular review of primary care records and by regular contact with the Coroner's Office to ascertain out-of-hospital deaths.

If a recurrent non-fatal vascular event was suspected, the patient was re-assessed by a study physician. Myocardial infarction in OXVASC was defined using standard criteria.⁶⁷ Sudden cardiac death was defined using recommendations in Epidemiology and Clinical Research Studies and required a definite history of preceding symptoms consistent with acute coronary ischaemia, or post-mortem evidence of either significant coronary atherosclerosis or acute thrombosis, or a documented myocardial infarction during the previous 28 days.⁶⁸ Recurrent ischaemic stroke was defined as new neurological deficit fitting the definition for ischaemic stroke occurring after a period of neurological stability or improvement. Definitions of myocardial infarction, sudden cardiac death and recurrent ischaemic stroke remained unchanged over the period.

Statistical analysis

We determined the 1-month and 1-year risk of coronary events (defined as myocardial infarction or sudden cardiac deaths) and of recurrent ischaemic stroke after TIA or ischaemic stroke, censored at death or September 30, 2014 from Kaplan-Meier analyses for three different study periods in OXVASC (April 1 2002-March 31 2007; April 1 2007-March 31 2012; and April 1 2012-March 31 2014). The three study periods were chosen based on changes implemented in secondary prevention management in OXVASC. From 2007, following the publication of the SPARCL trial that showed a significant reduction in the risk of coronary events or recurrent stroke with high dose of atorvastatin compared to placebo,¹⁷ our policy was to routinely prescribe high dose of statins. From 2012, we have implemented Bluetooth blood pressure home monitoring in order to achieve higher blood pressure control. Patients were asked to measure their blood pressure every day three times in the morning 5 minutes apart

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and three times in the evening. Home blood pressure measurements were seen regularly by one of our study physicians and nurses and changes on antihypertensive medication were implemented on a monthly basis to achieve blood pressure control <130/80 mmHg. We assessed the temporal trends of the absolute risk of coronary events and of recurrent ischaemic stroke after TIA or ischaemic stroke between the three study periods in OXVASC in all patients, and after stratification by age using trend tests.

We assessed the temporal trends in the baseline characteristics and medication at baseline and during follow-up using Chi-square test for trend analysis for categorical variables and linear regression analysis for continuous variables.

Additionally, we assessed the risk of coronary events and of recurrent ischaemic stroke for each change in study period using Cox analysis. We also assessed whether any change in the risk over time was independent of vascular risk factors (i.e. age, sex, prior hypertension, diabetes mellitus, hyperlipidaemia, history of smoking, previous TIA or ischaemic stroke, history of coronary or peripheral artery disease) and presence of large artery disease TIA/ischaemic stroke subtype, that have been shown to be associated with higher risk of recurrent ischaemic events, using multivariable analysis.

Eventually, we determined whether the effects of baseline factors for the risk of coronary events and of recurrent ischaemic stroke have changed over the three study periods.

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Results

During 2002-2014, 2,555 patients with a TIA or an ischaemic stroke were included in OXVASC (Table 7). Over the three study periods, patients were younger and were less likely to have had a previous TIA or ischaemic stroke, prior peripheral artery disease and prior hypertension (Table 7). Hence, the rates of antithrombotics and antihypertensives use at baseline significantly decreased over the three study periods (Table 7). The use of antithrombotic and antihypertensive therapies during follow-up were high and did not markedly vary over time (Table 7). In contrast, the use of statins both at baseline and during follow-up significantly increased over time. Over time, there was less TIA/ischaemic stroke due to small vessel disease and more TIA/ischaemic stroke due to more than one cause, while the proportion of TIA/ischaemic stroke due to large artery disease, cardioembolism and cryptogenic cause remained stable over time (Table 7).

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Table 7 : Baseline characteristics in TIA or ischaemic stroke patients, based on study periods in OXVASC (2002-2014)

Baseline characteristics	April 1, 2002- March 31, 2014 (n=2555)	April 1, 2002- March 31, 2007 (n=1045)	April 1, 2007- March 31, 2012 (n=1069)	April 1, 2012- March 31, 2014 (n=441)	P _{trend}
Demographics					
Mean age (SD), years	73.9 (13.0)	75.0 (11.8)	73.2 (13.7)	72.3 (13.8)	0.0022
Age ≥75 years	1404 (55.0)	610 (58.4)	568 (53.1)	226 (51.3)	0.0043
Men	1262 (49.4)	497 (47.6)	542 (50.7)	223 (50.6)	0.30
Prior comorbidities					
Previous TIA or ischaemic stroke	349 (13.7)	212 (20.3)	108 (10.1)	29 (6.6)	<0.001
Atrial fibrillation	522 (20.4)	211 (20.2)	208 (19.4)	103 (23.4)	0.23
Hypertension	1537 (60.1)	654 (62.6)	641 (60.0)	242 (54.9)	0.007
Diabetes mellitus	357 (14.0)	124 (11.9)	179 (16.7)	54 (12.2)	0.26
Hyperlipidaemia	782 (30.6)	330 (31.6)	319 (29.8)	133 (30.2)	0.67
History of smoking*	1416 (55.4)	597 (57.1)	566 (52.9)	253 (57.4)	0.61
Current smoker*	361 (14.1)	150 (14.4)	152 (14.3)	59 (13.5)	0.66
Coronary artery disease	538 (21.1)	236 (22.6)	216 (20.2)	86 (19.5)	0.13
Peripheral artery disease	191 (7.5)	100 (9.6)	69 (6.5)	22 (5.0)	0.0006
TOAST subtypes					
Cardioembolic	669 (26.2)	289 (27.7)	248 (23.2)	132 (29.9)	0.94
Large artery disease	280 (11.0)	98 (9.4)	137 (12.8)	45 (10.2)	0.25
Small vessel disease	317 (12.4)	152 (14.5)	125 (11.7)	40 (9.1)	0.002
Cryptogenic	811 (31.7)	323 (30.9)	346 (32.4)	142 (32.2)	0.53
More than one cause	90 (3.5)	26 (2.5)	44 (4.1)	20 (4.5)	0.0238
Unknown	331 (13.0)	142 (13.6)	137 (12.8)	52 (11.8)	0.34
Other causes	57 (2.2)	15 (1.4)	32 (3.0)	10 (2.3)	0.12
Baseline therapies					
Anti-thrombotics	1100 (43.1)	502 (48.0)	435 (40.7)	163 (37.0)	<0.001
Anti-hypertensives	1486 (58.2)	629 (60.2)	616 (57.6)	241 (54.6)	0.0423
Statins	684 (26.8)	228 (21.8)	327 (30.6)	129 (29.3)	<0.001
Secondary prevention at 1-month follow-up‡					
	n=2339	n=940	n=996	n=403	
Anti-thrombotics	2196 (93.9)	871 (92.7)	940 (94.4)	385 (95.5)	0.0299
Anti-hypertensives	1771 (75.7)	722 (76.8)	753 (75.6)	296 (73.4)	0.19
Statins	1755 (75.0)	670 (71.3)	775 (77.8)	310 (76.9)	0.0054
Secondary prevention at 1-year follow-up‡					
	n=1976	n=827	n=886	n=318	
Anti-thrombotics	1884 (95.3)	763 (92.3)	820 (92.6)	302 (95.0)	0.17
Anti-hypertensives	1572 (79.6)	644 (77.9)	686 (77.4)	242 (76.1)	0.55
Statins	1589 (80.4)	639 (77.3)	684 (77.2)	266 (83.6)	0.0450

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Data are numbers (%), unless otherwise specified. * data missing for 9 patients, ‡ patients who died before the follow-up were not included
p-value for comparison between the 3 periods by chi-squared test for trend analysis for categorical variables and linear regression analysis for continuous variables.

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During 9,148 patients-years of follow-up, there were 158 coronary events, 413 recurrent ischaemic strokes and 1118 deaths. The 1-month risk of coronary events after TIA/ischaemic stroke significantly decreased over the three study periods from 1.4% (95%CI 0.7-2.2, Table 8, Figure 9) in 2002-2007 to 0.3% (95%CI, 0-0.7; $p_{\text{trend}}=0.0019$) in 2012-2014. The decrease in the risk of coronary events over time was also observed at 1-year of follow-up (3.3%, 95%CI 2.2-4.5; versus 1.0%, 95%CI 0.1-2.0; $p_{\text{trend}}=0.0057$, Table 8, Figure 9), particularly in patients aged ≥ 75 years (4.7%, 95%CI 2.8-6.5 versus 1.1%, 95%CI 0.-2.6; $p_{\text{trend}}=0.0174$). The risk of recurrent ischaemic stroke also significantly decreased over the three study periods (Table 9, Figure 9). The 1-month risk of recurrent ischaemic stroke decreased from 7.9%, 95%CI 6.2-9.5, Table 9, Figure 9) in 2002-2007 to 2.5% (95%CI 1.1-4.0; $p_{\text{trend}}<0.001$) in 2012-2014. The time trend of a reduction in the risk of recurrent ischaemic stroke remained at 1 year (13.9%, 95%CI 11.6-16.0; versus 6.1%, 95%CI 3.7-8.5; $p_{\text{trend}}<0.001$, Table 9, Figure 9).

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Table 8 : Time trend in the absolute risk of coronary events in patients with TIA or ischaemic stroke (2002-2014)

	April 1, 2002-March 31, 2007 (n=1045)		April 1, 2007-March 31, 2012 (n=1069)		April 1, 2012-March 31, 2014 (n=441)		p _{trend}	April 1, 2002- March 31, 2014 (n=2555)*	
	N	% (95%CI)	N	% (95%CI)	N	% (95%CI)		N	% (95%CI)
All patients									
1 month	14	1.43 (0.68-2.17)	2	0.19 (0-0.45)	1	0.25 (0-0.73)	0.002	17	0.70 (0.37-1.03)
1 year	31	3.34 (2.18-4.49)	15	1.58 (0.78-2.38)	4	1.01 (0.02-2.00)	0.006	50	2.19 (1.59-2.80)
3 years	56	6.48 (4.81-8.11)	32	3.59 (2.36-4.80)	-	-	-	94	4.42 (3.54-5.29)
5 years	73	8.91 (6.92-10.87)	45	5.31 (3.78-6.81)	-	-	-	124	6.35 (5.24-7.45)
Age<75 years		n=435		n=501		n=215			n=1151
1 month	2	0.46 (0-1.11)	1	0.20 (0-0.59)	0	-	0.52	3	0.26 (0-0.56)
1 year	7	1.69 (0.44-2.92)	4	0.83 (0.02-1.64)	2	0.95 (0.00-2.26)	0.47	13	1.18 (0.54-1.81)
3 years	13	3.19 (1.47-4.88)	9	1.91 (0.66-3.14)	-	-	-	24	2.22 (1.33-3.09)
5 years	17	4.25 (2.25-6.22)	12	2.57 (1.12-4.00)	-	-	-	31	3.02 (1.96-4.07)
Age≥75 years		n=610		n=568		n=226			n=1404
1 month	12	2.18 (0.95-3.39)	1	0.18 (0-0.52)	1	0.51 (0-1.51)	0.005	14	1.08 (0.52-1.65)
1 year	24	4.68 (2.82-6.49)	11	2.36 (0.97-3.74)	2	1.07 (0.00-2.55)	0.017	37	3.15 (2.14-4.15)
3 years	43	9.49 (6.71-12.19)	23	5.50 (3.27-7.68)	-	-	-	70	6.75 (5.19-8.29)
5 years	60	13.53 (10.07-16.85)	33	8.78 (5.81-11.66)	-	-	-	93	10.20 (8.14-12.22)

N: cumulative number of coronary events, n: number of patients, CI: confidence interval

*Risks at 3 and 5 years were for 2002-2012

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Table 9 : Time trend in the absolute risk of recurrent ischaemic stroke in patients with TIA or ischaemic stroke (2002-2014)

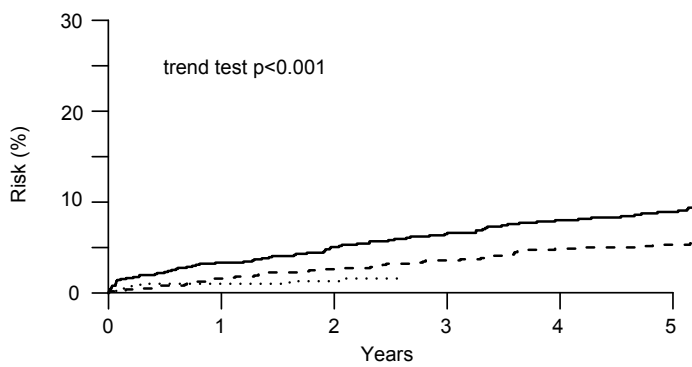
	April 1, 2002-March 31, 2007 (n=1045)		April 1, 2007-March 31, 2012 (n=1069)		April 1, 2012-March 31, 2014 (n=441)		ptrend	April 1, 2002- March 31, 2014 (n=2555)*	
	N	% (95%CI)	N	% (95%CI)	N	% (95%CI)		N	% (95%CI)
All patients									
1 month	79	7.85 (6.17-9.50)	48	4.61 (3.33-5.88)	11	2.54 (1.05-4.01)	<0.001	138	5.57 (4.66-6.47)
1 year	133	13.85 (11.63-16.02)	97	9.74 (7.88-11.57)	24	6.12 (3.70-8.49)	<0.001	254	10.78 (9.52-12.03)
3 years	175	19.10 (16.49-21.64)	127	13.34 (11.14-15.49)	-	-	-	331	15.26 (13.70-16.79)
5 years	204	23.32 (20.40-26.13)	145	16.76 (14.09-19.35)	-	-	-	378	19.24 (17.36-21.07)
Age<75 years		n=435		n=501		n=215			n=1151
1 month	45	10.48 (7.53-13.32)	21	4.22 (2.44-5.97)	4	1.86 (0.04-3.65)	<0.001	70	6.13 (4.73-7.52)
1 year	59	13.87 (10.52-17.09)	42	8.59 (6.07-11.04)	8	4.00 (1.23-6.69)	<0.001	109	9.71 (7.96-11.43)
3 years	71	16.91 (13.24-20.29)	57	11.87 (8.92-14.72)	-	-	-	136	12.79 (10.73-14.79)
5 years	84	20.37 (16.36-24.18)	64	14.09 (10.75-17.32)	-	-	-	156	15.79 (13.41-18.11)
Age≥75 years		n=610		n=568		n=226			n=1404
1 month	34	5.89 (3.95-7.80)	27	4.98 (3.13-6.80)	7	3.23 (0.85-5.56)	0.29	68	5.10 (3.91-6.28)
1 year	74	14.11 (11.05-17.06)	55	10.84 (8.08-13.51)	16	8.48 (4.37-12.42)	0.07	145	11.89 (10.04-13.70)
3 years	104	21.45 (17.63-25.09)	70	14.85 (11.51-18.06)	-	-	-	195	17.86 (15.48-20.18)
5 years	120	26.64 (22.24-30.79)	81	19.95 (15.53-24.14)	-	-	-	222	23.12 (20.13-26.00)

N: cumulative number of recurrent ischaemic stroke, n: number of patients, CI: confidence interval

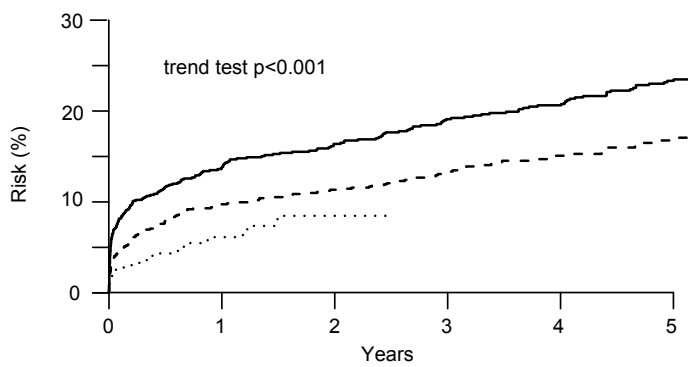
*Risks at 3 and 5 years were for 2002-2012

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

A. Coronary events



B. Recurrent ischaemic stroke



— 1st April 2002–31st March 2007
- - - 1st April 2007–31st March 2012
..... 1st April 2012–31st March 2014

Figure 9: Time trend in the risk of coronary events and of recurrent ischaemic stroke after TIA or ischaemic stroke for 2002-2014

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

Compared to the 1st study period (2002-2007), the risk of coronary events significantly decreased by approximately 50% in the second (2007-2012) and the 3rd study period (2012-2014, Table 10). Importantly, the time trend was independent of any change in vascular risk factors and presence of large artery disease TIA/ischaemic stroke subtype, with a multivariable adjusted HR of 0.56 (95% CI 0.39-0.79, $p=0.0011$; Table 10) in the 2nd study period and 0.47 (0.31-0.72, $p<0.0001$) in the 3rd study period, compared to the 1st study period. Interestingly, the risks of coronary events continued to significantly decrease between the 2nd and the 3rd study periods (multivariable adjusted HR=0.40, 95% CI 0.17-0.94, $p=0.036$; Table 10). The significant decrease in the risk of recurrent ischaemic stroke over the three study periods was also independent of any change in vascular risk factors and presence of large artery disease TIA/ischaemic stroke subtype over time (multivariable adjusted HR of 0.72, 95% CI 0.58-0.89, $p=0.0023$; Table 10) in the 2nd study period and of 0.69 (0.57-0.85, $p<0.0001$) in the 3rd study period, compared to the 1st study period.

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Table 10 : Comparison of the risk of coronary events and of recurrent ischaemic stroke over the three study periods in OXVASC

	Crude HR	Age-and sex-adjusted HR	Multivariable model 1- adjusted HR	Multivariable model 2 adjusted HR	p-value (model 2)
<i>2nd study period (April 1, 2007-March 31, 2012) versus 1st study period (April 1, 2002-March 31, 2007)</i>					
Coronary events	0.57 (0.41-0.80)	0.59 (0.42-0.83)	0.59 (0.42-0.83)	0.56 (0.39-0.79)	0.0011
Recurrent ischaemic stroke	0.68 (0.56-0.84)	0.71 (0.57-0.87)	0.72 (0.58-0.89)	0.72 (0.58-0.89)	0.0023
<i>3rd study period (April 1, 2012-March 31, 2014) versus 1st study (April 1, 2002-March 31, 2007)</i>					
Coronary events	0.22 (0.09-0.51)	0.23 (0.10-0.54)	0.48 (0.31-0.73)	0.47 (0.31-0.72)	<0.001
Recurrent ischaemic stroke	0.45 (0.30-0.67)	0.47 (0.31-0.70)	0.69 (0.57-0.85)	0.69 (0.57-0.85)	<0.001
<i>3rd study period (April 1, 2012-March 31, 2014) versus 2nd study (April 1, 2007-March 31 2012)</i>					
Coronary events	0.40 (0.17-0.94)	0.40 (0.17-0.95)	0.41 (0.17-0.96)	0.40 (0.17-0.94)	0.0365
Recurrent ischaemic stroke	0.68 (0.45-1.03)	0.68 (0.45-1.03)	0.68 (0.45-1.03)	0.68 (0.45-1.04)	0.07

HR: Hazard ratio. Multivariable model 1 adjusted Hazard Ratio: after controlling for vascular risk factors: age, sex, prior hypertension, diabetes mellitus, hyperlipidaemia, history of smoking, previous TIA or ischaemic stroke and presence of coronary or peripheral artery disease. Multivariable model 2 adjusted Hazard Ratio: after controlling for the variables included in the model 1 and presence of large artery disease TIA/ischaemic stroke subtype

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
absolute risks of recurrent stroke and myocardial infarction

For 2002-2014, each history of hypertension, diabetes, hyperlipidaemia, smoking, prior coronary or peripheral artery disease and large artery disease TIA/ischaemic stroke subtype were associated with an increased risk of follow-up coronary events, after adjustment for age and sex (Table 11). The effect of these variables as a predictor of follow-up coronary events did not markedly change over the three study periods (Table 11). Each history of atrial fibrillation, hypertension, diabetes and prior peripheral artery disease and large artery disease TIA/ischaemic stroke subtype were also associated with an increased risk of recurrent ischaemic stroke, after adjustment for age and sex (Table 12). There was no change in the effect of these predictors for the risk of recurrent ischaemic stroke over time (Table 12).

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Table 11 : Relative effects of risk factors for coronary events after TIA or ischaemic stroke according to the study period in OXVASC

Factors	Age- and sex-adjusted HR,*			p _{interaction}	Age- and sex-adjusted HR,*	p-value
	% (95%CI)				% (95%CI)	
	April 1, 2002- March 31, 2007	April 1, 2007- March 31, 2012	April 1, 2012- March 31, 2014		April 1, 2002- March 31, 2014	
Age (vs. <65 years)						<0.001
65-74	2.88 (1.24-6.72)	2.72 (0.94-7.84)	4.71 (0.03-15.07)	0.37	3.06 (1.59-5.89)	
75-84	5.65 (2.54-12.57)	5.86 (2.24-15.31)	7.44 (0.92-9.23)	0.07	6.25 (3.39-11.52)	
≥ 85	8.82 (3.71-20.96)	6.11 (2.08-17.93)	8.72 (0.15-12.08)	0.0080	7.79 (4.00-15.21)	
Male sex (vs. female)	1.36 (0.91-2.02)	1.74 (0.99-3.06)	1.21 (0.23-6.30)	0.70	1.45 (1.06-1.99)	0.0211
Previous TIA or ischaemic stroke	0.99 (0.62-1.60)	1.17 (0.46-2.95)	2.98 (0.35-6.37)	0.63	1.09 (0.60-1.38)	0.90
Atrial fibrillation	0.95 (0.57-1.59)	1.24 (0.63-2.42)	1.74 (0.31-9.78)	0.61	1.07 (0.72-1.60)	0.63
Hypertension	1.89 (1.19-2.99)	1.50 (0.82-2.74)	3.28 (0.37-29.00)	0.15	1.78 (1.24-2.56)	<0.001
Diabetes mellitus	2.46 (1.53-3.97)	2.08 (1.13-3.83)	1.16 (0.13-10.26)	0.0248	2.08 (1.44-3.01)	<0.001
Hyperlipidaemia	1.39 (0.93-2.08)	1.61 (0.93-2.79)	2.20 (0.44-11.08)	0.77	1.49 (1.09-2.04)	0.0147
History of smoking†	1.62 (1.05-2.49)	2.31 (1.22-4.37)	0.84 (0.16-4.31)	0.39	1.26 (1.10-1.45)	0.0013
Current smoking†	2.17 (1.27-3.72)	2.52 (1.23-5.16)	5.31 (0.88-9.54)	0.14	1.17 (0.98-1.41)	0.0014
TIA (vs. ischaemic stroke)	0.93 (0.62-1.39)	0.87 (0.50-1.50)	0.57 (0.10-3.12)	0.84	0.87 (0.63-1.19)	0.47
Coronary artery disease	1.62 (1.26-2.08)	1.84 (1.28-2.66)	5.29 (1.88-14.84)	0.51	2.54 (1.85-3.49)	<0.001
Peripheral artery disease	2.87 (1.73-4.76)	2.94 (1.43-6.08)	3.12 (0.33-28.98)	0.05	3.05 (2.03-4.59)	<0.001
TIA/ischaemic stroke subtype (vs. cryptogenic)						0.0319
Cardioembolic	1.33 (0.95-1.87)	1.73 (1.08-2.77)	5.54 (1.57-19.60)	0.15	1.40 (0.89-2.20)	
Large artery disease	1.25 (0.79-1.97)	2.06 (1.25-3.40)	1.81 (0.30-10.90)	0.0001	2.18 (1.37-3.46)	
Small vessel disease	1.12 (0.75-1.67)	1.96 (1.17-3.26)	4.14 (0.83-20.54)	0.71	1.18 (0.69-2.02)	

HR: hazard ratio. p-interaction by study period *Sex-adjusted HR for age categories and age-adjusted for male sex, † data missing for 9 patients

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke: absolute risks of recurrent stroke and myocardial infarction

Table 12 : Relative effects of risk factors for recurrent ischaemic stroke after TIA or ischaemic stroke according to the study period in OXVASC

Factors	Age- and sex-adjusted HR,*			p _{interaction}	Age- and sex-adjusted HR,*	p-value
	% (95%CI)				% (95%CI)	
	April 1, 2002- March 31, 2007	April 1, 2007- March 31, 2012	April 1, 2012- March 31, 2014		April, 1 2002- March 31, 2014	
Age (vs. <65 years)						<0.001
65-74	1.31 (0.87-1.97)	1.08 (0.67-1.75)	0.93 (0.23-3.74)	0.27	1.22 (0.90-1.65)	
75-84	1.51 (1.03-2.22)	1.19 (0.76-1.85)	2.91 (0.93-9.11)	0.35	1.50 (1.14-1.98)	
≥ 85	1.98 (1.27-3.708)	1.80 (1.11-2.91)	4.05 (1.21-13.56)	0.13	2.01 (1.48-2.76)	
Male sex (vs. female)	0.94 (0.73-1.22)	0.94 (0.68-1.31)	1.98 (0.91-4.29)	0.30	0.99 (0.81-1.20)	0.92
Previous TIA or ischaemic stroke	1.26 (1.01-1.45)	1.25 (0.80-1.53)	1.02 (0.24-4.30)	0.29	1.30 (1.11-1.45)	0.0251
Atrial fibrillation	1.32 (0.96-1.81)	1.41 (0.96-2.08)	2.17 (1.01-4.68)	0.75	1.39 (1.10-1.75)	0.0042
Hypertension	1.40 (1.06-1.85)	1.69 (1.18-2.43)	0.70 (0.33-1.47)	0.95	1.44 (1.17-1.78)	<0.001
Diabetes mellitus	1.07 (0.73-1.59)	1.90 (1.32-2.75)	0.61 (0.18-2.03)	0.06	1.32 (1.02-1.71)	0.0194
Hyperlipidaemia	1.04 (0.79-1.36)	1.31 (0.94-1.83)	1.46 (0.69-3.07)	0.49	1.17 (0.96-1.43)	0.14
History of smoking†	0.97 (0.74-1.27)	1.14 (0.81-1.60)	1.31 (0.59-2.91)	0.40	1.06 (0.87-1.30)	0.69
Current smoking†	1.20 (0.83-1.76)	1.48 (0.94-2.35)	1.01 (0.29-3.49)	0.61	1.31 (0.98-1.74)	0.07
TIA (vs. ischaemic stroke)	1.00 (0.75-1.18)	0.92 (0.75-1.07)	1.03 (0.89-1.54)	0.20	0.68 (0.55-0.83)	<0.001
Coronary artery disease	1.07 (0.87-1.31)	1.29 (0.99-1.69)	1.12 (0.62-2.01)	0.81	1.16 (1.00-1.35)	0.05
Peripheral artery disease	1.23 (0.79-1.92)	2.08 (1.24-3.46)	0.96 (0.22-4.12)	0.95	1.53 (1.11-2.12)	0.0198
TIA/ischaemic stroke subtype (vs. cryptogenic)						0.0007
Cardioembolic	1.33 (0.95-1.87)	1.73 (1.08-2.77)	5.54 (1.56-19.60)	0.55	1.56 (1.20-2.04)	
Large artery disease	1.25 (0.79-1.97)	2.06 (1.25-3.40)	1.81 (0.30-10.89)	0.84	1.51 (1.09-2.08)	
Small vessel disease	1.12 (0.75-1.67)	1.96 (1.17-3.26)	4.14 (0.83-20.54)	0.27	1.46 (1.07-1.99)	

HR: hazard ratio. p-interaction by time period *Sex-adjusted HR for age categories and age-adjusted for male sex, † data missing for 9 patients

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
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Discussion

In this contemporary population-based study of TIA or ischaemic stroke patients, we identified a significant decrease in the risk of follow-up coronary events and of recurrent ischaemic stroke over time for 2002-2014. The 1-year risk of coronary events significantly decreased from 3.3% in 2002-2007 to 1.0% in 2012-2014 and the 1-year of recurrent ischaemic stroke also significantly decreased from 13.9% in 2002-2007 to 6.1% in 2012-2014. Additionally, we showed that these time trends at the population level were independent of any change in vascular risk factors and presence of large artery disease TIA/ischaemic stroke subtype over time. We also showed that the effect of each vascular risk factor on the risk of coronary events and of recurrent ischaemic stroke did not markedly change over the study period. These time trends are likely to be due to the improvement of secondary prevention after TIA/ischaemic stroke over time, particularly with the use of higher dose of statin since 2007 and the home blood pressure monitoring we have implemented in OXVASC since 2012. Indeed, reduction in the risk of cardiovascular events has been shown to increase with decreasing levels of LDL cholesterol levels⁶⁹ while hypertension is a major risk factor for TIA or ischaemic stroke⁷⁰ and reduction in blood pressure levels reduces the risk of recurrent stroke.⁷¹⁻⁷³ Our findings highlight the need to continue to implement further strategies to lower the risk of recurrent events in TIA/ischaemic stroke patients.

A reduction in the risk of coronary events after TIA/ischaemic stroke over the last few decades has previously been reported,⁵⁹ but we have shown that the risk of coronary events in the last 15 years has continued to decrease in patients treated according to contemporary guidelines. Also, while the risk of recurrent stroke did not markedly change over the last few decades,⁵⁹ we showed a reduction in the risk since 2002. We used consistent methods for identifying follow-up events, with detailed face-to-face interview and cross-reference to hospital admission data, and kept the same definitions of follow-up events over the study period, therefore the reduction in the risks of coronary events and recurrent ischaemic stroke observed over time is likely to be genuine. Also, the consistent declines in the risk of follow-up events over the three study periods and across the different age groups suggest that these time trends are true.

Although we consider our findings to be valid, our study has limitations. First, although we record information on medication during follow-up in OXVASC, data on cholesterol levels, blood pressure control and on the number of antihypertensive drugs during follow-up were not available in all patients for this analysis. Second, our population consisted of a predominantly

I. Current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke:
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white British population, and therefore our findings apply to mainly Caucasian patients. Moreover, the duration of the last study period (2012-2014) was shorter than the first 2 study periods (2002-2007 and 2007-2012). The OXVASC study is an ongoing study and we planned to obtain data on follow-up events in TIA/ischaemic stroke patients up to 2017, so that each study period would be 5-year long, to re-do the analyses.

Our findings have implications for further research on secondary prevention after TIA or ischaemic stroke. Hence, in view of the relatively low absolute risk of recurrent ischaemic events in patients treated with current secondary prevention management (*i.e.* those recruited since 2012), future trials aiming to improve secondary prevention after TIA/ischaemic stroke would require a larger number of patients to show a significant risk reduction in recurrent ischaemic events than previous trials.

In conclusion, the risk of coronary events and of recurrent ischaemic stroke after TIA/ischaemic stroke has significantly decreased since 2002 at the population level, most likely due to the improvement of secondary prevention. Further improvement in reduction of the risk of recurrent ischaemic events in TIA/ischaemic stroke patients seems still possible, particularly with the new cholesterol therapies, protein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors, that have recently been reported to significantly lower the risk of coronary events in patients on high dose of statin.³⁵⁻³⁷

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

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II.1. Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke

Boulanger M, Li L, Lyons L, Lovett NG, Kubiak MM, Silver L, Touzé E, Rothwell PM on behalf of the Oxford Vascular Study.

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II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Abstract

Objective: To determine whether TIA or ischaemic stroke patients with co-existing cardiovascular disease (i.e. history of coronary or peripheral artery disease) are still at high risk of recurrent ischaemic events despite current secondary prevention guideline.

Methods: In a population-based study in Oxfordshire, United Kingdom (Oxford Vascular Study), we studied consecutive patients with TIA or ischaemic stroke for 2002-2014. Patients were treated according to current secondary prevention guidelines and we determined risks of coronary events, recurrent ischaemic stroke, and major bleeding stratified by the presence of co-existing cardiovascular disease.

Results: Among 2555 patients (9148 patient-years of follow-up), those (n=640; 25.0%) with co-existing cardiovascular disease (449 coronary only; 103 peripheral only; 88 both) were at higher 10-year risk of coronary events than those without (22.8%; 95%CI 17.4-27.9; versus 7.1%, 5.3-8.8; $p < 0.001$, age-and sex-adjusted Hazard Ratio [HR]=3.07, 2.24-4.21) and of recurrent ischaemic stroke (31.5%, 25.1-37.4; versus 23.4%, 20.5-26.2; $p = 0.0049$, age-and sex-adjusted HR=1.23, 0.99-1.53), despite similar rates of use of antithrombotic and lipid-lowering medication. However, in patients with non-cardioembolic TIA/ischaemic stroke, risk of extracranial bleeds was also higher in those with co-existing cardiovascular disease, particularly in patients aged <75 years (8.1%, 2.8-13.0; versus 3.4%, 1.6-5.3; $p = 0.0050$; age-and sex-adjusted HR=2.71, 1.16-6.30), although risk of intracerebral haemorrhage was not increased (age-and sex-adjusted HR=0.36, 0.04-2.99).

Conclusions: As in older studies, TIA/ischaemic stroke patients with co-existing cardiovascular disease still remain at high risk of recurrent ischaemic events despite current management. More intensive lipid-lowering might therefore be justified, but benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Introduction

Risk of recurrent vascular events in patients with transient ischaemic attack (TIA) and stroke remains significant, and there is a need for improved secondary prevention of stroke and also prevention of coronary events.^{19, 59} Antiplatelet monotherapy is currently standard for long-term secondary prevention, and there is evidence in certain subsets of patients that anticoagulation is associated with an high risk of intracerebral haemorrhage.^{74, 75} TIA/ischaemic stroke patients with co-existing stable atherosclerotic cardiovascular disease (coronary or peripheral artery disease) have been shown previously to be at high absolute risk of recurrent stroke and coronary events.⁴⁰⁻⁴² However, the absolute risk of coronary events after TIA/ischaemic stroke has decreased over the past few decades,⁵⁹ and there are relatively few recent data on the overall residual vascular risk in TIA/ischaemic stroke patients on current guideline-based management, particularly on long-term follow-up. Moreover, data on the long-term risk of major bleeding with antithrombotic therapies based on the presence of co-existing cardiovascular disease are scarce. If TIA/ischaemic stroke patients with co-existing stable atherosclerotic cardiovascular disease still have a high absolute risk of recurrent ischaemic stroke or coronary events then more intensive secondary prevention might result in a sufficient reduction in ischaemic events to counterbalance any increased risk of bleeding or increased cost of more intensive treatment.

In patients with stable atherosclerotic cardiovascular disease, the COMPASS trial reported a 50% relative reduction in risk of ischaemic stroke on Rivaroxaban plus aspirin versus aspirin alone, albeit with a 70% increased risk of major bleeding.³⁹ COMPASS excluded patients with recent TIA or stroke, but the subgroup of patients with carotid artery disease did benefit from combination treatment.⁷⁶ Moreover, the annual risk of stroke was <1% in the aspirin-alone group, which is lower than reported after TIA and ischaemic stroke in routine practice,⁷⁷ particularly in patients with co-existing coronary or peripheral artery disease.⁴¹ In patients with recent cryptogenic ischaemic stroke, the NAVIGATE ESUS trial reported no reduction in risk of recurrent ischaemic stroke on Rivaroxaban versus aspirin, but a higher risk of intracerebral haemorrhage.⁷⁴ However, cryptogenic TIA/ischaemic stroke patients have a low prevalence of co-existing cardiovascular disease, a relatively low absolute risk of recurrent ischaemic stroke,⁷⁸ and may be at higher risk of intracerebral haemorrhage.⁷⁹⁻⁸¹ In a similar population of patients with cryptogenic ischaemic stroke, the recent RE-SPECT ESUS trial also reported no reduction in risk of recurrent ischaemic stroke in patients treated with Dabigatran compared to those treated with aspirin.⁸²

Patients with TIA and ischaemic stroke also have a substantial long-term risk of myocardial infarction and cardiac death,¹⁷ and there is also increasing evidence that tighter control of cholesterol levels

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than the current guideline target (LDL<2.6mmol/L) may be necessary,⁸³ with randomized controlled trials of LDL reduction to <1.8mmol/L ongoing.⁸⁴ Trials of new cholesterol lowering therapies, proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors³⁵⁻³⁷ also focused on populations with stable cardiovascular disease and reported significant reductions in LDL-cholesterol and in myocardial infarction, as compared with placebo, in patients on high-dose statins with LDL level >1.8mmol/l. There was less evidence for a reduction in risk of ischaemic stroke with PCSK-9 inhibitors,^{36, 37} but dyslipidemia is estimated to account for a higher proportion of the risk of coronary events than of the risk of ischaemic stroke.^{85, 86} However, although PCSK-9 inhibitors reduced the relative risk of myocardial infarction by 27% in the FOURIER trial³⁶ and by 13% in the REVEAL trial,³⁷ the drugs are very costly³⁸ and may only be cost-effective in high-risk subgroups. The annual risk of myocardial infarction was only 1-2% in the trials, which is again lower than reported after TIA and ischaemic stroke in patients with co-existing coronary or peripheral artery disease.⁴¹

Given the potential that more intensive antithrombotic treatment and/or lipid-lowering might reduce the long-term risk of recurrent stroke and coronary events in TIA or stroke patients with co-existing stable cardiovascular disease, we aimed to determine the prognosis of this subgroup on current standard preventive treatment for both recurrent ischaemic events and for major bleeding. Up-to-date estimates of event rates will help clinicians assess potential benefits of more intensive treatment and facilitate the planning of future trials.

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Methods

Study population

The Oxford Vascular study (OXVASC) is an ongoing population-based study of the incidence and outcome of all acute vascular events.⁶³ The study population comprised all 92728 individuals, irrespective of age, registered with 100 family physicians in nine general practices in Oxfordshire, UK. In Oxfordshire, it is estimated that 97.1% of the true residential population is registered with a primary care practice, the majority of non-registered individuals being young adults. The analysis reported here included consecutive cases, irrespective of age, with a first TIA or ischaemic stroke from April 1, 2002, to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was only available in cases recruited from April 1, 2002, to March 31, 2012, with follow-up until March 31, 2013.

The OXVASC study design has been described in detail previously.⁶³ Briefly, multiple overlapping methods of hot and cold pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke.^{64, 65} These include: 1) a daily, rapid access “TIA and stroke clinic” to which participating general practitioners and the local emergency department refer individuals with suspected TIA or minor stroke; 2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; 3) daily searches of the local emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner’s reports for out of hospital deaths; 6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals. Patients gave written informed consent after an event or assent was obtained from a relative for patients who were unable to provide consent. OXVASC was approved by our local research ethics committee.

Standard WHO definitions were used for TIA and stroke, which have been reported previously.^{63, 64} All cases were investigated according to current guidelines and reviewed by a senior neurologist with stroke expertise (PMR) in order to ensure consistency over time. Differentiation between TIA and stroke was based on the WHO 24-hour cut-off for symptom duration (i.e. events were classified as TIA even if Diffusion Weighted Imaging [DWI] was positive if symptoms resolved within 24 hours) and we have kept the same definition over time. TIA/ischaemic stroke aetiology was categorised by PMR according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Appendix I).⁶⁶ Patients were prescribed standard secondary prevention medication according to contemporary guidelines, including antiplatelet or anticoagulant treatment, as appropriate, blood pressure lowering

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medication and statin treatment to achieve a target of blood pressure <140/90 and LDL <2.6mmol/L, both at baseline and at the time of study follow-up visits. It was our policy in patients with co-existing cardiovascular disease who were on antiplatelet treatment before the TIA/ischaemic stroke to continue dual therapy if already on dual (e.g. after recent stent etc) for as long as previously indicated and to add clopidogrel for 1 month only if on monotherapy beforehand, but revert to monotherapy after one month. Anticoagulation was also continued or started when clinically indicated, but was not used preferentially in patients with co-existing cardiovascular disease.

Demographic data, atherosclerotic risk factors (male sex, history of hypertension, diabetes mellitus, hypercholesterolemia, smoking [i.e. ex or current smoker], family history of premature myocardial infarction [defined as myocardial infarction occurring in a first-degree relative, siblings or parents, aged ≤55 years if male or aged ≤65 years if female]), previous atrial fibrillation, prior coronary artery disease, prior peripheral artery disease and medication were collected from face-to-face interviews and cross-referenced with primary care records. Renal insufficiency was defined as glomerular filtration rate <30 ml/min, calculated by the MDRD equation,⁸⁷ using the creatinine level closest to the date of TIA/ischaemic stroke. Patients were classified as having a prior coronary artery disease if they had at least one of the following: previous myocardial infarction; unstable angina; angina; previous percutaneous coronary intervention or coronary artery bypass graft surgery. Prior peripheral artery disease was defined as having at least one of the following: previous acute limb ischemia; critical limb ischemia; intermittent claudication; previous angioplasty or stenting; peripheral arterial bypass graft or amputation. For intermittent claudication, the diagnosis was based on the judgement of the study clinician based on both prior medical records and symptoms.

All patients were followed up face to face at 1, 6, 12, 60 and 120 months by a study nurse or physician and subsequent vascular events identified and risk factor control evaluated and treatment revised as necessary. For patients who had moved out of the study area, telephone follow-up was done, and patients with dementia were followed-up via a carer or by assessment in a nursing home. All recurrent events that presented to medical attention would also be identified by ongoing daily case-ascertainment of all acute vascular events in the study population. All study patients were also notified to the UK Office of National Statistics such that all deaths were reported back to the study with causes. Deaths were also identified by regular review of primary care records and by regular contact with the Coroner's Office to ascertain out-of-hospital deaths. If a recurrent non-fatal vascular event was suspected, the patient was re-assessed face to face by a study physician.

Myocardial infarction was defined using standard criteria.⁶⁷ Sudden cardiac death was defined using recommendations in Epidemiology and Clinical Research Studies and required a definite history of

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preceding symptoms consistent with acute coronary ischemia, or post-mortem evidence of either significant coronary atherosclerosis or acute thrombosis, or a documented myocardial infarction during the previous 28 days.⁶⁸ Fatal myocardial infarction was defined as any death within 30-days of a documented myocardial infarction. Definitions of myocardial infarction and sudden cardiac death remained unchanged over the period. We collected information on myocardial infarction (MI) subtype (ST-elevation [STEMI] and non-ST-elevation MI [N-STEMI]). Recurrent ischaemic stroke was defined as new neurological deficit fitting the definition for ischaemic stroke occurring after a period of neurological stability or improvement. Major bleeds were defined according to the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) criteria and were bleeds that were fatal or substantially disabling with persistent sequelae, symptomatic intracranial, intraocular bleeds leading to significant loss of vision, or bleeds requiring transfusion of ≥ 2 units of blood, use of intravenous inotropic agents or necessitating a surgical intervention (Appendix II).⁸⁸

Statistical analysis

We determined the 10-year risk of follow-up coronary events (defined as myocardial infarction or sudden cardiac deaths), recurrent ischaemic stroke, major ischaemic vascular events (defined as coronary event or recurrent ischaemic stroke, whichever happens first), and major bleeds (extracranial and intracerebral haemorrhage) from Kaplan-Meier analyses, stratified by history of co-existing cardiovascular disease, and assessed any difference with log-rank test. We used similar analyses for the 10-year risk stratified by stroke subtype. We also compared risks of follow-up events between patients with and without co-existing cardiovascular disease using logistic regression analysis adjusted for age and sex. All analyses were done using R version 3.1.3.

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Results

Of 2555 patients (949 TIA and 1606 ischaemic stroke; mean age=74 years; 21% aged ≥ 85 years), 443 (17.3%) had a previous TIA or stroke before their index event and 640 (25.0%) had history of co-existing stable cardiovascular disease (449 coronary artery disease only; 103 peripheral artery disease only; 88 both (Tables 13 and 14). At baseline, the mean total cholesterol level was 5.05 (+/-1.27) mmol/L, ranging from 4.86 (+/-1.30) mmol/L in patients on statin treatment prior to the TIA/ischaemic stroke to 5.12 (+/-1.25) mmol/L in those with no statin ($p < 0.001$).

Patients with co-existing cardiovascular disease were older (mean age=78 versus 73 years, $p < 0.001$), had more atherosclerotic risk factors and were more likely to be on antithrombotics, antihypertensives and statins before the TIA/ischaemic stroke than those without (Tables 13 and 15). Rates of use of secondary preventive therapies were high at 1-year follow-up, with similar rates of use of antithrombotics and statins in patients with and without co-existing cardiovascular disease but rate of use of antihypertensives remained higher in those with co-existing cardiovascular disease (Tables 13 and 15). Patients with TIA/ischaemic stroke due to large artery disease (TOAST classification) and cardioembolism had the highest prevalence of co-existing cardiovascular disease ($p < 0.001$, Table 14).

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Table 13 : Baseline characteristics in TIA or ischaemic stroke patients, stratified by history of co-existing cardiovascular disease

Baseline characteristics	Total (n=2555)	Co-existing cardiovascular disease		p
		Yes (n=640)	No (n=1915)	
Demographics				
Mean age (SD),years	73.9 (13.0)	78.0 (10.0)	72.6 (13.6)	<0.001
Age ≥ 75years	1404 (55.0)	444 (69.4)	960 (50.1)	<0.001
Men	1262 (49.4)	354 (55.3)	908 (47.4)	<0.001
Prior comorbidities				
Previous TIA	231 (9.0)	93 (14.5)	138 (7.2)	<0.001
Previous stroke	264 (10.3)	95 (14.8)	169 (8.8)	<0.001
Atrial fibrillation	522 (20.4)	204 (31.9)	318 (16.6)	<0.001
Hypertension	1537 (60.1)	492 (76.9)	1045 (54.6)	<0.001
Diabetes mellitus	357 (14.0)	156 (24.4)	201 (10.5)	<0.001
Hypercholesterolemia	782 (30.6)	334 (52.2)	448 (23.4)	<0.001
History of smoking*	1416 (55.4)	403 (63.0)	1013 (52.9)	<0.001
Current smoker*	361 (14.1)	64 (10.0)	297 (15.5)	<0.001
Family history of premature myocardial infarction†	224 (8.8)	86 (16.5)	138 (8.9)	<0.001
Renal insufficiency‡	132 (5.2)	56 (8.8)	76 (4.0)	<0.001
TIA/ischaemic stroke subtypes (TOAST classification)				
Large artery disease	280 (11.0)	85 (13.3)	195 (10.2)	0.03
Cardioembolic	669 (26.2)	226 (35.3)	443 (23.1)	<0.001
Small vessel disease	317 (12.4)	48 (7.5)	269 (14.0)	<0.001
Cryptogenic	811 (31.7)	140 (21.9)	671 (35.0)	<0.001
More than one cause	90 (3.5)	45 (7.0)	45 (2.3)	<0.001
Unknown	331 (13.0)	88 (13.8)	242 (12.6)	0.47
Other causes	57 (2.2)	8 (1.3)	49 (2.6)	0.05
Baseline therapies				
Antithrombotics	1100 (43.1)	496 (77.5)	603 (31.5)	<0.001
Antihypertensives	1486 (58.2)	530 (82.8)	956 (49.9)	<0.001
Statins	684 (26.8)	358 (55.9)	326 (17.0)	<0.001

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Secondary prevention medication at 1-month follow-up§	n=2339	n=559	n=1780	
Antithrombotics	2196 (93.9)	522 (93.4)	1673 (94.0)	0.60
Antihypertensives	1771 (75.7)	482 (86.2)	1288 (72.4)	<0.001
Statins	1755 (75.0)	451 (80.7)	1304 (73.3)	<0.001
Secondary prevention medication at 1-year follow-up§	n=1976	n=458	n=1518	
Antithrombotics	1884 (95.3)	437 (95.4)	1447 (95.3)	0.85
Antihypertensives	1572 (79.6)	398 (86.9)	1174 (77.3)	<0.001
Statins	1589 (80.4)	370 (80.8)	1219 (80.3)	0.87

Data are numbers (%), unless otherwise specified. p for comparison between patients with and without co-existing cardiovascular disease (χ^2 test for categorical variables and t-test for continuous variable) *data missing for 7 patients, † data missing for 476 patients, ‡ data missing for 13 patients, § patients who died before the follow-up were not included.

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Table 14 : Baseline characteristics in TIA or ischaemic stroke patients stratified by TIA/ischaemic stroke subtypes (TOAST classification)

Baseline characteristics	Large artery disease (n=280)	Cardioembolic (n=669)	Small vessel disease (n=317)	Cryptogenic (n=811)	p
Demographics					
Mean (SD) age, years	73.3 (10.3)	77.9 (11.9)	69.7 (12.6)	70.3 (12.8)	<0.001
Age ≥ 75years	137 (48.9)	469 (70.1)	121 (38.2)	346 (42.7)	<0.001
Men	172 (61.4)	306 (45.7)	182 (57.4)	402 (49.6)	<0.001
Prior comorbidities					
Co-existing cardiovascular disease	85 (30.6)	226 (33.8)	48 (15.1)	140 (17.3)	<0.001
Hypertension	198 (70.7)	454 (67.9)	183 (57.7)	419 (51.7)	<0.001
Diabetes mellitus	52 (18.6)	81 (12.1)	51 (16.1)	99 (12.2)	0.0172
Hypercholesterolemia	121 (43.2)	205 (30.6)	94 (29.7)	228 (28.1)	<0.001
History of smoking	183 (65.3)	348 (52.0)	197 (62.1)	443 (54.6)	<0.001
Baseline therapies					
Antithrombotics	106 (37.9)	427 (63.8)	101 (31.9)	273 (33.7)	<0.001
Antihypertensives	187 (66.8)	482 (72.0)	151 (47.6)	394 (48.6)	<0.001
Statins	102 (36.4)	191 (28.6)	70 (22.1)	205 (25.3)	0.03
Secondary prevention medication at 1-month follow-up§					
	n=273	n=556	n=317	n=808	
Antithrombotics	263 (96.3)	520 (93.5)	307 (96.8)	769 (95.2)	0.22
Antihypertensives	224 (82.1)	446 (80.2)	258 (81.4)	589 (72.9)	<0.001
Statins	232 (85.0)	380 (68.3)	266 (83.9)	649 (80.3)	<0.001
Secondary prevention medication at 1-year follow-up§					
	n=247	n=436	n=310	n=765	
Antithrombotics	239 (96.8)	411 (94.3)	292 (94.2)	719 (94.0)	0.53
Antihypertensives	213 (86.2)	359 (82.3)	246 (79.4)	573 (74.9)	<0.001
Statins	221 (78.9)	315 (72.2)	256 (82.6)	627 (82.0)	0.0011

Data are numbers (%), unless otherwise specified. p for comparison among all stroke subtypes (χ^2 test for categorical variables and one-way ANOVA test for continuous variable).

§ patients who died before the follow-up were not included.

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Table 15: Baseline characteristics of patients with non-cardioembolic TIA or ischaemic stroke and after exclusion of those on anticoagulants, stratified by history of co-existing cardiovascular disease

Baseline characteristics	Total (n=1886)	Co-existing cardiovascular disease		p
		Yes (n=414)	No (n=1472)	
Demographics				
Mean age (SD), years	72.5 (13.1)	76.9 (10.1)	71.2 (13.5)	<0.001
Age ≥ 75years	935 (49.6)	264 (63.8)	671 (45.6)	<0.001
Men	956 (50.7)	249 (60.1)	707 (48.0)	<0.001
Known comorbidities				
Previous TIA	158 (8.4)	60 (14.5)	98 (6.7)	<0.001
Previous stroke	173 (9.2)	58 (14.0)	115 (7.8)	<0.001
Atrial fibrillation	91 (4.8)	45 (10.9)	46 (3.1)	<0.001
Hypertension	1082 (57.4)	319 (77.1)	763 (51.8)	<0.001
Diabetes mellitus	276 (14.6)	163 (39.4)	113 (7.7)	<0.001
Hypercholesterolemia	577 (30.6)	231 (55.8)	346 (23.5)	<0.001
History of smoking*	1068 (56.6)	271 (65.5)	797 (54.1)	<0.001
Current smoker*	316 (16.8)	48 (11.6)	268 (18.2)	0.0019
Renal insufficiency‡	85 (4.5)	32 (7.7)	53 (3.6)	<0.001
TIA/ischaemic stroke subtypes (TOAST classification)				
Large artery disease	280 (11.0)	85 (13.3)	195 (10.2)	0.03
Small vessel disease	317 (12.4)	48 (7.5)	269 (14.0)	<0.001
Cryptogenic	811 (31.7)	140 (21.9)	671 (35.0)	<0.001
More than one cause	90 (3.5)	45 (7.0)	45 (2.3)	<0.001
Unknown	331 (13.0)	88 (13.8)	242 (12.6)	0.47
Other causes	57 (2.2)	8 (1.3)	49 (2.6)	0.05
Baseline therapies				
Antithrombotics	673 (35.7)	310 (74.9)	363 (24.7)	<0.001
Antihypertensives	1004 (53.2)	333 (80.4)	671 (45.6)	<0.001
Statins	493 (26.1)	246 (59.4)	247 (16.8)	<0.001
Secondary prevention at 1-month follow-up§				
	n=1783	n=379	n=1404	
Antithrombotics	1676 (94.0)	356 (93.9)	1319 (93.9)	0.99
Antihypertensives	1325 (74.3)	325 (85.8)	999 (71.2)	<0.001
Statins	1375 (77.1)	308 (81.3)	1067 (76.0)	0.0359
Secondary prevention at 1-year follow-up§				
	n=1595	n=318	n=1277	
Antithrombotics	1474 (92.4)	299 (94.0)	1175 (92.0)	0.27
Antihypertensives	1213 (76.1)	274 (86.1)	939 (73.5)	<0.001
Statins	1274 (79.9)	258 (81.1)	1016 (79.6)	0.58

Data are numbers (%), unless otherwise specified. p for comparison between patients with and without stable cardiovascular disease (χ^2 test for categorical variables and t-test for continuous variable)

*data missing for 4 patients, ‡ data missing for 10 patients, § patients who died before the follow-up were not include

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During 9148 patient-years of follow-up, there were 158 coronary events (29 STEMI; 89 N-STEMI; 40 sudden cardiac deaths), 413 recurrent ischaemic strokes and 1118 deaths. Patients with co-existing cardiovascular disease comprised 25% of all patients but accounted for 51% of coronary events and 28% of recurrent ischaemic stroke during follow-up. In patients with non-cardioembolic TIA/ischaemic stroke and after exclusion of those on anticoagulants, 82 extracranial bleeds and 20 intracerebral haemorrhages occurred.

The 10-year risk of coronary events (10.6%, 95%CI 8.8-12.4 overall) was higher in patients with co-existing cardiovascular disease than in those without (22.8%; 17.4-27.9; vs 7.1%, 5.3-8.8; $p < 0.001$, age- and sex-adjusted HR=3.07, 2.24-4.21, Table 16, Figures 10-12), particularly in patients aged <75 years (16.69%, 9.65-23.19; vs 3.78%, 2.09-5.44; $p < 0.001$, age- and sex-adjusted HR=4.33, 2.42-7.73, Table 16).

The 10-year risk of recurrent ischaemic stroke (25.3%, 22.6-27.8 overall) was also higher in patients with co-existing cardiovascular disease than those without (31.5%; 25.1-37.4; vs 23.4%, 20.5-26.3; $p = 0.0049$, age- and sex-adjusted HR=1.23, 0.99-1.53, Table 16, Figures 10 and 13), particularly in patients aged <75 years (30.3%, 21.4-38.3; vs 17.6%, 14.3-20.7; $p < 0.001$, adjusted HR=1.74, 1.23-2.46, Table 16). Patients with co-existing cardiovascular disease also had a higher 10-year risk of all major ischaemic vascular events than those without (45.1%, 38.4-51.1; vs 28.7%, 25.3-31.9; $p < 0.001$, age- and sex-adjusted HR=1.56, 1.30-1.88, Table 16, Figure 10, overall risk=32.5%, 29.5-35.3).

In patients with non-cardioembolic TIA/ischaemic stroke and after exclusion of those on anticoagulants, the 10-year risk of major extracranial bleeds (9.4%, 7.1-11.7 overall) was higher in those with co-existing cardiovascular disease (Table 16), particularly in patients aged <75 years (8.1%, 2.8-13.0; vs 3.5%, 1.6-5.3; $p = 0.0050$; age- and sex-adjusted HR=2.71, 1.16-6.30). The excess risk of major extracranial bleeds in those with co-existing cardiovascular disease was not limited only to the very early follow-up period (Figure 10). In contrast, patients with co-existing cardiovascular disease were not at increased risk of intracerebral haemorrhage (1.5%, 0-4.3; vs 2.5%, 1.0-4.0; $p = 0.09$, age- and sex-adjusted HR=0.17, 0.02-1.26, Table 16).

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Table 16 : 10-year risk of coronary events, recurrent ischaemic stroke, major ischaemic vascular events, intracerebral haemorrhage and major extracranial bleeds after TIA/ischaemic stroke in patients with versus without co-existing cardiovascular disease, stratified by age

Co-existing cardiovascular disease	Events, n/N		10-year risk, % (95%CI)		p	Crude HR (95%CI)	Age-and sex-adjusted HR (95%CI)	p
	Yes	No	Yes	No				
All patients								
Coronary events	80/640	78/1915	22.83 (17.40-27.91)	7.06 (5.30-8.79)	<0.001	3.83 (2.81-5.21)	3.07 (2.24-4.21)	<0.001
Recurrent ischaemic stroke	118/640	295/1915	31.51 (25.10-37.37)	23.43 (20.49-26.25)	0.0049	1.36 (1.10-1.68)	1.23 (0.99-1.53)	0.06
Major ischaemic events	175/640	345/640	45.12 (38.44-51.07)	28.65 (25.28-31.86)	<0.001	1.76 (1.47-2.11)	1.56 (1.30-1.88)	<0.001
Intracerebral haemorrhage*	1/414	19/1472	1.47 (0.00-4.29)	2.49 (0.97-3.99)	0.09	0.21 (0.03-1.54)	0.17 (0.02-1.26)	0.08
Major extracranial bleeds*	27/351	55/1226	11.14 (6.56-15.50)	7.44 (5.09-9.74)	0.0050	1.91 (1.21-3.03)	1.58 (0.99-2.52)	0.06
Age <75 years								
Coronary events	23/196	23/955	16.69 (9.65-23.19)	3.78 (2.09-5.44)	<0.001	5.38 (3.06-9.48)	4.33 (2.42-7.73)	<0.001
Recurrent ischaemic stroke	44/196	127/955	30.34 (21.43-38.25)	17.61 (14.34-20.74)	<0.001	1.87 (1.33-2.62)	1.74 (1.23-2.46)	0.0012
Major ischaemic events	59/196	141/955	39.68 (30.39-47.73)	20.96 (17.11-24.62)	<0.001	2.28 (1.69-3.09)	2.10 (1.54-2.87)	<0.001
Intracerebral haemorrhage*	1/150	8/801	2.27 (0.00-6.58)	2.23 (0.31-4.12)	0.66	0.63 (0.08-5.03)	0.36 (0.04-2.99)	0.41
Major extracranial bleeds*	9/126	16/653	8.07 (2.81-13.04)	3.45 (1.61-5.26)	0.0050	3.04 (1.34-6.88)	2.71 (1.16-6.30)	0.0209
Age ≥75 years								
Coronary events	57/444	55/960	27.99 (19.05-35.94)	12.44 (8.38-16.31)	<0.001	2.64 (1.83-3.82)	2.59 (1.79-3.77)	<0.001
Recurrent ischaemic stroke	74/444	168/960	33.81 (23.47-42.76)	32.19 (26.42-37.51)	0.89	1.02 (0.78-1.34)	1.05 (0.80-1.38)	0.79
Major ischaemic events	116/444	204/960	50.66 (39.87-59.51)	39.69 (33.37-45.41)	0.0096	1.35 (1.08-1.70)	1.37 (1.09-1.73)	0.0063
Intracerebral haemorrhage*	0/264	11/671	0	2.49 (0.76-4.20)	0.0443	0.01 (0.00-100)	0.01 (0.00-100)	0.59
Major extracranial bleeds*	18/225	39/573	19.21 (3.88-32.10)	14.15 (8.01-19.87)	0.34	1.31 (0.75-2.29)	1.28 (0.73-2.56)	0.39

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HR: Hazard ratio. Major ischaemic vascular event was a component of coronary event or recurrent ischaemic stroke. *Patients with cardioembolic TIA/ischaemic stroke and those on anticoagulants were excluded

Information on coronary events, recurrent ischaemic stroke and intracerebral haemorrhage was available in cases recruited from April 1, 2002 to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was available in cases recruited from April 1, 2002 to March 31, 2012, with follow-up until March 31, 2013.

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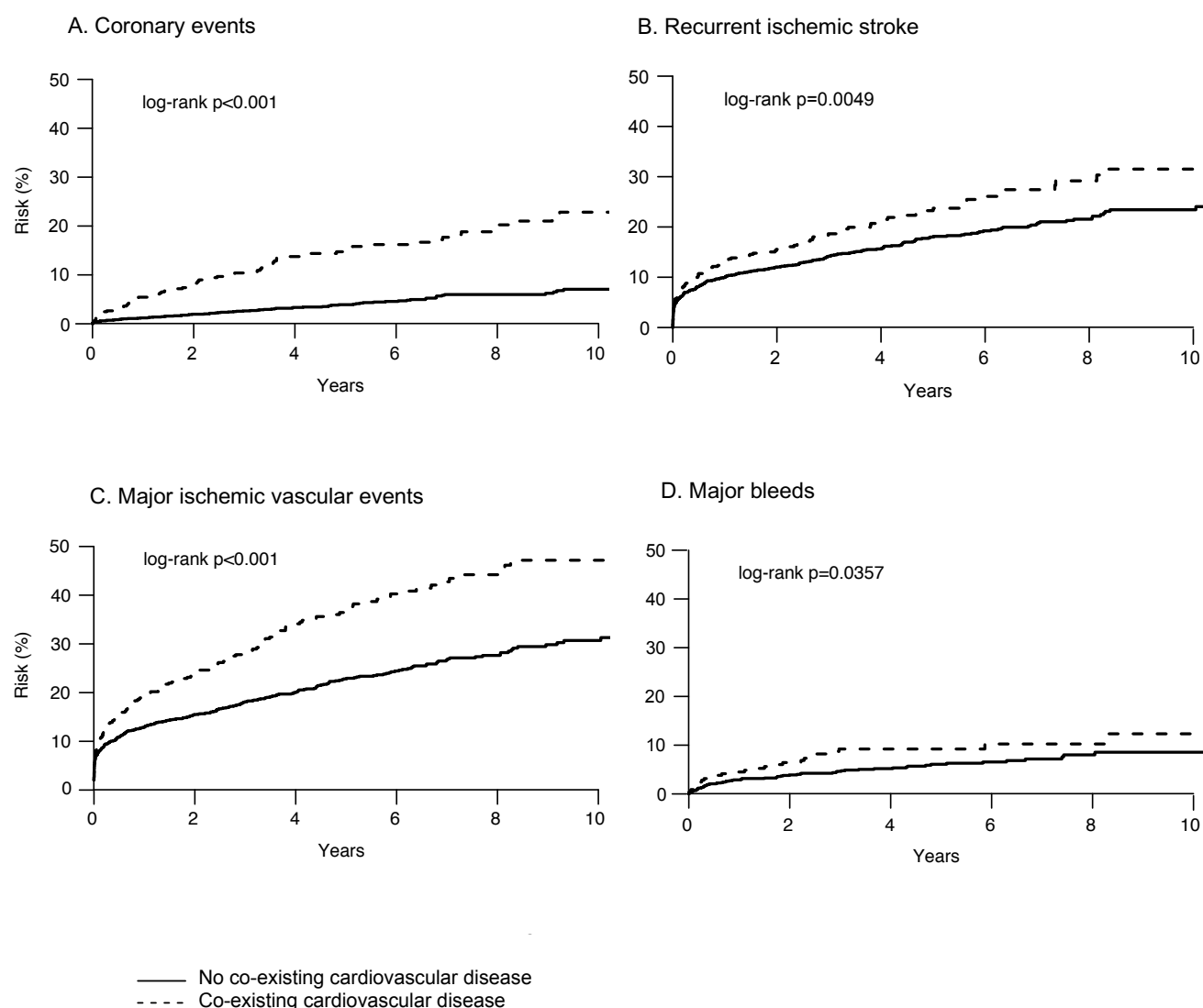


Figure 10 : Risks of coronary events, recurrent ischaemic stroke, major ischaemic vascular events and major bleeds after TIA or ischaemic stroke, stratified by history of co-existing cardiovascular disease

Major ischaemic vascular event was a component of coronary event or recurrent ischaemic stroke. Risk of major bleeds was calculated in non-cardioembolic TIA or ischaemic stroke patients and after exclusion of those on anticoagulants

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

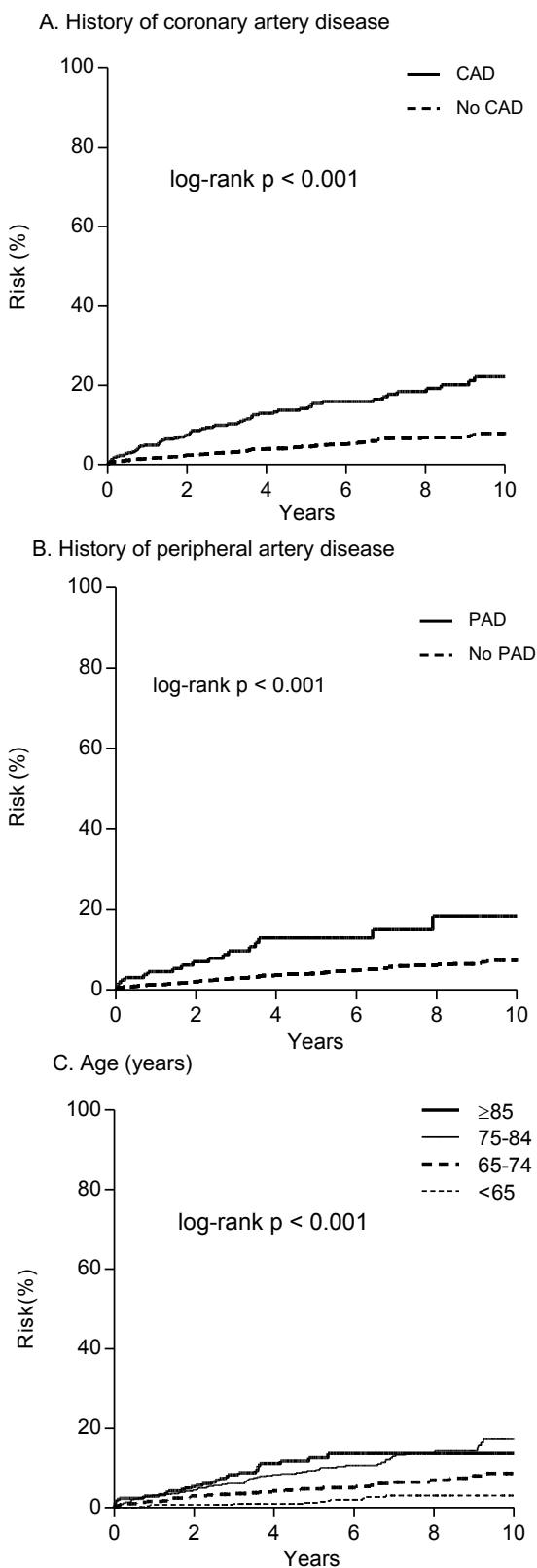


Figure 11 : Risk of coronary events after TIA or ischaemic stroke, stratified by history of coronary (CAD), peripheral artery disease (PAD) or age

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

- History of coronary artery disease
- No history of coronary artery disease

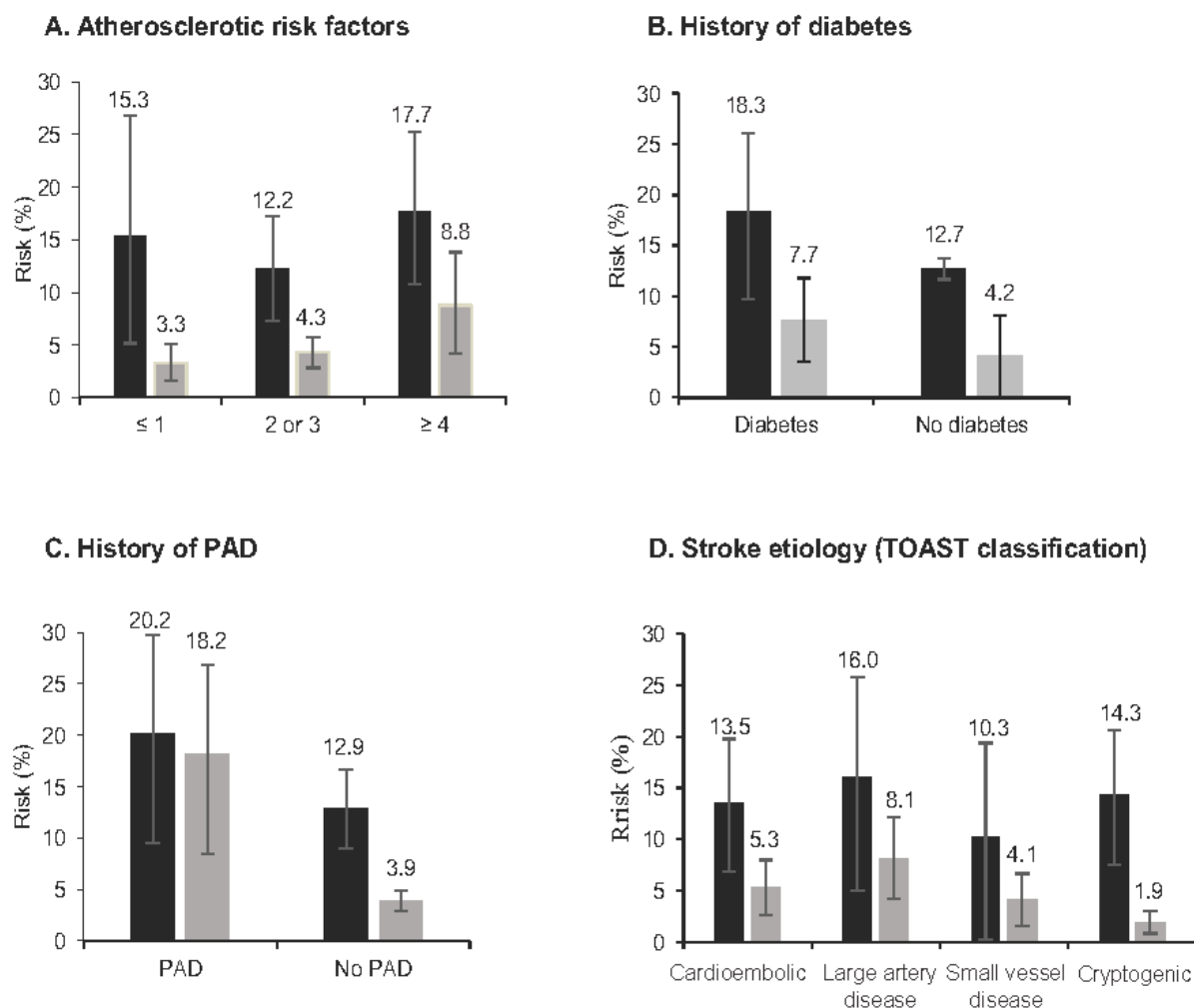


Figure 12 : 5 year-risk of coronary events in TIA or ischaemic stroke patients with and without history of coronary artery disease, stratified by number of atherosclerotic risk factors, history of diabetes, history of peripheral artery disease (PAD) or TIA/ischaemic stroke subtype

Bars indicate 95% confidence intervals.

Atherosclerotic risk factors were male sex, history of hypertension, diabetes mellitus, hypercholesterolemia, smoking (i.e. ex or current smoker) and family history of premature myocardial infarction (defined as myocardial infarction occurring in a first-degree relative, siblings or parents, aged ≤55 years if male or aged ≤65 years if female). Data missing for number of atherosclerotic risk factors for 479 patients.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

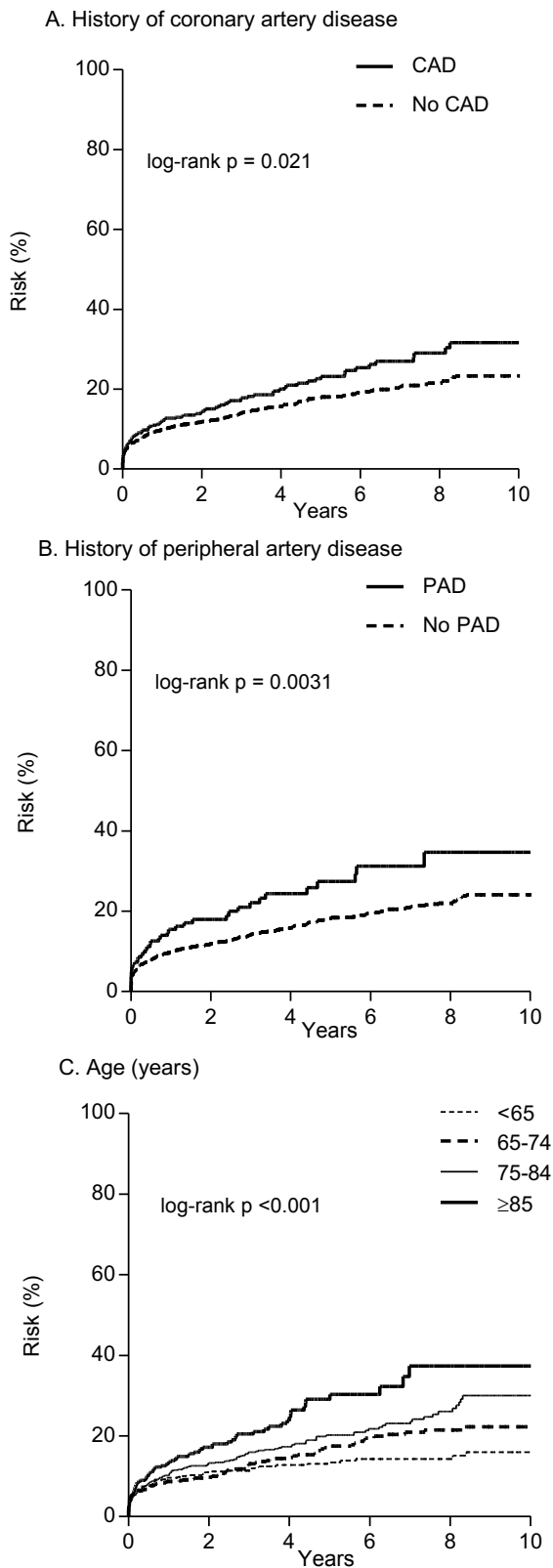


Figure 13 : Risk of recurrent ischaemic strokes in TIA or ischaemic stroke patients stratified by history of coronary (CAD), peripheral artery disease (PAD) or age

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

The subgroup of patients with (TOAST) large artery disease had the highest 10-year risk of coronary events compared to the other stroke subtypes (16.1%, 10.3-21.6, $p < 0.001$) and among the highest 10-year risk of recurrent ischaemic stroke (26.3%, 18.9-33.1, $p < 0.001$, Table 17, Figure 14). However, in patients with (TOAST) large artery disease, risk of coronary events remained increased in those with co-existing cardiovascular disease compared to those without (10-year risk=33.5%, 15.9-47.4; vs 9.5%, 4.2-14.6; $p < 0.001$, age- and sex-adjusted HR=3.39, 1.65-6.96) while risk of recurrent ischaemic stroke was high irrespective of presence of co-existing cardiovascular disease (10-year risk=26.4%, 12.6-38.1; vs 26.3%, 17.3-34.4; $p = 0.79$, age- and sex-adjusted HR=1.02, 0.57-1.83, Figure 15 and Table 18). Patients with (TOAST) large artery disease had also a high 10-year risk of major extracranial bleeds (11.1%, 1.8-19.5, $p = 0.85$) but a relatively low risk of intracerebral haemorrhage (0.4%, 0.0-1.1, $p = 0.26$, Tables 17 and 18). In contrast, the subgroup of patients with cryptogenic stroke had the lowest 10-year risk of recurrent ischaemic stroke (19.5%, 15.6-23.3, $p < 0.001$) and of coronary events compared to the other stroke subtypes (8.3%, 5.4-11.1, Table 17, Figure 14), but a relatively high 10-year risk of intracerebral haemorrhage (2.5%, 0.76-4.2, $p = 0.26$, Table 17).

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 17 : 10-year risk of coronary events, recurrent ischaemic stroke, major ischaemic vascular events, intracerebral haemorrhage and major extracranial bleeds after TIA or ischaemic stroke patients, stratified by stroke subtype

	Large artery disease (n=280)		Cardioembolic (n=669)		Small vessel disease (n=317)		Cryptogenic (n=811)		p
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
Coronary events	40	16.13 (10.28-21.60)	37	11.19 (6.91-15.27)	19	7.87 (4.22-11.38)	41	8.29 (5.38-11.11)	<0.001
Recurrent ischaemic stroke	54	26.34 (18.89-33.11)	114	31.91 (24.76-38.38)	64	25.91 (19.47-31.84)	111	19.50 (15.57-23.25)	<0.001
Major ischaemic vascular events	71	36.73 (28.18-44.26)	140	39.02 (31.35-45.84)	78	31.58 (24.82-37.74)	139	25.70 (20.87-30.23)	<0.001
Intracerebral haemorrhage*	1	0.37 (0.00-1.09)	NA	NA	2	1.90 (0.00-4.85)	11	2.50 (0.76-4.21)	0.26
Major extracranial bleeds*	11	11.09 (1.84-19.48)	NA	NA	16	7.65 (3.57-11.56)	31	7.31 (4.27-10.27)	0.85

N: number of follow-up events. p are log-rank p. Major ischaemic vascular event was a composite of recurrent ischaemic stroke or coronary event. *Patients with cardioembolic TIA/ischaemic stroke and those on anticoagulants were excluded.

Information on coronary events, recurrent ischaemic stroke and intracerebral haemorrhage was available in cases recruited from April 1, 2002 to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was available in cases recruited from April 1, 2002 to March 31, 2012, with follow-up until March 31, 2013, including 235 patients with large artery disease, 277 with small vessel disease and 669 with cryptogenic TIA/ischaemic stroke.

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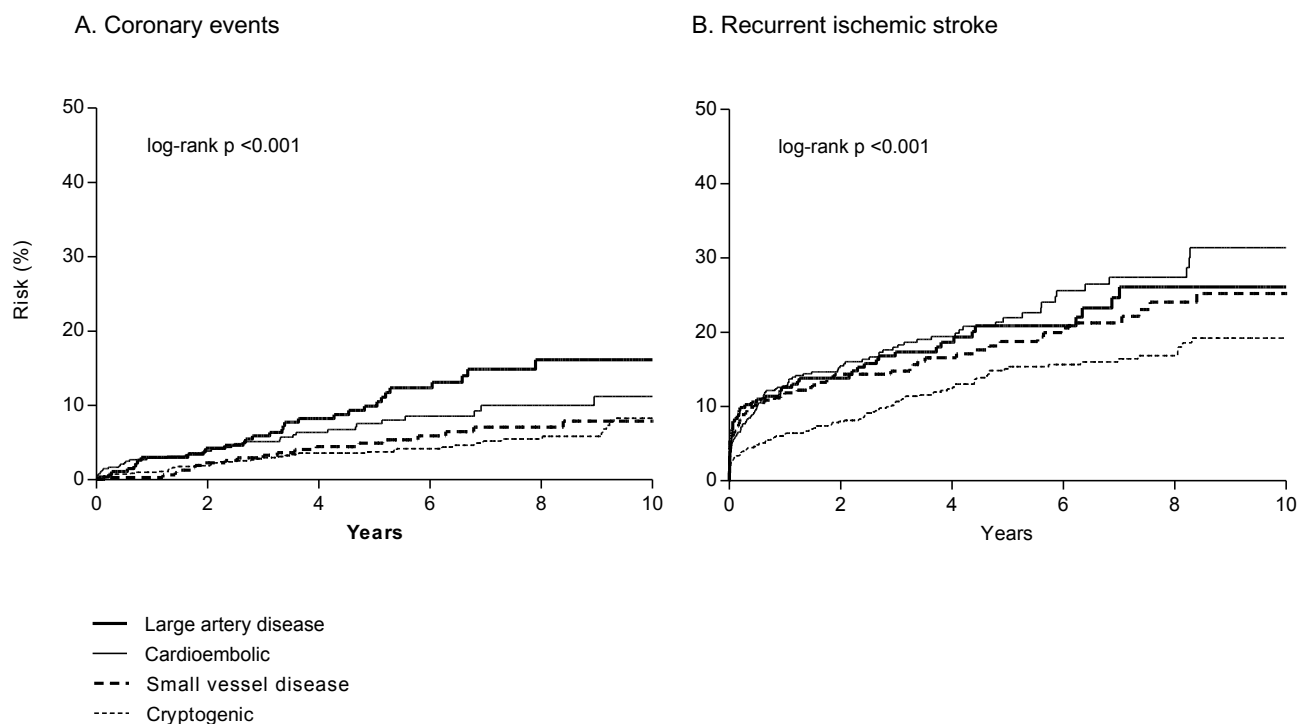


Figure 14 : Risks of coronary events and recurrent ischaemic stroke after TIA or ischaemic stroke, stratified by stroke subtype (TOAST classification)

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 18 : 10-year risk of coronary events, recurrent ischaemic stroke, major ischaemic vascular events, intracerebral haemorrhage and major extracranial bleeds in the subgroup of patients with TIA or ischaemic stroke due to large artery disease (TOAST classification), stratified by baseline history of co-existing cardiovascular disease

Co-existing cardiovascular disease	Events, n/N		10-year risk, % (95%CI)		p	Crude HR (95%CI)	Age-and sex-adjusted HR (95%CI)	p
	Yes	No	Yes	No				
Coronary events	18/85	13/195	33.49 (15.91-47.39)	9.53 (4.18-14.57)	<0.001	3.98 (1.97-8.09)	3.39 (1.65-6.96)	<0.001
Recurrent ischaemic stroke	17/85	37/195	26.4 (12.6-38.1)	26.3 (17.3-34.4)	0.79	1.08 (0.61-1.91)	1.02 (0.57-1.83)	0.94
Major ischaemic vascular events	29/85	48/195	49.90 (31.39-63.41)	31.07 (21.30-39.62)	0.0264	1.70 (1.06-2.72)	1.53 (0.95-2.48)	0.08
Intracerebral haemorrhage*	0/85	1/195	0	0.53 (0.00-1.55)	0.51	0.01 (0.00-100)	0.01 (0.00-100)	0.59
Major extracranial bleeds*	5/75	6/160	22.98 (0.00-44.70)	6.61 (0.14-12.67)	0.27	1.94 (0.59-6.37)	1.66 (0.49-5.60)	0.41

HR: Hazard ratio. Major ischaemic vascular event was a component of coronary event or recurrent ischaemic stroke. *Patients with cardioembolic TIA/ischaemic stroke and those on anticoagulants were excluded

Information on coronary events, recurrent ischaemic stroke and intracerebral haemorrhage was available in cases recruited from April 1, 2002 to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was only available in cases recruited from April 1, 2002 to March 31, 2012, with follow-up until March 31, 2013.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

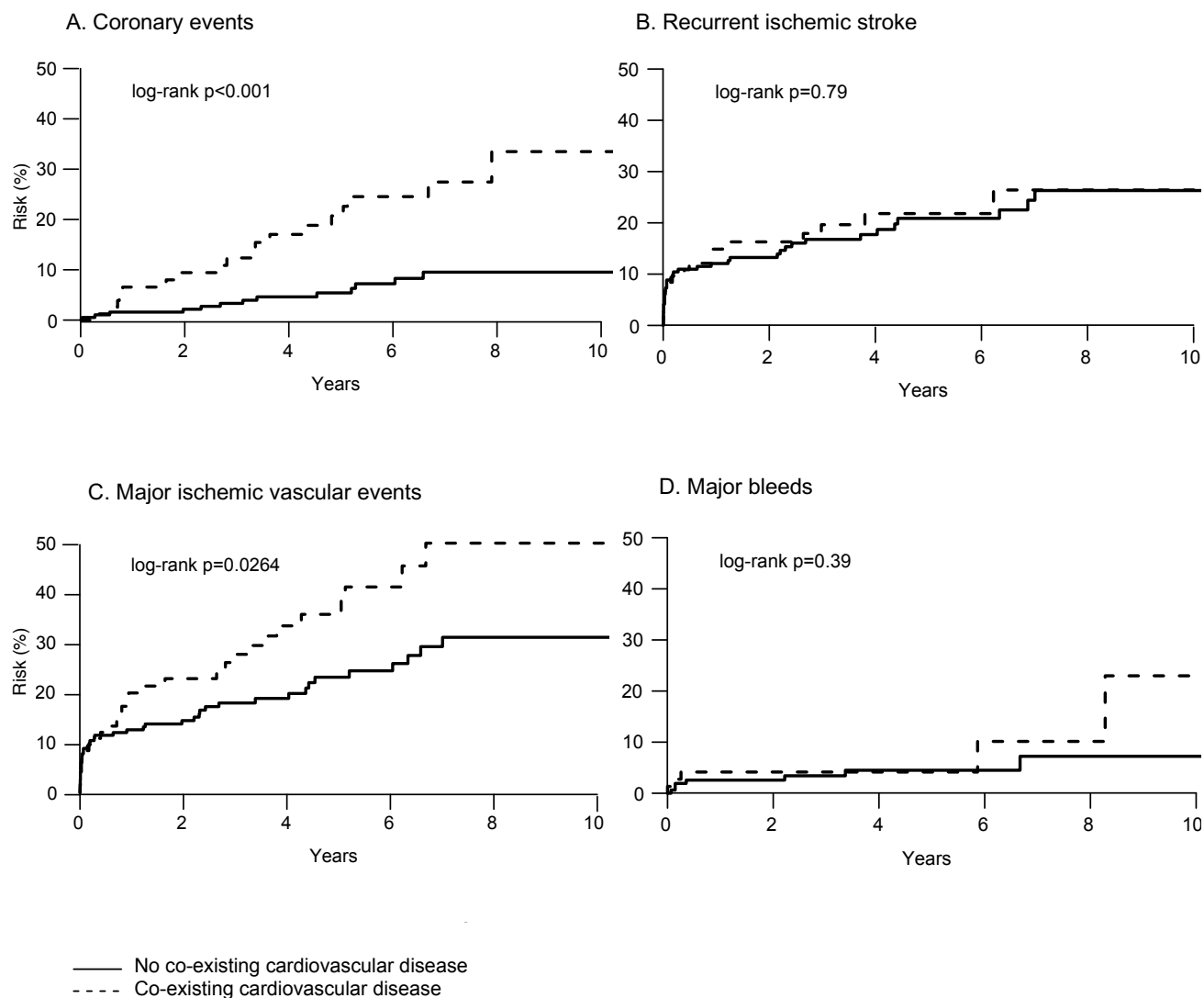


Figure 15 : Risks of coronary events, recurrent ischaemic stroke, major ischaemic vascular events and major bleeds after TIA or ischaemic stroke due to large artery disease (TOAST classification), stratified by history of co-existing cardiovascular disease

Major ischaemic vascular event was a component of coronary event or recurrent ischaemic stroke. Risk of major bleeds was calculated in non-cardioembolic TIA or ischaemic stroke patients and after exclusion of those on anticoagulants

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Discussion

In this population-based cohort of consecutive TIA/ischaemic stroke patients on current standard management, those with co-existing cardiovascular disease were at significantly higher 10-year risk of coronary events and recurrent ischaemic stroke than those without, particularly at age <75 years (16.7% vs 3.8% and 30.3% vs 17.6%, respectively). However, in younger patients with non-cardioembolic TIA/ischaemic stroke (i.e. on antiplatelet therapy for secondary prevention), 10-year risk of major extracranial bleeds was also higher in those with co-existing cardiovascular disease (8.1% vs 3.5%), although there was no increased risk of intracerebral haemorrhage. More intensive lipid lowering might be therefore justified in patients with co-existing cardiovascular disease, although economic evaluation of PCSK9-inhibitors in addition to statin therapy in similar patient populations suggests that treatment might still exceed the generally accepted cost-effectiveness threshold,⁸⁹ and there is probably still potential for more intensive treatment with statins and other lipid-lowering drugs. Benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding, particularly in older patients, in whom bleeds are more likely to be disabling or fatal.⁹⁰

We found that the subgroup of patients with large artery disease (TOAST classification) were at high risk of ischaemic events, consistent with previous findings.^{91, 92} However, the current absolute risk of ischaemic events (10-year risk of coronary events of 16.1% and 10-year risk of recurrent ischaemic stroke of 26.3%) was lower than previously reported (10-year risk >20% and >30%, respectively).^{91, 92} We also found that stratification by presence of co-existing cardiovascular disease identified individuals at higher risk of coronary events, with 10-year risk ranging from 9.5% in patients without co-existing cardiovascular disease to 33.5% in those with. The suggestion that carotid stenosis should be considered as a coronary heart disease equivalent (defined as 10-year risk $\geq 20\%$)⁹³⁴⁶ was based mainly on data from trials of endarterectomy performed in the 1980s and early 1990s, which reported risks of coronary events of more than 20% over 10 years.^{91, 92} The risk of myocardial infarction after TIA/ischaemic stroke has declined over time,⁵⁹ but only one recent study reported the risk in patients with TIA/ischaemic stroke due to large artery disease, with an annual risk of 0.8%,⁹⁴ although prevalence of coronary artery disease was lower (11%) than in our cohort (30%) and mean follow-up was only 2.1 years. We found that most coronary events occurred in the subset of patients with large artery disease who had prior co-existing cardiovascular disease.

We also found that patients with cryptogenic TIA/ischaemic stroke, in whom the prevalence of co-existing cardiovascular disease was relatively low, had the lowest risk of coronary events or recurrent ischaemic stroke, but a relatively high risk of intracerebral haemorrhage compared to the other non-cardioembolic subtypes. Patients with cryptogenic TIA/ ischaemic stroke were younger than those

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with other subtypes and had less hypertension and diabetes, which are known risk factors for intracerebral haemorrhage,^{85, 95} and their higher risk of intracerebral haemorrhage remains difficult to explain. Notwithstanding the results of ongoing trials of anticoagulation versus antiplatelet treatment in patients with cryptogenic stroke,⁹⁶ future trials on more intensive antithrombotic management might focus on subgroups of TIA/ ischaemic stroke patients with a high risk of recurrent ischaemic events and a lower risk of bleeding.

Hypertension is a strong predictor of intracerebral haemorrhage⁸⁵ and blood pressure management in TIA/ ischaemic stroke patients significantly reduces the risk of intracerebral haemorrhage, with benefit increasing over time.⁹⁷ The prevalence of history of hypertension was higher in patients with co-existing cardiovascular disease than in those without and the rates of use of antihypertensives at both baseline and 1 year were also higher, which might at least partly explain the relatively low risk of intracerebral haemorrhage in patients with co-existing cardiovascular disease.

Although we consider our findings to be valid, our study has limitations. First, our population consisted of a predominantly white British population, which will limit generalisability. Second, rates of use of secondary prevention medication were high, but were not 100%. However, our population-based cohort includes many frail and very elderly patients, often with dementia, prior gastrointestinal bleeding, or terminal illness, and some patients refuse medication for other reasons. Nevertheless, rates of medication use at 1-month and 1-year were higher than in the majority of other similar cohorts,⁹⁸⁻¹⁰¹ and can be regarded as being based closely on current guidelines for secondary prevention. Thirdly, although all hospital admissions for chest pain were reviewed, details were only collected for myocardial infarction and we did not report information on angina pectoris. Indeed, data on angina are considered to be less reliable than those on myocardial infarction because underdiagnosed angina is estimated to be common and not all patients with angina symptoms seek medical attention.¹⁰² Finally, diagnosis of myocardial infarction has evolved over the last two decades^{67, 103} and so our findings may not be fully generalisable to future clinical practice. Similarly, those centers that use a DWI-based definition of TIA versus ischaemic stroke may obtain higher estimate of recurrent stroke risk.

In conclusion, TIA/ischaemic stroke patients with co-existing cardiovascular disease have a high risk of recurrent ischaemic events on current standard management. More intensive lipid lowering might be therefore justified, but benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding, particularly in older patients.

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II.2. Essen risk score in prediction of myocardial infarction after TIA or ischaemic stroke without prior coronary artery disease

Boulanger M, Li L, Lyons L, Lovett NG, Kubiak MM, Silver L, Touzé E, Rothwell PM on behalf of the Oxford Vascular Study.
Stroke (accepted)

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Abstract

Background and Purpose: More intensive secondary prevention with newer drugs may be cost-effective in patients with coronary artery disease. Whether some subgroups of patients who had a TIA or ischaemic stroke but no prior coronary artery disease are at similar high risk of myocardial infarction as those with prior coronary artery disease remains unclear. We determined whether the Essen score identified a subset of TIA/ ischaemic stroke patients without known prior coronary artery disease who nevertheless had a high risk of myocardial infarction on current secondary prevention management.

Methods: In a population-based cohort (Oxford Vascular Study) of consecutive TIA or ischaemic stroke patients recruited from 2002-2014, 10-year actuarial risks of myocardial infarction and of recurrent ischaemic stroke were determined by face-to-face follow-up in patients with and without prior coronary artery disease using Kaplan-Meier analyses. Predictive value of the Essen score was assessed with c-statistic.

Results: Of 2555 TIA/ ischaemic stroke patients (13,070 patient-years of follow-up), 10-year risk of myocardial infarction in those without prior coronary artery disease (n=2017, 78.9%) ranged from 0.9% (95% Confidence Interval [CI] 0-1.9) at Essen score ≤ 1 to 29.8% (95%CI 7.7-46.6) in those with a score ≥ 5 (c-statistic=0.64, 95%CI 0.57-0.71; $p < 0.001$). The score tended to be less predictive (difference: $p = 0.0460$) for the risk of recurrent ischaemic stroke (c-statistic=0.57, 95%CI 0.54-0.60). Compared to patients with prior coronary artery disease (n=538, 21.1%), an Essen risk score of ≥ 4 (n=294, 11.5%) in those without prior coronary artery disease identified a subgroup at similar high 10-year risks of myocardial infarction (17.2%, 95%CI 6.9-26.3; versus 16.9%, 95%CI 11.5-22.0) and of recurrent stroke (40.4%, 95%CI 26.7-51.6; versus 32.4%, 95%CI 25.2-38.8).

Conclusions: The Essen score is a simple clinical score to risk-stratify TIA/ ischaemic stroke patients without prior coronary artery disease and to identify subsets who may be at sufficiently high risk of myocardial infarction and recurrent stroke to justify more intensive treatment or inclusion in trials.

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Introduction

The long-term risk of myocardial infarction and recurrent ischaemic stroke after a TIA (transient ischaemic attack) or ischaemic stroke is particularly high in patients with prior coronary artery disease.^{59, 104} Recent trials of more intensive secondary prevention, such as those of lipid lowering with the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors³⁵⁻³⁷ or those combining antithrombotic treatments,³⁹ focused on patients with prior coronary artery disease. However, whether some subgroups of TIA/ ischaemic stroke patients without prior coronary artery disease have a similar high long-term risk of myocardial infarction or recurrent ischaemic stroke remains uncertain. Although the SPARCL trial⁷ showed that higher dose of statin should be standard of care in TIA/ischaemic stroke patients, it is uncertain whether more intensive treatment might be justified in certain subgroups.

Long-term follow-up of TIA/ ischaemic stroke patients has shown that the risks of death due to recurrent stroke and death due to coronary events are similar.⁵⁹ However, risk stratification schemes tend to focus on risk of recurrent stroke.⁸⁻¹³ Nevertheless, since risk scores to predict the risk of recurrent ischaemic stroke are mostly based on risk factors for, or clinical manifestations of, atherosclerosis they may also predict coronary events. Therefore, rather than attempting to derive and validate a new score to predict coronary events after TIA/ischaemic stroke, we determined the predictive value of the Essen stroke risk score for risk of myocardial infarction after TIA/ischaemic stroke. The Essen risk score is a simple clinical score that was derived to predict the 1-year risk of recurrent ischaemic stroke after ischaemic stroke based on the presence of prior vascular comorbidities, including current smoking, previous TIA or ischaemic stroke, prior coronary artery disease, peripheral artery disease, hypertension, diabetes and age, and is one of the most established scores for stroke patients.^{11,13}

The Essen score has been validated previously, but further validation would be helpful for several reasons. Firstly, previous validations have looked only at short-term risk, predicting the 1-year risk of recurrent stroke,^{11,13-19} or the 1-year risk of the combined outcome of recurrent stroke, myocardial infarction and cardiovascular death^{14,17,19} or the 1-year risk of combined outcome of recurrent stroke or cardiovascular death.¹⁸ Secondly, the score was derived on patients recruited into a trial cohort in the early 1990s, and the validation cohorts involved patients recruited in trials or hospital-based registries, mostly in the early 2000s before the widespread use of higher-dose statins.⁷ The absolute risk of myocardial infarction after

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TIA/ischaemic stroke has decreased over the past few decades,⁵⁹ and there are relatively few recent data on the overall residual vascular risk in TIA/ischaemic stroke patients on current guideline-based management, particularly on long-term follow-up. Thirdly, previous validation studies have focussed mainly on patients with stroke due to large artery disease, have excluded patients with TIA, and have suggested that the score might perform less well in those with stroke due to small vessel disease.¹⁹ Finally, no study has looked at whether the score predicts risk of myocardial infarction as well as stroke, and none have assessed predictive value in patients with no prior coronary artery disease.

We aimed to determine whether the Essen score identified a subset of TIA/ischaemic stroke patients without known prior coronary artery disease who nevertheless had a high risk of myocardial infarction on current secondary prevention management and might therefore benefit from more intensive treatment or might be included in future trials.

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Material and methods

The Oxford Vascular study (OXVASC) is an ongoing population-based study of the incidence and outcome of all acute vascular events in 92728 individuals, irrespective of age, registered with 100 family physicians in nine general practices in Oxfordshire, UK.⁶³ The analysis reported here included consecutive cases, irrespective of age, with a TIA or ischaemic stroke from 2002 to 2014, with follow-up until 2016. The OXVASC study design has been described in detail previously.⁶³ Briefly, multiple overlapping methods of hot and cold pursuit were used to achieve near complete ascertainment of all individuals with transient ischaemic attack (TIA) or stroke.⁶⁴⁶⁵ These include: 1) a daily, rapid access “TIA and stroke clinic” to which participating general practitioners and the local emergency department refer individuals with suspected TIA or minor stroke; 2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; 3) daily searches of the local emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner’s reports for out of hospital deaths; 6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

Demographic data, prior comorbidities and medication were collected from face-to-face interviews and cross-referenced with primary care records. All cases were investigated and treated according to current guidelines. Patients were classified as having a prior coronary artery disease if they had at least one of the following: previous myocardial infarction; unstable angina; angina; previous percutaneous coronary intervention or coronary artery bypass graft surgery. Written informed consent or assent from relatives was obtained in all patients. OXVASC was approved by our local research ethics committee.

Standard WHO definitions were used for TIA and stroke, which have been reported previously.^{63, 64} All cases were investigated according to current guidelines and reviewed by a senior neurologist with stroke expertise (PMR) to ensure consistency over time and TIA/ischaemic stroke aetiology was categorised according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Appendix I).⁶⁶ Differentiation between TIA and stroke was based on the WHO 24-hour cut-off for symptom duration (i.e. events were classified as TIA even if Diffusion Weighted Imaging [DWI] was positive if symptoms resolved within 24 hours) and we have kept the same definition over time. Patients were prescribed standard secondary prevention medication according to contemporary guidelines, including antiplatelet

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or anticoagulant treatment, as appropriate, blood pressure lowering medication and statin treatment to achieve a target of blood pressure <140/90 and LDL <2.6mmol/L, both at baseline and at the time of study follow-up visits.

All patients were followed up face-to-face at 1, 6, 12, 60 and 120 months by a study nurse or physician and subsequent vascular events identified and risk factor control evaluated and treatment revised as necessary. For patients who had moved out of the study area, telephone follow-up was done, and patients with dementia were followed-up via a carer or by assessment in a nursing home. All myocardial infarctions that presented to medical attention would also be identified by ongoing daily case-ascertainment of all acute vascular events in the study population. All study patients were also notified to the UK Office of National Statistics such that all deaths were reported back to the study with causes. Deaths were also identified by regular review of primary care records and by regular contact with the Coroner's Office to ascertain out-of-hospital deaths.

Myocardial infarction was defined using standard criteria and remained unchanged over the study period.⁶⁷ Recurrent ischaemic stroke was defined as new neurological deficit fitting the definition for ischaemic stroke occurring after a period of neurological stability or improvement.

Statistical analysis

We determined the 10-year actuarial risk of myocardial infarction and of recurrent ischaemic stroke from Kaplan-Meier analyses in TIA/ischaemic stroke patients with and without prior coronary artery disease. Among the latter subgroup, we stratified risk by the Essen score, but excluded the 'history of other cardiac disease' (i.e. cardiac disease other than myocardial infarction or atrial fibrillation; Table 19) because this variable was not fully defined in previous reports.^{11,14,15} Essen scores in patients without prior coronary artery disease therefore ranged from 0 to 7: 1 point is attributed for age 65-75 years; 2 for age >75 years and 1 for each history of prior hypertension, diabetes mellitus, peripheral artery disease, current smoking or previous TIA or ischaemic stroke. A small number of patients with missing value on the Essen score were excluded from the analyses. Discrimination (i.e. how well the score distinguished between people with the outcome and those without) was assessed with the c-statistic. Difference in the discrimination of the score for the risk of myocardial infarction and for the risk of recurrent ischaemic stroke was assessed by a Z-test. Age- and sex-adjusted risk associations between variables of the Essen score and myocardial infarction were determined by Cox regression. In additional analyses in patients without prior coronary artery disease, we

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determined the 10-year risk of myocardial infarction or recurrent ischaemic stroke based on the Essen score and stratified by presence of large artery disease (TOAST) subtype, which have been shown to carry one of the highest risks of myocardial infarction and recurrent ischaemic stroke,² and difference was assessed by log-rank p. Also, we determined the predictive value of adding the variable “presence of large artery disease (TOAST) subtype” as a categorical variable to the Essen score for the risk of myocardial infarction and of recurrent ischaemic stroke, with 1 point being attributed for the presence of large artery disease subtype and 0 point for any other subtypes than large artery disease. All analyses were done using R version 3.1.3.

Table 19 : The Essen risk score^{11,13}

Variables of the Essen score	Points
Age (years)	
-<65	0
-65-75	1
->75	2
History of hypertension	1
History of diabetes mellitus	1
History of peripheral artery disease	1
History of previous myocardial infarction	1
History of other cardiovascular disease (except myocardial infarction and atrial fibrillation)	1
Current smoking	1
Additional TIA or ischaemic stroke in addition to the qualifying event (i.e. previous TIA/ ischaemic stroke)	1

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Results

Of 2555 TIA/ischaemic stroke patients, those without prior coronary artery disease (n=2017; 79%) were younger, had less prior vascular comorbidities, except for current smoking, and were less likely to be on antithrombotics, antihypertensives and statins before the TIA/ischaemic stroke than those with (p<0.001, Table 20). Rates of secondary preventive therapies use were high at 1-year follow-up, but rates of antithrombotics and antihypertensives use remained lower in patients without coronary artery disease than in those with (Table 20). The prevalence of TIA/ischaemic stroke due to large artery disease was similar in patients with and without prior coronary artery disease but TIA/ischaemic stroke was less often due to cardioembolism in patients without coronary artery disease (Table 20).

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Table 20 : Baseline characteristics in TIA or ischaemic stroke patients included in the analysis and medication at baseline and on follow-up

	Prior coronary artery disease		p
	No (n=2017)	Yes (n=538)	
Mean (SD) age, years	72.7 (13.5)	78.4 (9.8)	<0.001
Men	971 (48.1)	291 (54.1)	0.0162
Prior comorbidities			
Previous TIA or ischaemic stroke	248 (12.3)	101 (18.8)	<0.001
Atrial fibrillation	339 (16.8)	183 (34.0)	<0.001
Peripheral artery disease	103 (5.1)	88 (16.4)	<0.001
Hypertension	1128 (55.9)	409 (76.0)	<0.001
Diabetes mellitus	225 (11.2)	132 (24.5)	<0.001
Hypercholesterolaemia	493 (24.4)	289 (53.7)	<0.001
Smoking status			
Present*	321 (15.9)	40 (7.4)	<0.001
Past**	771 (38.2)	282 (52.4)	<0.001
TIA/ischaemic stroke subtype			
Cardioembolic	471 (23.3)	198 (36.8)	<0.001
Large artery disease	216 (10.7)	64 (11.9)	0.48
Small vessel disease	276 (13.7)	41 (7.6)	<0.001
Cryptogenic	689 (34.1)	122 (22.7)	<0.001
More than one cause	54 (2.7)	36 (6.7)	<0.001
Unknown	261 (12.9)	70 (13.0)	0.99
Other causes	50 (2.5)	7 (1.3)	0.14
Baseline medication			
Antithrombotics	659 (32.7)	441 (82.0)	<0.001
Antihypertensives	1027 (50.9)	459 (85.3)	<0.001
Statins	367 (18.2)	317 (58.9)	<0.001
Secondary prevention medication at 1-year follow-up†			
	n=1639	n=392	
Antithrombotics	1511 (92.2)	374 (95.4)	0.035
Antihypertensives	1228 (74.9)	344 (87.8)	<0.001
Statins	1279 (78.0)	310 (79.1)	0.70

Data are numbers (%), unless otherwise specified. p for comparison between patients with and without coronary artery disease (χ^2 test for categorical variables and t-test for continuous variable). *missing data for 7 patients (5 patients without prior CAD and 2 with prior CAD), ** missing data for 9 patients (6 patients without prior CAD and 3 with prior CAD), †patients who died before follow-up were not included

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

During 13,070 patient-years of follow-up, there were 118 myocardial infarctions after a median (range) of 5.6 (0-14.6) years, of which 70 (59.3%) occurred in patients without prior coronary artery disease. Five (0.2% of patients had a missing value for one of the Essen score variables and were excluded from subsequent analyses. Among patients without prior coronary artery disease, those with an Essen score ≤ 1 comprised 565 (28.1%) of all patients but accounted for 3 (4%) of follow-up myocardial infarction, whereas those with a score ≥ 4 comprised 14.6% (n=294) of all patients but accounted for 31% (n=22) of myocardial infarction (Table 21). There were also 413 recurrent ischaemic strokes during follow-up, of which 313 (75.7%) occurred among patients without prior coronary artery disease.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

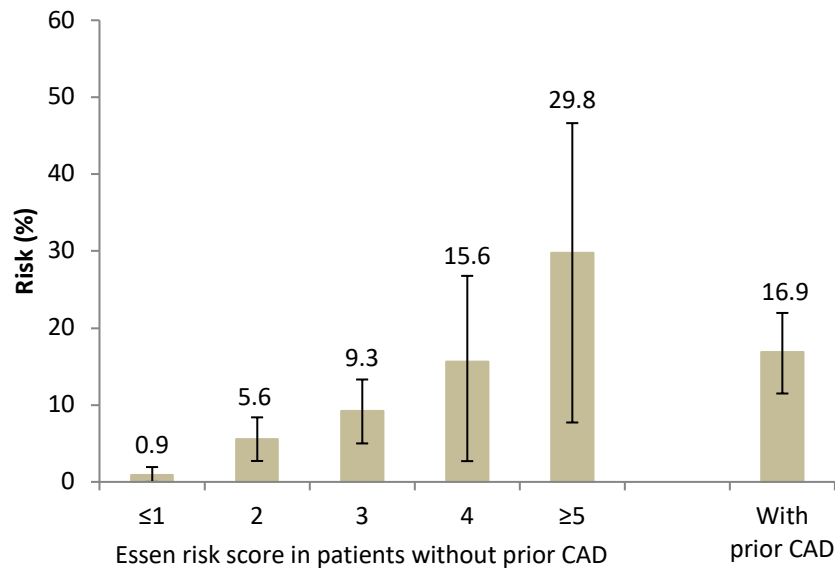
Table 21 : 10-year risks of myocardial infarction and recurrent ischaemic stroke after TIA or ischaemic stroke in patients without prior coronary artery disease (CAD), stratified by the Essen risk score, and in those with prior CAD

Prior CAD status	Myocardial infarction		Recurrent ischaemic stroke	
	Cumulative events, n/N	10-year risk, % (95% CI)	Cumulative events, n/N	10-year risk, % (95% CI)
All patients	118/2555	8.01 (6.38-9.61)	413/2555	25.25 (22.58-27.83)
No prior CAD				
Essen score*:				
≤1	3/565	0.89 (0-1.93)	52/565	11.15 (7.91-14.27)
2	18/577	5.60 (2.72-8.39)	98/577	24.10 (18.99-28.89)
3	27/576	9.25 (5.00-13.31)	107/576	32.12 (25.12-38.47)
4	14/240	15.59 (2.70-26.78)	43/240	40.95 (23.94-54.16)
≥5	8/54	29.82 (7.72-46.63)	13/54	39.51 (17.20-55.82)
Total	70/2012	5.97 (4.39-7.53)	313/2012	23.60 (20.73-26.37)
Prior CAD	48/538	16.89 (11.49-21.96)	100/538	32.34 (25.20-38.80)

CI: confidence interval, *data missing for 5 patients.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Myocardial infarction



Recurrent ischaemic stroke

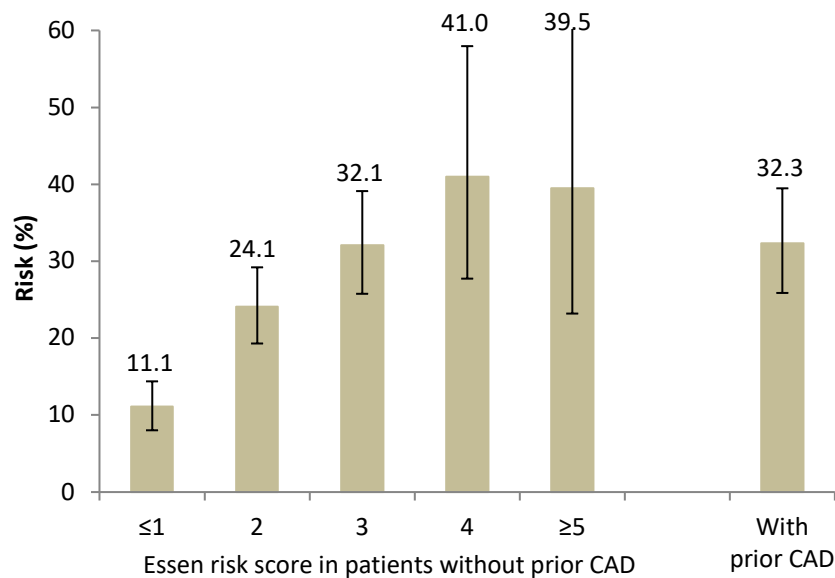


Figure 16 : 10-year actuarial risk of myocardial infarction and of recurrent ischaemic stroke in TIA or ischaemic stroke patients based on presence of prior coronary artery disease (CAD) and the Essen score

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 22 : Variables of the Essen score and risk of myocardial infarction in TIA/ischaemic stroke patients without prior coronary artery disease

Variables of the Essen score	Events, n/N	Crude HR (95%CI)	Age- and sex-adjusted HR (95%CI)	p
Age (vs. <65years)				
-65-75	20/544	4.08 (1.53-10.86)	4.08 (1.53-10.86)	0.0049
->75	45/977	7.63 (3.02-19.26)	7.66 (3.01-19.47)	<0.001
Hypertension	50/1128 vs. 20/889	2.14 (1.28-3.60)	1.66 (1.00-2.80)	0.05
Diabetes	13/225 vs. 57/1792	1.91 (1.05-3.49)	2.00 (1.09-3.66)	0.025
Peripheral artery disease	11/103 vs. 59/1914	4.49 (2.36-8.55)	3.93 (2.05-7.52)	<0.001
Current smoking*	17/321 vs. 53/1691	1.48 (0.86-2.55)	3.27 (1.82-5.88)	<0.001
Prior TIA/ischaemic stroke	15/248 vs. 55/1769	2.13 (1.20-3.77)	1.66 (0.94-2.96)	0.08

CI: confidence interval, *data missing for 5 patients. HR: hazard ratio

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Compared to patients with prior coronary artery disease (n=538, 21.1%), an Essen risk score of ≥ 4 (n=294, 11.5%) in those without prior coronary artery disease identified a subgroup at similarly high 10-year risk of myocardial infarction (17.2%, 6.9-26.3; versus 16.9%, 11.5-22.0, Tables 21 and 23) The subgroup of patients without prior coronary artery disease with an Essen risk score of ≥ 4 were also at significantly higher 10-year risk of myocardial infarction than those with a score of < 4 (17.2%, 6.9-26.3 versus 4.7%, 3.2-6.2, $p < 0.001$, age-and sex-adjusted HR=2.23, 1.32-3.76, Tables 23 and 24), with no interaction by TIA/ischaemic stroke subtype (p -interaction=0.93). The risk of myocardial infarction was approximately linear with time in patients with prior coronary artery disease and in those without (Figure 17).

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 23 : Stratification by Essen score of ≥ 4 versus < 4 and risk of myocardial infarction and of recurrent ischaemic stroke in TIA/ischaemic stroke patients without prior coronary artery disease

Essen score*	Events, n/N		10-year risk, % (95% CI)		p	Crude HR (95%CI)	Age- and sex-adjusted HR (95%CI)	p
	<4	≥ 4	<4	≥ 4				
Follow-up events:								
Myocardial infarction	48/1718	22/294	4.71 (3.22-6.17)	17.19 (6.92-26.32)	<0.001	3.60 (2.17-5.97)	2.23 (1.32-3.76)	0.0028
Recurrent ischaemic stroke	257/1718	56/294	21.55 (18.70-24.30)	40.42 (26.67-51.59)	0.0063	1.49 (1.12-1.98)	1.21 (0.90-1.63)	0.21

CI: confidence interval, *data missing for 5 patients. HR: hazard ratio, p for comparison between Essen score ≥ 4 versus < 4

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 24 : Stratification by Essen score of ≥ 4 versus < 4 and risk of myocardial infarction and of recurrent ischaemic stroke in TIA/ischaemic stroke patients without prior coronary artery disease, stratified by TIA/ischaemic stroke subtype (TOAST classification)

Essen score*	10-year risk, % (95% CI)		p	Crude Hazard Ratio (95%CI)	Age- and sex-adjusted Hazard Ratio (95%CI)	p
	<4	≥ 4				
All patients						
Myocardial infarction	4.71 (3.22-6.17)	17.19 (6.92-26.32)	<0.001	3.60 (2.17-5.97)	2.23 (1.32-3.76)	0.0028
Recurrent ischaemic stroke	21.55 (18.70-24.30)	40.42 (26.67-51.59)	0.0063	1.49 (1.12-1.98)	1.21 (0.90-1.63)	0.21
Stroke subtypes				<i>p</i> -interaction=0.93 for myocardial infarction <i>p</i> -interaction=0.91 for recurrent ischaemic stroke		
Cardioembolic						
Myocardial infarction	7.10 (1.88-12.04)	8.23 (0-18.60)	0.45	1.61 (0.45-5.73)	1.09 (0.30-3.98)	0.90
Recurrent ischaemic stroke	29.10 (20.26-36.97)	35.65 (13.31-52.23)	0.22	1.42 (0.81-2.50)	1.07 (0.60-1.89)	0.81
Large artery disease						
Myocardial infarction	7.39 (1.90-12.57)	28.56 (10.29-43.10)	<0.001	7.55 (2.87-19.86)	5.69 (1.81-17.88)	0.0029
Recurrent ischaemic stroke	21.61 (12.81-29.52)	47.97 (22.74-64.96)	0.0014	2.74 (1.44-5.23)	2.90 (1.40-60.2)	0.0043
Small vessel disease						
Myocardial infarction	4.36 (1.24-7.39)	19.72 (0-35.91)	0.0014	5.72 (1.71-19.19)	3.57 (0.92-13.92)	0.06
Recurrent ischaemic stroke	22.18 (15.43-28.39)	51.73 (0-79.95)	0.93	0.96 (0.38-2.41)	1.01 (0.38-2.66)	0.90
Cryptogenic						
Myocardial infarction	2.78 (0.92-4.61)	11.10 (0-24.14)	0.17	2.38 (0.66-8.54)	1.16 (0.32-4.20)	0.82
Recurrent ischaemic stroke	15.40 (11.78-18.87)	37.51 (15.38-53.86)	0.0440	1.73 (1.01-2.97)	1.31 (0.74-2.29)	0.35

*Data on Essen score missing in 5 patients. *p*-interaction between the TIA/ischaemic stroke subtypes

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

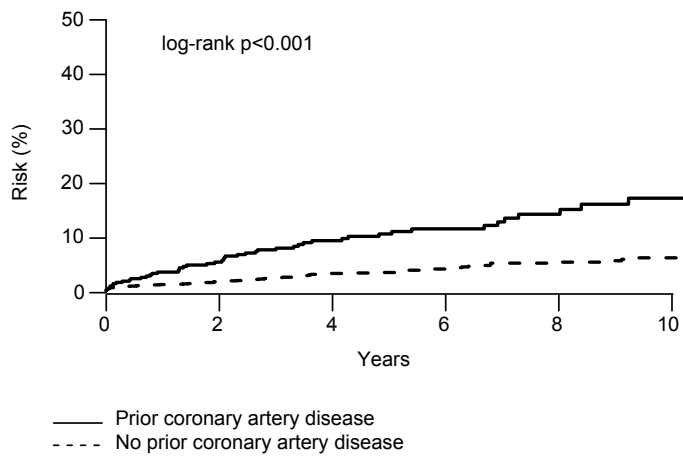


Figure 17 : Risk of myocardial infarction in TIA or ischaemic stroke patients stratified by history of presence of prior coronary artery disease

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

The 10-year risk of recurrent ischaemic stroke was 23.6% (20.7-26.4) overall in patients without prior coronary artery disease, ranging from 11.2% (7.9-14.3) in those with an Essen score ≤ 1 to 39.5% (17.2-55.8) in those with a score ≥ 5 (Figure 16, Table 21). The score tended to be less predictive (difference: $p=0.0460$) for the risk of recurrent ischaemic stroke (c-statistic=0.57, 0.54-0.60) than for the risk of myocardial infarction.

An Essen risk score of ≥ 4 also identified a subgroup at similarly high 10-year risk of recurrent ischaemic stroke to those with prior coronary artery disease (40.4%, 26.7-51.6; versus 32.4%, 25.2-38; Table 23). Although the risk of recurrent ischaemic stroke increased with an increasing Essen score (Figure 16), the subgroup with an Essen risk score of ≥ 4 were not at significantly higher 10-year risk than those with an Essen risk score of < 4 (40.4%, 26.7-51.6 versus 21.6%, 18.7-24.3, $p=0.0063$, age-and sex-adjusted HR=1.21, 0.90-1.63), with no interaction observed by TIA/ischaemic stroke subtype (p -interaction=0.91, Table 23 and 24). After the early high risk-period, the risk of recurrent ischaemic stroke was approximately linear with time in patients with prior coronary artery disease and in those without (Figure 18).

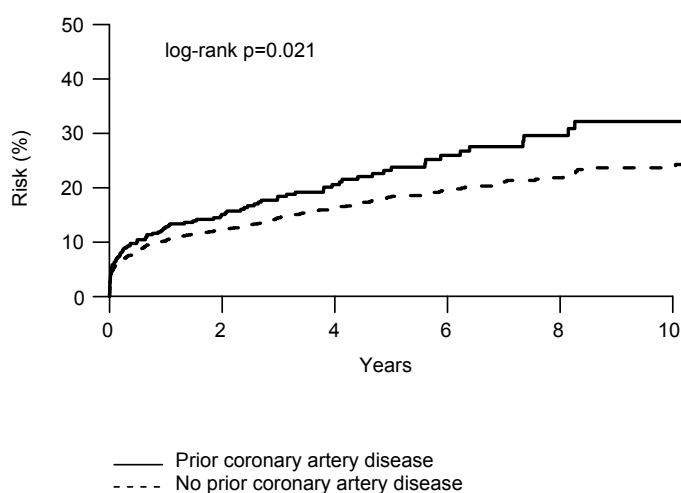


Figure 18 : Risk of recurrent ischaemic strokes in TIA or ischaemic stroke patients stratified by presence of prior coronary artery disease

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

In patients without prior coronary artery disease, 10-year risk of myocardial infarction or recurrent ischaemic stroke increased with an increasing Essen score in patients with large artery disease (TOAST) subtype and in those without (Table 25). 10-year risk of myocardial infarction or recurrent ischaemic stroke in the subgroup of patients with large artery disease subtype (overall risk=27.5%, 2.37-34.1) ranged from 15.6% (5.1-25.0) in those with an Essen score ≤ 1 to 74.6% (16.2-92.3) in those with a score ≥ 5 while 10-year risk in the subgroup of patients with other TIA/ischaemic stroke subtypes than large artery disease (overall risk=24.3%, 21.5-26.9) ranged from 10.5% (7.5-13.4) in those with an Essen score ≤ 1 to 50.0% (23.8-67.1) in those with a score ≥ 5 .

Table 25: 10-year risk of myocardial infarction or recurrent ischaemic stroke after TIA or ischaemic stroke based on presence of large artery disease (TOAST) subtype in patients without prior coronary artery disease (CAD), stratified by the Essen risk score, and in those with prior CAD

Prior CAD status	Large artery disease TIA/ischaemic stroke subtype		All other TIA/ischaemic stroke subtypes	
	Cumulative events, n/N	10-year risk, % (95% CI)	Cumulative events, n/N	10-year risk, % (95% CI)
No prior CAD				
Essen score*:				
≤ 1	8/52	15.62 (5.06-25.00)	47/513	10.48 (7.45-13.42)
2	13/62	25.20 (11.50-36.79)	97/514	24.91 (19.85-29.65)
3	11/62	23.46 (8.68-35.86)	116/514	35.50 (28.62-41.72)
4	13/31	48.09 (22.66-65.16)	39/209	41.60 (24.71-54.70)
≥ 5	6/9	74.60 (16.20-92.30)	14/45	49.97 (23.80-67.15)
Total	51/216	27.54 (20.37-34.08)	313/1795	24.27 (21.52-26.94)
Prior CAD	19/64	39.50 (22.41-52.82)	116/473	38.25 (31.28-44.50)

CI: confidence interval, *data missing for 5 patients

All other TIA/ischaemic stroke subtypes include cardioembolism, small vessel disease, cryptogenic, more than one cause, unknown and other causes

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Compared to cryptogenic subtype, cardioembolism, large artery disease and small vessel disease subtypes were all associated with a higher risk of myocardial infarction and of recurrent ischaemic stroke after adjustment for age and sex and the associations remained unchanged after further adjustment for the Essen score (Table 26).

Table 26 : Association between TIA/ischaemic stroke subtype (TOAST classification) and risk of myocardial infarction and of recurrent ischaemic stroke in TIA or recurrent ischaemic stroke patients without prior coronary artery disease

TIA/ischaemic stroke subtype	Crude Hazard Ratio (95%CI)	Age-and sex-adjusted Hazard Ratio (95%CI)	Age-, sex- and Essen score-adjusted Hazard Ratio (95%CI)	p
Cardioembolic				
Myocardial infarction	2.52 (1.21-5.24)	1.95 (0.93-4.08)	1.97 (0.94-4.13)	0.07
Recurrent ischaemic stroke	1.97 (0.94-4.13)	1.64 (1.20-2.23)	1.60 (1.18-2.18)	0.0028
Large artery disease				
Myocardial infarction	4.37 (2.15-8.87)	4.07 (2.00-8.29)	3.58 (1.76-7.30)	<0.001
Recurrent ischaemic stroke	3.58 (1.76-7.30)	1.66 (1.15-2.40)	1.55 (1.08-2.24)	0.0186
Small vessel disease				
Myocardial infarction	2.11 (0.98-5.46)	2.19 (1.01-4.75)	2.13 (1.00-4.61)	0.05
Recurrent ischaemic stroke	2.13 (0.98-4.61)	1.43 (1.01-2.02)	1.38 (0.98-1.95)	0.06
Cryptogenic	1 (reference)	1 (reference)	1 (reference)	-

CI: confidence interval

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Adding the variable “presence of large artery disease (TOAST) subtype” as a categorical variable to the Essen score did not significantly increase the predictive value of the score for the risk of myocardial infarction (c-statistic=0.74, 0.57-0.71, Tables 27 and 28) and of recurrent ischaemic stroke (c-statistic=0.58, 0.54-0.60).

Table 27 : 10-year risk of myocardial infarction and of recurrent ischaemic stroke after TIA or ischaemic stroke in patients without prior coronary artery disease (CAD), stratified by the modified Essen risk score (after adding the variable “presence of large artery disease TIA/Stroke subtype” to the score), and in those with prior CAD

Prior CAD status	Myocardial infarction		Recurrent ischaemic stroke	
	Cumulative events, n/N	10-year risk, % (95% CI)	Cumulative events, n/N	10-year risk, % (95% CI)
No prior CAD				
Modified Essen score*:				
≤1	3/522	0.96 (0-2.08)	44/522	10.46 (7.12-13.68)
2	14/557	4.45 (1.77-7.06)	95/557	23.58 (18.55-28.31)
3	27/576	9.16 (5.12-13.04)	109/576	32.18 (25.24-38.47)
4	13/271	12.75 (3.41-21.19)	40/271	33.19 (20.26-44.02)
≥5	13/86	24.62 (10.74-36.34)	25/86	45.04 (27.02-58.62)
Total	70/2012	5.97 (4.39-7.53)	313/2012	23.60 (20.73-26.37)
Prior CAD	48/538	16.89 (11.49-21.96)	100/538	32.34 (25.20-38.80)

CI: confidence interval, *data missing for 5 patients.

Modified Essen score in patients without prior CAD ranged from 0 to 8: 1 point is attributed for age 65-75 years; 2 for age >75 years and 1 for each history of prior hypertension, diabetes mellitus, peripheral artery disease, current smoking or previous TIA or ischaemic stroke; and 1 point for presence of large artery disease (TOAST) subtype.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 28 : Stratification by modified Essen score (after adding the variable “presence of large artery disease subtype” to the score) of ≥ 4 versus < 4 and risk of myocardial infarction and of recurrent ischaemic stroke in TIA/ischaemic stroke patients without prior coronary artery disease

Modified Essen score*	Events, n/N		10-year risk, % (95% CI)		p	Crude HR (95%CI)	Age- and sex-adjusted HR (95%CI)	p
	<4	≥ 4	<4	≥ 4				
Follow-up events:								
Myocardial infarction	44/1655	26/357	4.46 (2.99-5.90)	15.67 (7.75-22.92)	<0.001	3.49 (2.15-5.68)	2.21 (1.33-3.65)	0.0020
Recurrent ischaemic stroke	248/1655	65/357	21.50 (18.60-24.29)	36.37 (25.59-45.60)	0.0146	1.40 (1.07-1.83)	1.44 (0.87-1.51)	0.34

CI: confidence interval, *data missing for 5 patients. HR: hazard ratio, p for comparison between modified Essen score ≥ 4 versus < 4 .

Modified Essen scores in patients without prior CAD ranged from 0 to 8: 1 point is attributed for age 65-75 years; 2 for age > 75 years and 1 for each history of prior hypertension, diabetes mellitus, peripheral artery disease, current smoking or previous TIA or ischaemic stroke; and 1 point for presence of large artery disease (TOAST) subtype.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Information on antithrombotic therapy at the time of the follow-up myocardial infarction was available for 102 of the 118 patients with myocardial infarction (87 on antiplatelet therapy only and 15 on anticoagulant therapy). Antithrombotic therapy had been withdrawn within 30 days of the myocardial infarction in 7 (7%) patients (3 for bleeding and 4 for surgery, Table 29). None of these 7 patients had prior coronary artery disease, but the myocardial infarction was fatal in 5 cases.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 29 : Characteristics of the seven TIA or ischaemic stroke patients who experienced a myocardial infarction (MI) during follow-up after withdrawal of antithrombotic therapy

Sex	Age (years)	CAD	PAD	HTN	DM	Previous TIA/IS	Current smoking	Essen score	TIA/ischaemic stroke subtype	Antithrombotic drug used prior to the MI	Reason for withdrawal of antithrombotic drug	Date (type) of stroke	Date (type) of MI	Date (cause) of death
F	71	No	No	Yes	No	Yes	No	3	CE	Aspirin	Surgery	10/08/02 (TIA)	12/08/02 (N-STEMI)	No
F	92	No	No	Yes	Yes	Yes	No	5	SVD	Aspirin	Bleeding	27/08/02 (IS)	09/03/05 (STEMI)	09/03/05 (cardiac)
F	84	No	Yes	Yes	No	Yes	Yes	6	LAD	Clopidogrel	Bleeding	04/03/03 (IS)	23/05/03 (N-STEMI)	06/06/03 (non-cardiac)
F	88	No	No	Yes	No	No	No	3	Crypt.	Aspirin + Clopidogrel	Surgery	08/09/03 (TIA)	02/10/03 (N-STEMI)	21/12/05 (cardiac)
M	91	No	No	Yes	No	Yes	No	4	Crypt.	Clopidogrel	Surgery	17/08/05 (TIA)	30/10/07 (N-STEMI)	30/10/07 (cardiac)
M	92	No	No	No	No	Yes	No	3	Crypt.	Aspirin	Surgery	25/12/05 (TIA)	28/10/08 (N-STEMI)	10/11/08 (cardiac)
M	68	No	No	Yes	No	No	No	2	SVD	Rivaroxaban	Bleeding	11/10/10 (IS)	25/09/14 (STEMI)	No

Discontinuation was recommended by a physician-based for 5 patients (2 for surgery and 3 for bleeding) and the reason was not documented for the other 2 patients M: male, F: female, CAD: coronary artery disease, PAD: peripheral artery disease, HTN: hypertension, DM: diabetes mellitus, IS: ischaemic stroke, CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, Crypt.: cryptogenic, STEMI: ST-elevation myocardial infarction, N-STEMI: Non-ST-elevation myocardial infarction, cardiac: cardiac death, non-cardiac: death not attributable to cardiac cause

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Among patients with non-cardioembolic TIA/ischaemic stroke and after exclusion of those on anticoagulants, the 10-year risk of major extracranial bleeds averaged >10% in patients with prior coronary artery disease (12.5%, 6.1-18.4) and in those without prior coronary artery disease and with an Essen score of ≥ 4 (20.9%, 0-37.9). 10-year risk was 8.3% (5.9-10.6) in patients without prior coronary artery disease and with an Essen score of <4.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Discussion

In this population-based cohort of consecutive TIA or ischaemic stroke patients on current secondary prevention management, the Essen score risk-stratified individuals without prior coronary artery disease for the risk of follow-up myocardial infarction and of recurrent ischaemic stroke. An Essen score of ≥ 4 in those without prior coronary artery disease identified a subgroup at similarly high 10-year risk of myocardial infarction to those with prior coronary artery disease and of recurrent ischaemic stroke. Thus, in addition to the 538 patients with known prior coronary artery disease, an Essen risk score of ≥ 4 identified a further 257 high-risk TIA/ischaemic stroke patients. Since trials of more intensive secondary prevention have reported significant reductions in the risk of recurrent ischaemic events in patients with prior coronary artery disease,^{35-37, 39} trials of such treatment might also be justified in high-risk patients without prior coronary artery disease.

The Essen score was previously shown to predict the 1-year risk of recurrent ischaemic stroke in patients with TIA/ischaemic stroke due to large artery disease,¹⁰⁵⁻¹⁰⁹ but we have shown predictive value in a broader range of patients with longer follow-up. We also showed that the score predicted risk of myocardial infarction better than recurrent stroke, perhaps because all patients already had established cerebrovascular disease and so discrimination for stroke risk was more difficult. We found a two-fold increase in the risk of myocardial infarction and a 20% rise in the risk of recurrent ischaemic stroke in patients with Essen score of ≥ 4 compared to those with a score of < 4 . We also found that the predictive value of the score was similar for patients with different TIA/ischaemic stroke TOAST subtypes, although larger studies would be required to confirm this finding. In TIA/ischaemic stroke patients without prior coronary artery disease, a few scores have been shown to predict the presence of asymptomatic coronary lesions (PRECORIS score)^{25,26} or the risk of myocardial infarction (Framingham score).²⁷ However, these scores involved patients recruited in trials or hospital-based cohorts, with more potential selective biases than population-based cohorts, and only looked at the short-term risk and their clinical utility for predicting the long-term risk is unknown. Interestingly, we also found that

Although we consider our findings to be valid, our study has limitations. First, our cohort was predominantly made up of Caucasian patients, which might limit generalisability. Second, although we aimed for very high rates of secondary prevention, our population-based cohort included many frail and very elderly patients, often with dementia, prior bleeding, or terminal

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

illness, and some patients refused medication or it was contraindicated for other reasons. However, 1-year medication rates were higher than in other similar cohorts,²⁸⁻³¹ and can be regarded as being based closely on current guidelines for secondary prevention. We also showed that very few myocardial infarctions were accounted for by discontinuation of antithrombotic therapy. Third, in our cohort, baseline characteristics were well-defined, and although we make recommendations to primary care physicians about changes to risk factors and medication at study follow-up visits, we have limited information on the control of vascular risk factors during the whole of follow-up. Fourth, we excluded the 'other cardiovascular disease' variable from our analysis of the Essen score due to a lack of clarity of what conditions and what severity of disease are required to satisfy the definition.¹⁰⁵ However, this omission is likely to have reduced predictive value and so our findings are probably somewhat conservative. The c-statistics of the score were of moderate predictive value for the risk of myocardial infarction and of recurrent ischaemic stroke, however, in certain clinical situation, the score would still provide clinically important information. In the subgroups of TIA/ischaemic stroke patients without prior coronary artery disease and with a score of ≥ 4 , 10-year risk of myocardial infarction was 17% and 10-year risk of recurrent ischaemic stroke was 40%, which was as high as in patients with prior coronary artery disease.

In conclusion, the Essen score is a simple clinical score to risk-stratify TIA/ischaemic stroke patients without prior coronary artery disease and to identify patients who may be at sufficiently high risk of myocardial infarction and recurrent stroke to justify more intensive treatment or inclusion in trials.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

II.3. Long-term cost of myocardial infarction during follow-up after transient ischaemic attack or ischaemic stroke

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*equal contribution
Heart (under review)

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Abstract

Background: Up-to-date data on the cost of myocardial infarction after transient ischaemic attack (TIA) or ischaemic stroke would facilitate estimation of measures of cost-effectiveness of costly second-line treatments.

Objective: To determine the cost of myocardial infarction after TIA or ischaemic stroke and the likely long-term myocardial infarction-related cost saving from routine co-prescription with PCSK-9 inhibitors.

Methods: In a population-based cohort of consecutive TIA or ischaemic stroke patients treated according to current guidelines, we determined the cost of myocardial infarction during 10-year follow-up. Costs associated with myocardial infarction were averaged across all patients, and compared with the cost of routine co-prescription of PCSK-9 inhibitors until myocardial infarction or death.

Results: Among 2555 TIA/ischaemic stroke patients, there were 118 myocardial infarctions. The total mean (SD) cost of myocardial infarction was \$9182 (12,757). The 10-year mean cost of myocardial infarction averaged across all patients was \$424 (95%CI 333-525). The corresponding costs of routine life-long co-prescription of PCSK-9 inhibitors were \$34,767 (33,968-35,679). Myocardial infarction treatment costs were higher in those with prior coronary (\$787, 493-1151; versus. \$326, 234-434, $p=0.009$), peripheral artery disease (\$893, 440-1472; versus \$386, 288-496, $p=0.05$) or diabetes mellitus (\$1042, 602-1554; versus. \$324, 242-417, $p=0.005$). Cost of routine co-prescription of PCSK9-inhibitors remained over \$24,000 per patient in the subgroups at higher risk of myocardial infarction.

Conclusion: After TIA/ischaemic stroke, the long-term risk and cost of myocardial infarction is significantly increased in patients with prior coronary or peripheral artery disease or diabetes mellitus. Routine co-prescription of PCSK9 inhibitors is unlikely to be offset by the health benefits gained purely by reducing rates of myocardial infarction in TIA/ischaemic stroke patients.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Introduction

Patients with transient ischaemic attack (TIA) or stroke have a significant long-term risk of coronary events despite current management.^{17, 59} Trials of new cholesterol lowering therapies, such as proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors,³⁵⁻³⁷ have reported significant reduction in risk of myocardial infarction as compared with placebo, in patients with stable cardiovascular disease on high-dose statins.

However, PCSK-9 inhibitors are costly, with treatment with evolocumab pre-filled disposable injections 140mg/1ml costing £170 every 2 weeks.¹¹⁰ As a result, PCSK-9 inhibitor therapy, in addition to current statin treatment, has been found not to be cost-effective by a majority of studies,¹¹¹ including in the USA, which has much higher cost-effectiveness thresholds than other developed countries.¹¹² However, certain jurisdictions are recommending reimbursement of PCSK-9 inhibitor therapy for secondary prevention as cost-effective,¹¹³ hence, further evidence on good value for money is still required. Up-to-date data on the cost of myocardial infarction after TIA/ ischaemic stroke would facilitate measures of cost-effectiveness of secondary prevention, which are required by health care policy makers before recommending the implementation of costly second-line treatments.

A prospective population-based cohort study would provide more generalizable estimates of the risk and cost of myocardial infarction after TIA/ischaemic stroke than a randomized controlled trial, which tends to select younger and healthier participants than in clinical practice. However, no population-based cohort has assessed the cost of myocardial infarction during follow-up after TIA/ischaemic stroke. The cost of hospitalized myocardial infarction may well capture all costs of myocardial infarction because although not all patients with myocardial infarction are admitted to hospital, those who did not reach hospital are likely to die soon after the event, with therefore little impact on the care cost.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Methods

The Oxford Vascular Study (OXVASC) is an ongoing population-based study of the incidence and outcome of all acute vascular events in a population of 92,728 individuals, irrespective of age, registered with 100 general practitioners in nine general practices in Oxfordshire, UK. Methods and definition of vascular events have been described previously.^{63, 64} In this analysis, we reported consecutive patients with TIA or ischaemic stroke from 2002-2014 with follow-up to September 2016.

All cases were investigated and treated according to current guidelines with TIA/ ischaemic stroke subtype categorised according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Appendix I). Written informed consent or assent from relatives was obtained in all patients. OXVASC was approved by our local research ethics committee.

Statistical analysis

We determined the total means costs and standard deviation (SD) of hospitalized myocardial infarction for all patients with a follow-up myocardial infarction, and assessed any variation by baseline clinical characteristics (baseline event [TIA versus ischaemic stroke], TIA/ischaemic stroke subtype, sex, age, prior coronary [CAD], peripheral artery disease [PAD] and diabetes). Mean costs of myocardial infarction were averaged across all patients to determine the 10-year mean cost of myocardial infarction per person, stratified by the same baseline clinical characteristics. The 95% confidence intervals (CIs) of the mean censor-adjusted costs were calculated using 1,000 bootstrap estimates. Costs incurred by patients after the first year were discounted using an annual rate of 3.5%.

We also assessed the likely cost implications of routinely prescribing PCSK-9 inhibitors in all TIA/ ischaemic stroke patients and by the same baseline characteristics. The cost of evolocumab pre-filled disposable injections 140mg/1ml, £170 (\$246) every 2 weeks⁸ was applied until myocardial infarction or death, with 10-year mean costs of PCSK-9 inhibitor co-prescription also adjusted for censoring. Based on the 27% risk reduction of myocardial infarction with routine PCSK-9 inhibitor co-prescription (i.e. relative risk of 0.73),³⁶ we estimated the 10-year mean net costs of routine PCSK-9 inhibitor co-prescription per person. All analyses were done using STATA13.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Results

Of TIA/ ischaemic stroke 2555 patients (mean age=74years), 1293 (50.6%) were female and 538(21.1%) had prior coronary artery disease (Table 30). Despite high rates of use of secondary prevention therapies, there were 118 myocardial infarctions during 13,071 patient-years of follow-up (Table 30), of which 31(26.3%) were fatal within 30 days after the event.

Table 30 : Baseline characteristics in TIA or ischaemic stroke patients

	All patients (n=2555)	Patients with follow-up myocardial infarction (n=118)
Baseline characteristics		
Mean age(SD),years	74(13)	78(9)
Age≥75years	1404(55)	79(67)
Females	1293(51)	58(49)
Diabetes	357(14)	29(25)
Coronary artery disease	538(21)	48(41)
Peripheral artery disease	191(8)	18(15)
Baseline event		
Ischaemic stroke	1606(63)	73(62)
TIA	949(37)	45(38)
TIA/ischaemic stroke subtypes		
Large artery disease	280(11)	25(22)
Cardioembolic	669(26)	26(22)
Small vessel disease	317(12)	18(15)
Cryptogenic	811(32)	32(27)
Others	478(19)	17(14)
Secondary prevention medication at 1-year follow-up†		
Antithrombotics	n=2031	n=101
Antihypertensives	1884(93)	96(81)
Statins	1572(77)	91(95)
	1589(78)	78(77)

Data are numbers (%) unless otherwise specified. †patients who died before the follow-up were not included

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

The total mean hospital cost of myocardial infarction was \$9182 (SD 12,757, Table 31) for all patients with a follow-up myocardial infarction, with a mean of 13 days (SD=18) spent in hospital. Cost differed by TIA/ischaemic stroke subtype ($p=0.035$, Table 31) but there were no differences in cost by sex ($p=0.24$), baseline event (TIA versus ischaemic stroke, $p=0.66$), prior coronary ($p=0.84$), or peripheral artery disease ($p=0.89$) or diabetes ($p=0.11$).

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 31 : Costs of myocardial infarction (MI) for all 118 TIA or ischaemic stroke patients with a follow-up MI

	Accident & Emergency department	Ambulance	Inpatient stay	Day cases	Total
All patients with follow-up MI	110 (122)	168 (205)	8880 (12,719)	26 (168)	9182 (12,757)
Baseline event					
TIA	116 (100)	172 (171)	8179 (13,072)	48 (234)	8514 (13,132)
Ischaemic stroke	107 (133)	164 (226)	9311 (12,569)	13 (109)	9,593 (12,595)
TIA/ischaemic stroke subtypes					
Cardioembolic	107 (101)	142 (169)	6700 (8,427)	0	6949 (8436)
Large artery disease	96 (101)	161 (171)	4845 (4871)	0	5103 (4894)
Small vessel disease	145 (93)	236 (152)	13,022 (17,067)	0	13,401 (16,948)
Cryptogenic	106 (113)	156 (190)	7507 (10,220)	43 (245)	7812 (10,245)
Coronary artery disease					
Yes	97 (100)	137 (165)	8821 (12,091)	0	9055 (12,072)
No	129 (145)	208 (249)	8964 (13715)	64 (259)	9366 (13,825)
Peripheral artery disease					
Yes	88 (101)	133 (171)	9313 (12,596)	0	9534(12,551)
No	114 (124)	172 (211)	8802 (12,803)	30 (182)	9119(12,855)
Diabetes mellitus					
Yes	103 (101)	151 (171)	12,214 (16,993)	26 (142)	12,495 (17,085)
No	111 (127)	172 (216)	7793 (10,880)	26 (177)	8103 (10,896)
Age (years)					
<75	146 (156)	223 (272)	13,538 (18,101)	26 (140)	13,933 (18,210)
≥75	97 (104)	148 (175)	7291 (9916)	26 (177)	7562 (9893)
Sex					
Male	110 (107)	171 (179)	7,508 (11,394)	23 (179)	7812 (11,398)
Female	110 (136)	162 (232)	10297 (13,918)	29 (156)	10,599 (13,984)

Data are mean (SD) cost reported in \$. Day cases: hospitalisations during which patients were admitted and discharged on the same day

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

The 10-year mean cost of myocardial infarction averaged across all patients was \$424 (95%CI 333-525) per person (Table 32) and was significantly higher in those with coronary artery disease (\$787 versus \$326, $p=0.009$), peripheral artery disease (\$893 versus \$386, $p=0.050$) or diabetes (\$1042 versus \$324, $p=0.005$) than those without, all due to their increased risk of myocardial infarction rather than to greater cost of treatment of individual events (Table 33). The 10-year mean cost of myocardial infarction did not markedly vary by sex ($p=0.50$), baseline event ($p=0.95$) or age ($p=0.71$).

Routine PCSK-9 inhibitor co-prescription after TIA/ischaemic stroke would reduce the 10-year mean cost of myocardial infarction from \$424 to \$310 per person (Table 32). However, the mean costs of routine PCSK-9 inhibitor co-prescription over 10 years would be \$34,767 per person, generating mean net additional costs of \$34,365 (33,867-35,576) per person (Table 32). Routine co-prescription in patients with coronary artery disease (\$28,333, Table 32), peripheral artery disease (\$24,104), those aged ≥ 75 years (\$25,670) and those with cardioembolic TIA/ischaemic stroke (\$25,292) would have the lowest mean net additional costs per person.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 32 : 10-year cost of myocardial infarction (MI) averaged across all TIA or ischaemic stroke patients

	(A) Mean costs of MI per person (without routine PCSK-9 inhibitor co-prescription), \$ (95%CI)	(B) Relative risk of MI with routine PCSK- 9 inhibitor (95%CI)	(C)* Estimated mean costs of MI per person with routine PCSK-9 inhibitor, \$ (95%CI)	(D) Mean costs per person of routine PCSK-9 inhibitor, \$ (95%CI)	(E)† Estimated mean additional costs per person with routine PCSK-9 inhibitor, \$ (95%CI)
All patients	424 (333-525)	0.73 (0.65-0.82)	310 (236-399)	34,767 (33,968-35,679)	34,653 (33,867-35,576)
Baseline event					
Ischemic stroke	421 (308-548)		307 (220-410)	31,192 (30,025-32,378)	31,078 (29,889-32,268)
TIA	427 (282-628)		311 (204-469)	40,842 (39,657-41,964)	40,726 (39,522-41,861)
TIA/ischaemic stroke subtypes					
Large artery disease	459 (302-632)		334 (214-478)	39,835 (37,537-42,149)	39,711 (37,381-42,016)
Cardioembolic	281 (171-423)		205 (126-313)	25,368 (23,692-26,880)	25,292 (23,692-26,880)
Small vessel disease	606 (304-1027)		443 (203-766)	44,877 (43,140-46,486)	44,713 (42,741-46,324)
Cryptogenic	347 (208-530)		253 (149-389)	44,405 (43,292-45,414)	44,311 (43,191-45,334)
Coronary artery disease					
Yes	787 (493-1151)		575 (356-868)	28,546 (26,716-30,482)	28,333 (26,465-30,284)
No	326 (234-434)		237 (171-320)	36,430 (35,434-37,330)	36,342 (35,366-37,247)
Peripheral artery disease					
Yes	893 (440-1472)		651 (317-1072)	24,346 (21,311-27,330)	24,104 (20,912-27,151)
No	386 (288-496)		282 (208-365)	35,635 (34,737-36,551)	35,531 (34,644-36,453)
Diabetes mellitus					
Yes	1042 (602-1554)		761 (433-1174)	32,441 (29,997-34,641)	32,161 (29,761-34,398)
No	324 (242-417)		237 (175-315)	35,145 (34,220-36,064)	35,058 (34,135-35,984)
Age(years)					
<75	401 (242-589)		292 (177-434)	45,805 (44,839-46,753)	45,696 (44,692-46,650)
≥75	441 (327-579)		323 (236-433)	25,789 (24,689-26,951)	25,670 (24,553-26,816)
Sex					
Male	388 (258-528)		284 (184-389)	36,878 (35,648-38,022)	36,774 (35,528-37,922)
Female	459 (315-632)		334 (227-475)	32,724 (31,465-33,967)	32,599 (31,337-33,857)

CI: confidence interval. *C=AXB. †E=C-A+D

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Table 33 : 10-year risk of follow-up myocardial infarction in TIA or ischaemic stroke patients determined by Kaplan-Meier method, based on baseline clinical characteristics

Baseline characteristics	Myocardial infarction		p
	Events, n/N	10-year risk, % (95%CI)	
All patients	118/2555	8.01 (6.38-9.61)	
Baseline event			0.35
TIA	146/949	7.17 (4.87-9.41)	
Ischaemic stroke	72/1606	8.60 (6.32-10.83)	
TIA/ischaemic stroke subtype			0.0040
Cardioembolic	26/669	8.45 (4.44-12.30)	
Large artery disease	25/280	13.06 (7.67-18.14)	
Small vessel disease	17/317	7.09 (3.59-10.46)	
Cryptogenic	32/811	6.22 (3.74-8.64)	
Coronary artery disease			<0.001
Yes	48/538	16.89 (11.49-21.95)	
No	70/2017	5.97 (4.39-7.53)	
Peripheral artery disease			<0.001
Yes	18/191	18.12 (8.32-26.87)	
No	100/2364	7.38 (5.75-8.99)	
Diabetes mellitus			<0.001
Yes	29/537	13.43 (8.32-18.26)	
No	89/2198	7.17 (5.46-8.85)	
Sex			0.92
Male	60/1262	8.28 (5.98-10.53)	
Female	58/1293	7.72 (5.38-10.01)	
Age (years)			<0.001
< 75	39/1151	5.12 (3.38-6.83)	
≥ 75	79/1404	11.97 (8.69-15.14)	

CI: confidence interval. p are log-rank p.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

Discussion

In this population-based prospective cohort of TIA/ischaemic stroke patients, the 10-year mean hospital cost of myocardial infarction was \$424 per person and was increased in those with prior coronary artery disease (\$787), peripheral artery disease (\$893), or diabetes mellitus (\$1042) due to their higher risk. We also found that the additional cost of routine co-prescription of PCSK9-inhibitors averaged \$34,767 per person over 10 years in all TIA/ischaemic stroke patients and remained over \$24,000 per person in the subgroups at higher risk of myocardial infarction.

Although we consider our findings to be valid, our study has limitations. Firstly, we determined the cost of hospitalized myocardial infarction, which did not include the cost of long-term consequences after myocardial infarction (such as heart failure). Moreover, a few patients with myocardial infarction are not admitted to hospital and some die prior to admission. However, these cases have little impact on the care costs. Secondly, we reported the likely cost implication of routine co-prescription of PCSK9-inhibitors for prevention of myocardial infarction and did not explore those for prevention of recurrent ischaemic stroke or cardiac death. However, there is less evidence of a reduction in the risk of recurrent stroke or cardiac death with co-prescription of PCSK9-inhibitors.³⁵⁻³⁷

Although our results do not represent a definitive cost-effectiveness analysis, we can conclude that routine co-prescription of PCSK9 inhibitors will generate substantial additional costs, which are unlikely to be offset by the health benefits gained purely by reducing rates of myocardial infarction in TIA/ischaemic stroke patients.

II. Identification of individuals at high risk of recurrent stroke or myocardial infarction after TIA or ischaemic stroke

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Conclusions of the thesis

Despite secondary prevention management in patients with TIA or ischaemic stroke, the risk of recurrent stroke remains significant. It has also been suggested that TIA/ischaemic stroke patients were at substantial high risk of coronary events and that they were more likely to die from cardiac events than from recurrent stroke. Because the number of patients with a TIA or ischaemic stroke is projected to increase worldwide, there is a need to improve the secondary prevention of TIA/ischaemic stroke to reduce its burden. The aim of this thesis was to determine the long-term prognosis of TIA or ischaemic stroke patients on current management and to identify subgroups at higher risk of recurrent vascular events, who might benefit from more intensive secondary prevention.

In Part I of the thesis, I studied the long-term absolute risks of recurrent ischaemic stroke and coronary events after TIA or ischaemic stroke. Firstly, in a systematic review and a meta-analysis of 58 studies of TIA/ischaemic stroke patients (n=131,299) with long-term follow-up, I found that the risk of death from myocardial infarction was not increased compared to the risk of death from recurrent stroke. Interestingly, the risk of myocardial infarction has decreased over time since 1970s while there was no evidence for a decrease in the risk of recurrent stroke over time. However, secondary prevention improved further in the last few decades and there were relatively few studies of patients recruited after 2000s in the systematic review.

Then, I used data from a population-based cohort study of consecutive TIA/ischaemic stroke patients recruited from 2002 to 2014 (OXVASC study) to determine the risks of recurrent ischaemic stroke and coronary events in patients treated according to current secondary prevention guidelines. The current overall 10-year absolute risk of recurrent ischaemic stroke was 25.3% (22.6-27.8) and the 10-year risk of coronary events was 10.6% (8.8-12.4). For 2002-2014, the risks of recurrent ischaemic stroke and coronary events have significantly decreased over time (Part I. 2 of the thesis). Importantly, these time trends at the population level were independent of change in vascular risk factors and presence of large artery disease TIA/ischaemic stroke subtype over the study period while the effect of each vascular risk factor on the risk of coronary events and of recurrent ischaemic stroke did not markedly change over time. These findings suggest that the reductions in the risks of coronary events and recurrent ischaemic stroke in TIA/ischaemic stroke patients are likely to be explained by the improvement of secondary prevention after TIA/ischaemic stroke over the last 15 years. These

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results also highlight the need for clinicians and policy makers to ensure that contemporary secondary prevention guidelines are accurately implemented in TIA/ischaemic stroke patients.

Then, in Part II of the thesis, I aimed to identify the subgroups of TIA/ischaemic stroke patients who remain at high absolute risk of recurrent ischaemic events despite current secondary prevention management and might benefit from more intensive treatment. One can argue that an overall absolute annual risk of recurrent ischaemic stroke of 2.5% and of coronary events of 1% after TIA/ischaemic stroke is relatively low and that the systematic implementation of additional strategies to further lower the risk of recurrent ischaemic events in TIA/ischaemic stroke patients would have a small impact in clinical practice. Indeed, the initiation of a novel secondary prevention treatment, even with a large relative risk reduction in the risk of recurrent ischaemic events, would still have a small clinical impact if the absolute risk of recurrent ischaemic events with standard management is low. Although this statement is correct, it is nevertheless worth reminding that TIA/ischaemic stroke patients are already on secondary prevention management aiming to prevent any recurrent ischaemic events; and that the absolute risk of recurrent ischaemic events may well vary among subgroups of patients, based on the presence of vascular risk factors and TIA/ischaemic stroke subtypes, and some subgroups might be at increased absolute risk.

Among the 2555 consecutive TIA/ischaemic stroke patients in OXVASC, those with co-existing cardiovascular disease (25%) were at significantly higher risk of coronary events (10-year risk=22.8% versus 7.1%) and recurrent ischaemic stroke (10-year risk=31.5% versus 23.4%) than those without. However, in patients with non-cardioembolic TIA/ischaemic stroke (i.e. on antiplatelet therapy for secondary prevention), 10-year risk of major extracranial bleeds was also higher in those with co-existing cardiovascular disease (11.4% versus 7.4%), although there was no increased risk of intracerebral haemorrhage. Interestingly, although the subgroup of patients with large artery disease TIA/ischaemic stroke subtype had among the highest risk of coronary events or recurrent ischaemic stroke compared to the other stroke subtypes, the risk of coronary events remained increased in those with co-existing cardiovascular disease compared to those without (10-year risk=33.5% versus 9.5%) while the risk of recurrent ischaemic stroke was high irrespective of presence of co-existing cardiovascular disease (10-year risk=26.4% versus 26.3%). Patients with TIA/ischaemic stroke due to large artery disease had also a high 10-year risk of major extracranial bleeds (11.1%) but a relatively low risk of intracerebral haemorrhage (0.4%).

In Part II.2 of the thesis, I estimated whether some subgroups of TIA/ischaemic stroke patients without prior coronary artery disease were at similar high-risk of myocardial infarction than

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those with prior coronary artery disease and might still benefit from more intensive secondary prevention management, using the Essen risk score. The Essen score is one of the most established score to predict the risk of recurrent ischaemic stroke in ischaemic stroke patients but no study had assessed whether the score also predicts the risk of myocardial infarction after ischaemic stroke. The main advantage of the score is that it is based on the presence of vascular factors that are easily available at the time of TIA/ischaemic stroke, thus individuals at increased risk of recurrent ischaemic stroke, who might therefore justify more intensive secondary prevention, can rapidly be identified. Compared to patients with prior coronary artery disease, an Essen risk score of ≥ 4 in those without prior coronary artery disease identified a subgroup at similarly high 10-year risk of myocardial infarction (17.2% versus 16.9%). An Essen risk score of ≥ 4 also identified a subgroup at similarly high 10-year risk of recurrent ischaemic stroke to those with prior coronary artery disease (40.4% versus 32.4%). Also, the addition of the variable “presence of large artery disease (TOAST) subtype” did not increase the predictive value of the score for the risk of myocardial infarction or recurrent ischaemic stroke. Of note, the predictive value of the Essen risk score was stronger for the risk of myocardial infarction than for the risk of recurrent ischaemic stroke.

In Part II.3 of the thesis, I determined the long-term cost of myocardial infarction after TIA/ischaemic stroke in the OXVASC study. I also assessed the likely cost implication of routine prescription of the new lipid-lowering treatment, the PCSK-9 inhibitors, in TIA/ischaemic stroke patients. The total mean hospital cost of myocardial infarction was \$9182. The 10-year mean hospital cost of myocardial infarction averaged across all patients was \$424 (95%CI 333-525) per person and was higher in those with prior coronary (\$787, 493-1151; versus. \$326, 234-434, $p=0.009$), peripheral artery disease (\$893, 440-1472; versus \$386, 288-496, $p=0.05$) or diabetes (\$1042, 602-1554; versus. \$324, 242-417, $p=0.005$) than those without, all due to their increased risk of myocardial infarction rather than to greater cost of treatment of individual events. I also found that cost of routine co-prescription of PCSK9-inhibitors remained over \$24,000 per patient in the subgroups at higher risk of myocardial infarction.

Despite current secondary prevention, the subgroups of TIA/ischaemic stroke patients with prior coronary artery disease and those without prior coronary disease and with an Essen score of ≥ 4 remain at sufficiently high absolute residual risk of recurrent ischaemic events to justify more intensive treatment. We discussed that further lipid lowering might be therefore justified in these high-risk subgroups, although economic evaluation of PCSK9-inhibitors in addition to statin therapy suggests that treatment might still exceed the generally accepted cost-effectiveness threshold,⁸⁹ and there is probably still potential for more intensive treatment

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with statins and other lipid-lowering drugs. We also discussed that the reduction in risk of coronary events with further reduction in LDL levels is expected to be higher than of the risk of recurrent ischaemic stroke as dyslipidemia is estimated to account for a higher proportion of the risk of coronary events than of the risk of recurrent ischaemic stroke.^{85, 86} Additionally, although the use of long-term more intensive antithrombotic therapies would probably decrease the risk of recurrent ischaemic events in these high-risk subgroups, the benefit is likely to be offset by the risk of bleeding since these high-risk individuals have also an increased risk of extracranial bleeding. Eventually, I showed that the absolute residual risk of recurrent ischaemic stroke after TIA/ischaemic stroke remains higher than the residual risk of coronary events and future strategies aiming to improve secondary prevention should, perhaps, prioritize on those that reduce the risk of recurrent ischaemic stroke. High blood pressure is the main risk factor for ischaemic stroke⁸⁵ but whether more intensive blood pressure control than currently recommended would further reduce the risk of recurrent ischaemic stroke is unknown.

Implications for future research and clinical practice

My findings have several implications for further research on secondary prevention of TIA/ischaemic stroke and clinical practice.

In this thesis, I showed that the absolute residual risks of coronary events and recurrent ischaemic stroke after TIA or ischaemic stroke have decreased over time, likely due to the improvement of secondary prevention and further reduction of these risks seems therefore achievable. In view of the relatively low current overall residual absolute risk of recurrent ischaemic events after TIA/ischaemic stroke, the systematic initiation of future costly strategies to further reduce risk of recurrent ischaemic events would probably not be cost-effective if implemented in all patients. However, further reduction in risk of recurrent ischaemic events in the subgroups who remain at high residual absolute risk despite current secondary prevention management have the potential to substantially improve their prognosis.

The accurate identification of high-risk individuals appears crucial to improve secondary prevention of TIA/ischaemic stroke. To be clinically useful, risk assessment models for long-term recurrent ischaemic events after TIA/ischaemic stroke should primarily be based on objective criteria, which can be measured independently of the person assessing the patient. In addition, these criteria need to be easily available at the time of stroke, i.e. during the period of the initial assessment of the patient when the etiological investigations of the event are performed and secondary prevention (antiplatelet or anticoagulant therapy) is initiated or planned. Also, the level of detail of the evaluation criteria must be balanced with the level of efforts, expertise and costs required to obtain such criteria. I showed that the presence of prior coexisting cardiovascular disease in patients with TIA or ischaemic stroke and the use of the Essen score, which is based on the presence of vascular risk factors, in those without prior coronary artery disease remain good predictors of the risks of long-term coronary events or recurrent ischaemic stroke. I also showed that even in the subgroup of patients with TIA/ischaemic stroke due to large artery disease, who have among the highest risk of recurrent ischaemic events, the stratification by presence of prior co-existing cardiovascular disease or by the Essen score identifies high-risk individuals.

However, some uncertainties remain. Whether further detailed information on these clinical parameters, in particular data on the duration of co-existing cardiovascular disease and on duration of exposure and control of vascular risk factors (i.e. hypertension, diabetes mellitus and current smoking) at the time of TIA/ischaemic stroke, would increase the clinical utility of these parameters to risk stratify patients for risk of recurrent ischaemic events is unclear. Reliable data on the association between duration of vascular risk factors and risk of ischaemic

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events are scarce, probably because accurate information on the duration of vascular risk factors might be challenging to record as some risk factors can be asymptomatic or diagnosed years after the start of the exposure (for example the exposure to diabetes mellitus or hypertension might start well ahead of the time of their diagnosis, which usually is made when patients suffer from related complications). Nevertheless, there are evidence that the risk of ischaemic events increases with increasing duration of exposure to high LDL cholesterol levels.¹¹⁴ I also showed that the relative increase in the risk of recurrent ischaemic events based on this stratification by clinical parameters was higher for the risk of coronary events (age-and sex-adjusted HRs of 2 to 3) than for the risk of recurrent ischaemic stroke (age-and sex-adjusted HRs of 1.2). Unlike coronary events that are almost entirely due to atherosclerosis, ischaemic stroke is a heterogenous disease with more than hundreds of causes and this might partly explain this finding. This highlights the limitations of the scores purely based on clinical factors to risk-stratify patients for the risk of both coronary events and recurrent ischaemic stroke. In addition to clinical scores, the use of imaging and biological parameters would certainly lead to a more accurate identification of high-risk subgroups. Thus, evidence suggest some associations between biomarkers of systemic inflammation (such as CRP) or cardiac function (such as nt-proBNP) taken at the acute phase of the ischaemic stroke and risk of recurrent ischemic events.¹¹⁵ Also, biomarkers of inflammation have been reported to be associated with a higher risk of ischaemic events in a large cohort of more than 28,000 healthy women, after adjustment for vascular risk factor¹¹⁶ and biomarkers of inflammation have also been reported to be associated with the presence of left atrial thrombus in patients with non-valvular atrial fibrillation.¹¹⁷ LDL cholesterol level is used in clinical routine practice as a marker of risk of recurrent ischaemic events for secondary prevention of TIA/ischaemic stroke (with a guideline target of <1g/L) as the risk of ischaemic events increases with increasing LDL levels.⁶⁹ However, a meta-analysis suggest that the level of apolipoprotein B might be a more accurate marker of risk of ischaemic events than LDL cholesterol or than non-HDL cholesterol levels.¹¹⁸ Although levels of apolipoprotein B, non-HDL and of LDL are usually well correlated, discordances between apolipoprotein B and LDL cholesterol levels and between apolipoprotein B and non-HDL cholesterol levels exist and may concern up to a quarter of the general population.¹¹⁹ Notably, statins and PCSK-9 inhibitors are estimated to reduce levels of LDL cholesterol significantly more than they reduce levels of apolipoprotein B.^{37, 120} Besides, data from trials of TIA/ischaemic stroke patients treated with statins showed that patients who have low HDL cholesterol and high triglycerides levels despite treatment are at higher residual risk of recurrent ischaemic events than those without.¹²¹ Measurements of apolipoprotein B, HDL cholesterol and triglycerides levels, in addition to the currently recommended measurement of LDL cholesterol level, in patient with TIA/ischaemic stroke

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might help to identify individuals at substantial residual risk of recurrent ischaemic events despite normal or low LDL cholesterol levels.

In addition to plasma biomarkers, the development of further non-invasive imaging methods to better quantify the degree of cervico-encephalic and coronary atherosclerosis would certainly add valuable information to risk-stratify patients for the risk of recurrent ischaemic events. Thus, the presence of asymptomatic coronary artery lesions detected by CT coronary angiography in TIA/ischaemic stroke patients with no history of coronary artery disease has been reported to be associated with the presence and extent of cervico-encephalic atherosclerosis.^{43, 122} Unsurprisingly, the prevalence of asymptomatic coronary artery lesions was also related to the presence of vascular risk factors.¹²²

In addition, genetic studies with new genome-wide genotyping arrays (genome-wide association studies [GWAS]) and next generation sequencing (DNA, genome or exome sequencing) in characterized cohorts of TIA/ischaemic stroke patients might well be interesting to explore the contribution of risk factors other than conventional vascular risk factors and identify additional high-risk individuals.¹²³⁻¹²⁷ Because genetic variants predisposing to recurrent ischaemic events may act at various levels, from modulating the effect of vascular risk factors (such as diabetes mellitus or hypertension) to modulating the arteries' susceptibility to ischemic injury (for example via an increased risk of thrombosis), genetic studies will also help to better understand the underlying biological pathways of recurrent ischaemic events in TIA/ischaemic stroke patients. Furthermore, mendelian randomization in TIA/ischaemic stroke patients would help to explore the causal relationship between a factor (clinical parameter or biomarker) and risk of recurrent ischaemic events. Genetic studies would facilitate the identification of novel potential targets for future therapeutics that are therefore likely to be effective in reducing risk of recurrent ischaemic events, and optimize the design of further secondary prevention trials and the implementation of new strategies in clinical practice. Although not currently available in routine clinical practice, advanced imaging techniques and plasma and genetic biomarkers might be more easily available in the future with the advent of personalized medicine. These tools have the potential to shed new light on the prognosis of TIA/ischaemic stroke patients.

Future secondary prevention trials should focus on high-risk subgroups of TIA/ischaemic stroke patients because of the relatively low overall residual absolute risk of recurrent ischaemic events with current management. Also, with the improvement of secondary prevention over time, further secondary prevention therapies are less likely to be associated with a large relative risk reduction than previous studies. For these two reasons, future trials of secondary prevention would require a very large sample size to have sufficient statistical

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power to detect any difference in prognosis between a novel therapy and current management. Indeed, the trials of PCSK-9 inhibitors, which focused on high-risk individuals (patients with cardiovascular diseases), were designed to detect a 15% relative risk reduction in risk of recurrent ischaemic events with PCSK-9 inhibitors compared to placebo and more than 27,500 patients were needed.^{36, 37, 128} Importantly, the absolute risk reduction with a therapy reflects more its clinical impact than the relative risk reduction. The relative risk reduction in recurrent ischaemic events between PCSK-9 inhibitors and placebo ranged between 9% and 13% in the trials but the absolute risk reduction was very modest, being less than 1 percentage point (approximately 10% versus 11% after a median follow-up between 2 and 4 years).³⁵⁻³⁷ Moreover, a randomized controlled trial of secondary prevention involves a more selective population than a population-based cohort, with younger and healthier participants and people who survived the acute phase of the event, while strategies are implemented to maximise adherence to treatment. The residual absolute risk of recurrent ischaemic events in a trial of TIA/ischaemic stroke patients are therefore likely to be lower than the one found in OXVASC. The overall absolute risk of recurrent ischaemic events in the TIA/ischaemic stroke patients of the population-based cohort of OXVASC was found to be 15% at 2 years and the 2 year-risk was 21% in the subgroups of patients with co-existing cardiovascular disease. Assuming an absolute risk of recurrent ischaemic events of 12% at 2 years, a trial aiming to show a relative risk reduction of 15% in the risk of recurrent ischaemic events at 2 years after TIA/ischaemic stroke with a new strategy compared to standard management, with 90% statistical power and a 0.05 2-sided p-value, a total of 12,800 patients would be needed. The same trial designed to detect a similar relative risk reduction in the high-risk subgroups (assuming an absolute risk of recurrent ischaemic events of 18% at 2 years) would require a smaller number of patients (a total of 6500 patients).

Although the identification of new therapeutic targets and the implementation of novel therapies would help to further reduce risk of recurrent ischaemic events, I discussed that the expected relative and therefore absolute risk reduction might be limited. Thus, the importance of medication adherence of currently recommended treatments with proven benefit should not be forgotten and strategies to ensure good compliance should be favoured as well. The World Health Organization recommends the establishment of therapeutic patient education for chronic diseases.¹²⁹ Evidence suggest that therapeutic patient interventions improve adherence to recommended clinical practice and favourable outcomes.¹³⁰ The effect of patient therapeutic education has been studied in randomized controlled trials of patients with coronary artery disease and its implementation was reported to be associated with improved

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control of vascular risk factors^{131, 132} and reduction in the number of recurrent coronary events and stroke.¹³³

After TIA/ischaemic stroke, secondary prevention management along with patient education are essential. Individualized educational information should be offered to patients, in accordance to their level of understanding, aiming to optimize their care, wellbeing and quality of life. The patient-centered interventions should include the following objectives: to increase patients' knowledge on the presence and management of their risk factors, favour medication adherence, provide health promotion interventions (such as physical exercise and healthy diet); and to raise awareness of symptoms suggestive of recurrent ischaemic events. In addition, data suggest that continuing medical education with educational meetings might improve professional practice with better adherence to recommendations and healthcare outcomes for the patients.¹³⁴

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Appendices

Appendix 1: Critical appraisal of the cohort studies used in the systematic review

The Critical Appraisal Skills Programme (CASP) checklist for cohorts includes the following questions:

- 1. Did the study address a clearly focused issue?
Studies were observational cohorts studies or randomized controlled trials that looked at the long-term prognosis after TIA/ischaemic stroke. TIA and ischaemic stroke had to be defined according to the World Health Organization as a minimum. We agree that not all studies were specifically dedicated to study the risk of myocardial infarction after TIA/ischaemic stroke.
- 2. Was the cohort recruited in an acceptable way?
Our inclusion criteria correspond to what we can consider as “acceptable”. Studies with highly selected population (e.g. young age, specific race, patients with a rare cause of stroke) were not included. To reduce the risk of chance findings due to small sample size, we restricted our inclusion to studies involving ≥ 100 patients).
- 3. Was the exposure accurately measured to minimise bias?
Exposure corresponds to risk factors for myocardial infarction in our systematic review. We only considered pre-specified traditional risk factors, which have relatively universal and reproducible definitions.
- 4. Was the outcome accurately measured to minimise bias?
Only studies with relevant methods for detecting outcomes (i.e. active or administrative follow-up) were included (table S1). In studies dedicated to the identification of predictors of myocardial infarction after TIA/ischaemic stroke, measurement methods for myocardial infarction were similar in all subgroups of patients, irrespective of exposure status.
- 5a. Have the authors identified all important confounding factors?
As in any other study-level meta-analysis, we were unable to control for confounders and reported the unadjusted pooled rate ratios for the risk of myocardial infarction in patients with a potential risk factor compared with those without.

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- 5b. Have they taken account of the confounding factors in the design and/or analysis ?
We did not address this point as this was not our objective.
- 6a. Was the follow up of subjects complete enough?
Observational studies which did not report completeness of follow-up but described attempts to minimise loss to follow-up were not excluded.
- 6b. Was the follow up of subjects long enough?
This criteria was taken into account in our inclusion criteria. We restricted inclusion to studies with at least one year of follow-up.
- 7. What are the results of this study?
This is not relevant for this review. We only included studies in which the number of patients with a subsequent event (myocardial infarction, recurrent stroke, cardiac or vascular deaths) could be extracted.
- 8. How precise are the results?
This is not relevant for this review. We only included studies in which the number of patients with a subsequent event (myocardial infarction, recurrent stroke, cardiac or vascular deaths) could be extracted. Precision of estimates depends on the sample size of the study, therefore we restricted our inclusion criteria to studies involving ≥ 100 patients.
- 9. Do you believe the results?
Only studies deemed to have used robust methodologies and minimized biases (please see above) were included. Therefore, we consider our results as valid
- 10. Can the results be applied to the local population?
This criteria was taken into account in our inclusion criteria. We used large selection criteria for studies irrespective of language of publication or study setting. We also excluded highly selected population restricted to specific age ranges, race or rare cause of stroke.
- 11. Do the results of this study fit with other available evidence?
This is not relevant for this review. The objective of a systematic review is to summarize results across a number of carefully designed studies to draw high-level conclusions around a specific research question.
- 12. What are the implications of this study for practice
We did not address this point as results from one observational study rarely offer sufficiently strong evidence to provide changes to clinical practice or implications for future research. Replication in independent

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populations is required to support findings from one observational study. A systematic review provides therefore stronger evidence.

Appendices

Appendices

Appendix 2: Electronic search strategies used in the systematic review

OVID (Medline)

1. cerebrovascular event.mp.
2. myocardial infarction.mp. or Myocardial Infarction/
3. cardiac event.mp.
4. coronary event.mp.
5. vascular death.mp.
6. Brain Ischemia/ or Stroke/ or Cerebral Infarction/ or isch?emic stroke.mp. or Ischemic Attack, Transient/
7. 1 or 6
8. 2 or 3 or 4 or 5
9. 7 and 8
10. limit 9 to humans

OVID (Embase)

1. cerebral infarct\$.mp. or brain infarction/
2. isch?emic stroke.mp. or brain ischemia/
3. transient isch?emic attack.mp. or transient ischaemic attack/
4. myocardial infarction.mp. or heart infarction/
5. vascular death.mp.
6. coronary event.mp.
7. 1 or 2 or 3
8. 4 or 5 or 6
9. 7 and 8
10. limit 9 to human
11. limit 10 to conference abstract
12. 10 not 11

Appendices

Appendix 3: List of the included studies in the systematic review

- 1 Achterberg S, Pruissen DM, Kappelle LJ, Algra A for the Smart Study Group. Risk of vascular events after nondisabling small and large vessel cerebral ischemia. *Cerebrovascular Diseases*. 2013;36: 190-195.
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Appendices

Appendix 4: Criteria for the modified TOAST classification for stroke aetiology

TOAST subtypes	Definition
Large artery disease (LAD)	Imaging abnormality of atherosclerosis of intra or extracranial artery supplying the ischaemic field with either occlusive or stenosis ($\geq 50\%$ diameter reduction).
Small vessel disease (SVD)	Clinical lacunar syndromes with no cerebral cortical dysfunction and normal imaging; OR Imaging evidence of a relevant acute infarction < 20 mm within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery.
Cardioembolic (CE)	Major-risk cardioembolic source of embolism <ul style="list-style-type: none"> • Prosthetic cardiac valve • Mitral stenosis • Permanent or paroxysmal AF (> 30s) • Sustained atrial flutter • Intracardiac thrombus • Sick sinus syndrome • Recent myocardial infarction (< 4 weeks) • Atrial myxoma or other cardiac tumors • Infective endocarditis • Valvular vegetations • Congestive heart failure (Ejection fraction $< 30\%$) • PFO and concomitant PE or DVT or long-haul flight preceding the cerebrovascular event with clinical presentation of an embolic event
Unknown causes	The absence of diagnostic tests that, under the examiner's judgment, their presence would have been essential to uncover the underlying aetiology.
Other determined causes	The presence of a specific disease process that involves clinically appropriate brain arteries and disorders that bear a clear and close temporal or spatial relationship with the acute event. <ul style="list-style-type: none"> • Abnormalities of thrombosis and hemostasis • Arterial dissection • Acute disseminated intravascular coagulation • Clinically relevant aneurysm • Drug-induced event • Fibromuscular dysplasia • Hyperviscosity syndromes • Hypoperfusion syndromes • Iatrogenic causes • Meningitis • Migraine-induced event • Mitochondrial myopathy encephalopathy with lactic acidosis and stroke-like episodes • Moyamoya disease • Primary antiphospholipid antibody syndrome • Primary infection of the arterial wall • Segmental vasoconstriction or vasospasm • Sickle cell disease • Sneddon syndrome • Thrombotic thrombocytopenic purpura • Other
Several causes	The presence of > 1 evident mechanism in which there is either probable evidence for each.
Cryptogenic	Patient who has had at least one type of brain imaging (CT/MR/autopsy), ECG and at least one type of vascular imaging (Carotid Doppler/MRA/CTA/DSA/TCD/autopsy) but no aetiology was identified.

Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischaemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke*. 1993;24:35-41

Appendices

ORIGINAL PUBLICATIONS

Long-Term Risk of Myocardial Infarction Compared to Recurrent Stroke After Transient Ischemic Attack and Ischemic Stroke: Systematic Review and Meta-Analysis

Marion Boulanger, MD; Yannick Béjot, PhD; Peter M. Rothwell, FRCP; Emmanuel Touzé, PhD

Background—Uncertainties remain about the current risk of myocardial infarction (MI) after ischemic stroke or transient ischemic attack.

Methods and Results—We undertook a systematic review to estimate the long-term risk of MI, compared to recurrent stroke, with temporal trends in ischemic stroke/transient ischemic attack patients. Annual risks and 95% confidence intervals (95% CI) of MI and recurrent stroke were estimated using random-effect meta-analyses. We calculated incidence ratios of MI/recurrent stroke, for fatal and nonfatal events, using similar analyses. Rate ratios for MI in patients with potential risk factors compared to those without were calculated using Poisson regression. A total of 58 studies (131 299 patients) with a mean (range) follow-up of 3.5 (1.0-10.0) years were included. The risk of MI was 1.67%/y (95% CI 1.36-1.98, $P_{\text{het}} < 0.001$ for heterogeneity) and decreased over time ($P_{\text{int}} = 0.021$); 96% of the heterogeneity between studies was explained by study design, study period, follow-up duration, mean age, proportion of patients on antithrombotic therapy, and incident versus combined ischemic stroke/transient ischemic attack. The risk of recurrent stroke was 4.26%/y (95% CI 3.43-5.09, $P_{\text{het}} < 0.001$), with no change over time ($P_{\text{int}} = 0.63$). The risk of fatal MI was half the risk of recurrent strokes ending in fatality (incidence ratio=0.51, 95% CI 0.14-0.89, $P_{\text{het}} = 0.58$). The risk of nonfatal MI was 75% smaller than the risk of recurrent nonfatal stroke (incidence ratio=0.25, 95% CI 0.02-0.50, $P_{\text{het}} = 0.68$). Male sex, hypertension, coronary and peripheral artery diseases were associated with a doubled risk of MI.

Conclusions—After ischemic stroke/transient ischemic attack, the risk of MI is currently $< 2\%/y$, and recurrent stroke is a more common cause of death than MI. (*J Am Heart Assoc.* 2018;7:e007267. DOI: 10.1161/JAHA.117.007267.)

Key Words: ischemic • myocardial infarction • stroke

Although there is evidence that patients suffering a transient ischemic attack (TIA) or ischemic stroke (IS) are at high risk of coronary artery disease (CAD),¹⁻⁵ current guidelines for prevention of coronary events in high-risk

individuals do not include stroke patients.^{6,7} A writing group committee suggested the inclusion of large atherosclerosis IS, while other subtypes of IS are thought to carry a lower risk of CAD.⁸ In a previous systematic review, the annual risk of myocardial infarction (MI) after TIA or IS was shown to be 2.2%.⁵ However, the current risk of MI remains difficult to predict because the improvement of secondary prevention therapies may be counterbalanced by the aging of the population. Additionally, long-term estimates were scarce, and several cohort studies have been published since this meta-analysis. Moreover, whether coronary events or stroke is the main cause of death in IS/TIA patients remains uncertain. There are also no reliable data on predictors of MI among IS/TIA patients.

Therefore, we undertook a systematic review and meta-analysis to determine the long-term risk of MI, with temporal trends, along with the risks of recurrent stroke, cardiac, and vascular deaths, in IS/TIA patients. Additionally, we compared the risks of MI and recurrent stroke, for fatal and nonfatal events, and the risks of cardiac death versus fatal recurrent stroke, and assessed the risk factors for MI among IS/TIA patients.

From the Normandie Université UNICAEN, Inserm U1237, CHU Caen, Caen, France (M.B., E.T.); Stroke Prevention Research Unit, University Department of Clinical Neurology, John Radcliffe Hospital, University of Oxford, United Kingdom (M.B., P.M.R.); Department of Neurology, Dijon Stroke Registry, Pathophysiology and Epidemiology of Cerebro-Cardiovascular Diseases (PEC2) Team, EA7460, CHU Dijon, University of Burgundy, Dijon, France (Y.B.).

Accompanying Data S1, S2, Tables S1 through S5, and Figures S1 through S13 are available at <http://jaha.ahajournals.org/content/7/2/e007267/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- In the absence of conclusive data pertaining to the long-term risk of myocardial infarction (MI) after stroke, we undertook a systematic review and meta-analysis and found that the current overall risk of MI after stroke was below 1.3%/y.
- The risk of MI after stroke was 1.0%/y in stroke patients with no history of coronary artery disease (CAD) and 3.6%/y in those with CAD. In addition, the risk of MI after stroke did not differ across stroke etiology.
- Although the risk of MI after stroke decreased over time, the risk of recurrent stroke did not markedly vary over time. Furthermore, the risk of fatal MI was half the risk of recurrent strokes leading to death.
- Male sex, history of hypertension, CAD, and peripheral artery disease were associated with a doubled risk of MI after stroke.

What Are the Clinical Implications?

- Our report shows that the contemporary overall risk of MI after stroke is below the usual threshold considered to classify high-risk patients ($\geq 20\%$ at 10 years).
- In view of the moderate risk for recurrent MI after stroke among patients without CAD and the fact that stroke patients are more likely to die from recurrent strokes than a fatal MI, systematic screening for asymptomatic CAD after stroke appears unlikely to reduce mortality after stroke.
- Stroke patients with vascular risk factors remain at higher risk for subsequent MI, reinforcing the need for optimal secondary prevention to prevent MI as well as recurrent stroke in these patients.

Methods

The data, analytic methods, and study materials used have been made available to other researchers for purposes of reproducing the results or replicating the procedure.

We declare that all supporting data are available within the article and its online supplementary files.

Study Selection and Data Collection

We report our study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.⁹ Eligible studies were observational cohort studies or randomized controlled trials (RCTs) including ≥ 100 IS or TIA patients with at least 1 year of follow-up and reporting data on subsequent (fatal or nonfatal) MI. In these studies we also extracted data on recurrent stroke and cardiac and vascular deaths and compared the risks of MI and recurrent stroke as well as the risks of cardiac death and recurrent stroke in the same

cohorts. To minimize bias in cardiac and vascular deaths definitions and to increase quality of studies reporting cardiac and vascular deaths, we only selected studies reporting these events if information on MI was given separately. When they were reported in studies, we collected data on risk factors for subsequent MI after IS/TIA. We excluded studies with highly selected populations (eg, young age, specific race, patients with a rare cause of stroke). Studies of stroke patients with a small (<15%) proportion of hemorrhagic stroke were not excluded. In cases of multiple publications pertaining to the same population, we included only the publication with the largest amount of data relevant to this review. IS and TIA had to be defined according to the World Health Organization as a minimum.¹⁰ We relied on authors' definitions of MI and of cardiac and vascular deaths.

We extracted data on study design (community-, hospital-based study, RCT), year of enrollment, duration of follow-up, completeness of follow-up, population characteristics (age, stroke etiology, proportion of TIA and IS, proportion of patients under antithrombotic therapies at some point during follow-up), potential risk factors for MI (sex, history of hypertension, diabetes mellitus, current smoking, atrial fibrillation, peripheral artery disease and coronary artery disease [CAD], cardiac biomarkers [such as troponin and brain natriuretic peptide], and genetic variants). Assessment of risk of bias was undertaken at the study level based on study design, type of ischemic event (TIA, IS), incident or combined (incident and recurrent) IS/TIA, methods of ascertainment for IS/TIA and follow-up events, completeness of follow-up, delay from stroke onset to study inclusion, and definitions of each event. Critical appraisal of the cohort studies is presented in Data S1.¹¹

Search Strategy

We used electronic search strategies (Data S2) to identify studies indexed in Medline and Embase until December 11, 2016, which reported information on MI after IS/TIA. We screened the bibliographies of relevant studies. We screened all titles and abstracts to determine potentially eligible studies and undertook data collection using a prespecified data extraction file. We did not restrict inclusion by language or date of publication or by study setting or study period.

Statistical Analysis

The annual absolute risk and the 95% confidence interval (CI) of MI were calculated using a random-effects model meta-analysis. We explored the time trend of this risk using random effects meta-regressions with the midyear of the study period as covariate and reported *P*-values (P_{int}) obtained from random-effects meta-regressions analyses. To assess whether

the annual risk of MI varied with the duration of follow-up, random-effects meta-regressions against the duration of follow-up were performed. When possible, stratification of the risk of MI by history of CAD was performed. In additional analyses we investigated whether the risk of MI differs by study design, type of ischemic event (TIA, IS, or stroke), stroke etiology, or incident versus combined (incident or recurrent) or unspecified IS/TIA using random-effects meta-regressions. Furthermore, the proportions of overall heterogeneity in the absolute risk of MI across studies that could be accounted for by study design, study period, duration of follow-up, mean age, proportion of antithrombotic and incident versus combined (incident and recurrent) or unspecified IS/TIA were determined by random-effects meta-regression against all above covariates. Sensitivity analyses were undertaken to explore the risk of MI in studies with delay from IS/TIA to inclusion <1 month and in those with completeness of follow-up $\geq 90\%$.

Similar analyses were undertaken to estimate the annual risks of recurrent stroke and cardiac and vascular deaths. Additionally, we explored whether the risks of MI and recurrent stroke differ by the presence of an explicit definition of these events reported in studies through meta-regressions. We also examined the temporal trends of the main known vascular risk factors: mean age, mean systolic blood pressure at stroke admission, prevalence of current smokers, and male sex.

Then, to compare the risks of MI and recurrent stroke for fatal and nonfatal events separately, we selected studies reporting data on both MI and recurrent stroke and calculated annual incidence ratios of MI/recurrent stroke for fatal and nonfatal events. We also investigated time trends and variation with duration of follow-up. Similar analyses were done for the annual incidence ratio of cardiac death/fatal recurrent stroke.

Finally, we explored the risk factors for MI by selecting the studies reporting the number of patients with and without a potential risk factor and the number of MI in each group. The unadjusted rate ratios (RRs) and 95% CIs for the risk of MI were calculated in patients with a potential risk factor compared to those without, using Poisson regression. Heterogeneity of risks across studies was analyzed by χ^2 tests, and the P -value (P_{het}) of the test was reported. Statistical analyses were performed in R software version 3.1.3 and STATA version 13.

Results

Of the 7635 titles identified from searching databases, 686 abstracts were screened, leading to the assessment of 180 full texts. Bibliography screening of these eligible full texts resulted in the screening of 45 additional full texts. A total of 167 full texts were finally excluded, leaving 58 studies for

inclusion in the meta-analysis (Figure S1). Characteristics of the included studies and definitions of MI, recurrent stroke, and cardiac and vascular deaths are reported in Tables S1 to S4. The frequency and the annual risks of each outcome in individual studies are given in Table S5.

There were 7 community-based studies, 25 hospital-based studies, and 26 RCTs, involving a total of 131 299 patients with a mean (range) follow-up of 3.5 (1.0-10.0) years. Seven studies included patients with TIA only, 15 with IS only, 30 with TIA or IS, and 6 with IS and a small proportion of hemorrhagic stroke. Eight studies were restricted to incident IS/TIA, and 50 involved combined or unspecified IS/TIA. Delay from stroke onset to inclusion was <7 days in 9 studies, <1 month in 5, <3 months in 13, <6 months in 11, <12 months in 1, <5 years in 1 study, and not reported in 18 studies. Mean ages ranged from 59 to 77 years, and the prevalence of history of CAD from 38% to 88%. Active prospective follow-up was undertaken in all except 4 studies, in which administrative follow-up was used. The proportions of patients treated at some point during follow-up with antithrombotic therapy ranged from 50% to 100%, with the lowest prevalence in old RCTs comparing antiplatelet therapy to placebo. The majority of the studies (41 [71%]) had a completeness of follow-up $\geq 90\%$. In the remaining studies, completeness of follow-up ranged from 73% to 88% in 4 studies and was unspecified in 13 studies.

Twenty-three (40%) studies provided an explicit definition of MI, which was based on clinical parameters, biological markers, ECG changes, or the *International Classification of Diseases* (ICD) (Table S4). An explicit definition of recurrent stroke was given in 15 (38%) studies: a neurologic deficit lasting ≥ 24 hours was the definition used in most of the studies, and only 1 required a period of neurological stability between index stroke and recurrent stroke (Table S5). Table shows the pooled risks of MI, recurrent stroke, and cardiac and vascular deaths, overall and in the prespecified subgroups, with differences among subgroups assessed by meta-regressions.

Risk of MI

The annual risk of MI was 1.67% (95% CI 1.36-1.98, 46 studies, 100 786 patients, with significant heterogeneity across studies, $P_{\text{het}} < 0.001$); 96% of the heterogeneity across studies was explained by study design, study period, duration of follow-up, mean age, prevalence of antithrombotic therapy, and incident versus combined IS/TIA. The annual risk of MI significantly decreased over time ($P_{\text{int}} = 0.021$, Figure 1). This time trend did not differ between community-based studies (7 studies, 34 749 patients) and hospital-based studies and RCTs (51 studies, 96 550 patients, $P_{\text{int}} = 0.58$). The risk of MI was lower in studies that enrolled patients after 2005 (0.90%,

Table. Annual Risks of MI, Recurrent Stroke, and Cardiac and Vascular Deaths after TIA or Ischemic Stroke in Subgroup Analyses

Population	Total MI			Total Recurrent Stroke		
	N; n	Annual Risk, % (95% CI)	<i>P</i> _{int}	N; n	Annual Risk, % (95% CI)	<i>P</i> _{int}
All	46; 101 786	1.67 (1.36-1.98)		34; 73 184	4.26 (3.43-5.09)	
Study design			0.48			0.18
RCT	21; 53 592	1.80 (1.26-2.34)		14; 30 359	4.58 (3.26-5.91)	
Community-based studies	6; 33 638	1.35 (0.93-1.76)		5; 30 940	2.55 (0.50-4.60)	
Hospital-based studies	19; 13 556	1.62 (1.14-2.09)		15; 11 885	4.54 (3.35-5.72)	
Type of ischemic event			0.42			0.35
TIA	5; 2296	2.26 (1.62-2.89)*		3; 1092	4.42 (2.24-6.59)	
IS	12; 43 274	1.50 (0.82-2.18)		9; 32 986	5.21 (3.46-6.97)	
Mixed TIA and IS	23; 45 609	1.67 (1.22-2.12)		17; 29 876	4.26 (3.06-5.46)	
Stroke	6; 9607	1.51 (0.61-2.41)		5; 9230	2.60 (0.93-4.27)	
Stroke etiology			0.91			
Large-artery atherosclerosis	11; 16 214	1.46 (0.85-2.08)		
Small-vessel disease	3; 307	1.49 (0.57-2.42) [†]		
Cardioembolism	2; 260	1.50 (0.81-2.19) [‡]		
Incident IS/TIA			0.62			0.95
Incident	8; 32 699	1.47 (0.95-2.00)		7; 32 322	4.68 (3.41-5.94)	
Combined or unspecified	38; 69 087	2.06 (1.29-2.82)		27; 40 862	4.15 (3.15-5.15)	
	Fatal MI			Fatal Recurrent Stroke		
All	30; 50 364	0.66 (0.46-0.86)		18; 34 445	0.77 (0.45-1.10)	
Study design			0.96			0.36
RCT	15; 37 696	0.63 (0.41-0.85)		9; 27 272	0.63 (0.40-0.86)	
Community-based studies	3; 4920	0.57 (0.24-0.89)		2; 823	1.44 (0.19-2.69) [§]	
Hospital-based studies	12; 7748	0.76 (0.30-1.22)		7; 6350	0.78 (0.02-1.57)	
Type of ischemic event			0.88			0.87
TIA	4; 2075	0.94 (0.27-1.62)		2; 812	1.12 (0.86-3.09)	
IS	4; 7791	0.35 (0.04-0.75)		3; 1360	0.78 (0.09-1.65) [‡]	
Mixed TIA and IS	19; 35 893	0.64 (0.40-0.87)		9; 23 437	0.60 (0.46-0.73)	
Stroke	3, 4605	0.87 (0.01-1.92)		4; 8836	1.15 (0.26-2.59)	
Incident IS/TIA			0.95			
Incident	4, 1860	0.29 (0.03-0.61)		4; 1667	0.65 (0.11-1.42)	0.58
Combined or unspecified	26, 48 504	0.73 (0.51-0.96)		14; 32 778	0.81 (0.44-1.19)	
	Nonfatal MI			Recurrent Nonfatal Stroke		
All	31; 65 808	0.88 (0.70-1.07)		20; 51 568	2.92 (2.22-3.62)	
Study design			0.020			0.51
RCT	13; 33 352	1.15 (0.81-1.49)		7; 24 062	3.73 (2.70-4.77)	
Community-based studies	2; 3809	0.47 (0.38-0.56) [#]		2; 823	2.15 (0.19-6.43)	
Hospital-based studies	16; 28 647	0.73 (0.52-0.95)		11; 26 683	2.49 (1.73-3.26)	
Type of ischemic event			0.84			0.092
TIA	4; 2138	0.88 (0.27-1.50)		2; 812	4.23 (3.41-5.05) [†]	
IS	6; 8923	0.88 (0.14-1.62)		5; 2492	3.11 (1.46-4.76)	
Mixed TIA and IS	18; 50 141	0.92 (0.71-1.13)		9; 39 428	3.06 (2.00-4.12)	

Continued

Table. Continued

	Nonfatal MI			Recurrent Nonfatal Stroke		
Stroke	3, 4605	0.87 (0.01-1.75)		4; 8836	1.84 (0.57-3.10)	
Incident IS/TIA			0.67			0.83
Incident	4, 1860	0.80 (0.27-1.34)		4, 1667	3.90 (2.04-5.76)	
Combined or unspecified	27, 63 948	0.90 (0.69-1.10)		16; 19 901	2.71 (1.96-3.47)	
	Cardiac Death			Vascular Death		
All	11; 15 050	1.38 (0.96-1.81)		38; 76 501	2.17 (1.75-2.59)	
Study design			0.60			0.62
RCT	7; 13 290	1.59 (1.14-2.03)		18; 43 170	2.38 (1.92-2.85)	
Community-based studies	1; 184	2.50 (1.32-3.67)		1; 184	4.99 (3.36-6.63)	
Hospital-based studies	3; 1576	0.60 (0.20-1.01) [#]		19; 33 147	1.83 (1.18-2.49)	
Type of ischemic event			0.51			0.65
TIA	2; 1074	2.27 (1.69-2.84)		5; 2251	2.69 (1.05-4.32)	
IS	3; 1592	0.78 (0.05-1.52)		10; 11 835	2.09 (1.23-2.96)	
Mixed TIA and IS	6; 12 834	1.44 (0.96-1.91)		20; 54 218	2.06 (1.65-2.48)	
Stroke		3, 8197	2.49 (1.00-5.99)	
Incident IS/TIA			0.71			0.91
Incident	2, 894	1.36 (0.69-3.42)		6; 3710	1.36 (0.05-2.66)	
Combined or unspecified	9, 14 156	0.56 (0.27-0.86)		32; 72; 791	2.32 (1.90-2.74)	

Numbers are percentage unless otherwise indicated; CI indicates confidence interval; IS, ischemic stroke; MI, myocardial infarction; N, number of studies; n, number of patients; RCT, randomized controlled trial; Stroke, ischemic and hemorrhagic stroke; TIA, transient ischemic attacks; P_{int} , P interaction against study design (RCT, community-based, hospital-based studies); type of ischemic event (TIA, IS or mixed TIA and IS); stroke etiology (stroke attributable to large artery atherosclerosis, small vessel disease or cardioembolism); incident IS/TIA (incident vs combined [incident and recurrent] or unspecified TIA/IS). There was a significant heterogeneity across studies in all analyses with $P < 0.001$, except * $P = 0.0179$, † $P = 0.79$, ‡ $P = 0.14$, § $P = 0.0274$, || $P = 0.0301$, # $P = 0.74$.

95% CI 0.49-1.32, 6 studies, 59 14 patients) than in those that enrolled patients between 1990 and 2005 (1.53%, 95% CI 1.14-1.91, 26 studies, 83 884 patients), and before 1990 (2.32%, 95% CI 1.63-3.00, 14 studies, 10 988 patients, $P_{int} = 0.015$). The mean systolic blood pressure at stroke admission ($P_{int} = 0.02$) and the prevalence of current smokers ($P_{int} = 0.04$) have decreased over time, whereas the mean age ($P_{int} = 0.81$) and the proportion of men ($P_{int} = 0.65$) have not. The risk of MI did not significantly vary with the duration of follow-up (range 1.0-10.0 years, $P_{int} = 0.88$, Figure 2). The annual risk of MI was higher in studies restricted to patients with history of CAD (1.91%, 95% CI 1.45-2.37, 5 studies, 2309 patients) than in those without (0.85%, 95% CI 0.56-1.14, 3 studies, 7795 patients, $P_{int} = 0.036$). When restricted to studies with a midyear period ≥ 2000 , the annual risk of MI was 1.02% (95% CI 0.68-5.69, 3 studies, 3351 patients) in patients with no history of CAD and 3.64% (1.59-5.69, 3 studies, 1163 patients) in those with CAD ($P_{int} < 0.001$).

There was no significant difference in the risk of MI among study designs ($P_{int} = 0.48$), types of ischemic event ($P_{int} = 0.42$), and incident versus combined or unspecified IS/TIA ($P_{int} = 0.62$,

Table, Figures S2 through S4). Although the number of studies reporting the risk of MI by stroke etiology was small, the risk did not seem to differ among large-artery atherosclerosis, small-vessel disease, and cardioembolism ($P_{int} = 0.91$, Table). The annual risk of MI did not differ according to whether an explicit definition of MI was reported or not ($P_{int} = 0.54$, Tables S2 and S3). The sensitivity analyses restricted to studies with recruitment delay < 1 month from stroke onset (2.10%, 95% CI 1.30-2.90, 11 studies, 3015 patients, $P_{het} < 0.001$) and those with completeness of follow-up $\geq 90\%$ (1.78%, 95% CI 1.39-2.17, 41 studies, 111 729 patients, $P_{het} < 0.001$) found a similar risk of MI to the overall risk.

The annual risk of fatal MI was 0.66% (95% CI 0.46-0.86, 30 studies, 50 364 patients, $P_{het} < 0.001$). There was a significant decrease in the annual risk of fatal MI over time ($P_{int} = 0.002$, Figure 1), with no variation with the duration of follow-up (range 1.0-10.0 years, $P_{int} = 0.25$, Figure 2). There were no significant differences in the risk between study designs ($P_{int} = 0.96$), types of ischemic event ($P_{int} = 0.88$), or incident versus combined or unspecified IS/TIA ($P_{int} = 0.95$, Table).

The annual risk of nonfatal MI was 0.88% (95% CI 0.70-1.07, 31 studies, 65 808 patients, $P_{het} < 0.001$). The risk of

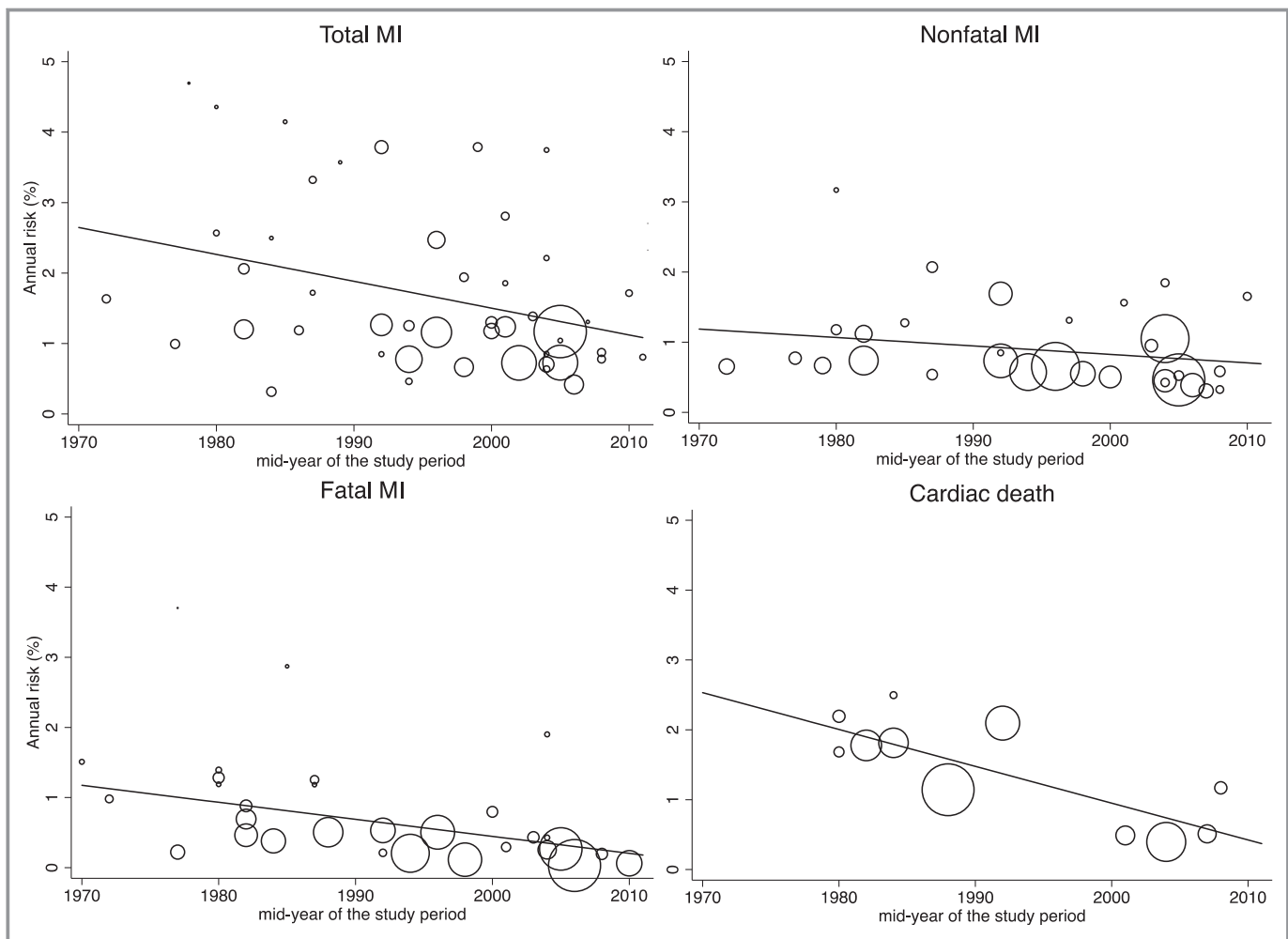


Figure 1. Evolution of the annual risks of myocardial infarction (MI) and cardiac death in IS/TIA patients over time. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

nonfatal MI was higher in RCTs (1.15%, 95% CI 0.81-1.49, 13 studies, 33 352 patients) than in community- (0.47%, 95% CI 0.38-0.56, 2 studies, 3809 patients) and hospital-based studies (0.73%, 95% CI 0.52-0.95, 16 studies, 28 647 patients, $P_{\text{int}}=0.020$). There was no evidence for a variation over time ($P_{\text{int}}=0.14$, Figure 1) or with the duration of follow-up (range 1.0-10.0 years, $P_{\text{int}}=0.45$, Figure 2). There was no difference in the risk between types of ischemic event ($P_{\text{int}}=0.84$) and incident versus combined or unspecified IS/TIA ($P_{\text{int}}=0.67$, Table).

Risk of Recurrent Stroke

The annual risk of recurrent stroke was 4.26% (95% CI 3.43-5.09, 34 studies, 73 184 patients, $P_{\text{het}}<0.001$); 60% of the heterogeneity across studies was explained by the study design, study period, duration of follow-up, mean age, proportion of patients on antithrombotic therapy, and incident versus combined IS/TIA. The risk of recurrent stroke did not

vary markedly over time ($P_{\text{int}}=0.63$, Figure 3) and significantly decreased with the duration of follow-up (range 1.0-10.0 years, $P_{\text{int}}<0.001$, Figure 4).

The risk of recurrent stroke tended to be higher in RCTs (4.58%, 95% CI 3.26-5.91, 14 studies, 30 359 patients) and hospital-based studies (4.54%, 95% CI 3.35-5.72, 15 studies, 11 885 patients) than in community-based studies (2.55%, 95% CI 0.50-4.60, 5 studies, 30 940 patients, $P_{\text{int}}=0.18$, Table, Figures S5 through S7). No significant difference in the risk of recurrent stroke was observed in incident versus combined or unspecified IS/TIA ($P_{\text{int}}=0.95$) and types of ischemic event ($P_{\text{int}}=0.35$), although the risk in studies reporting ischemic stroke as well as a small proportion of hemorrhagic stroke was estimated to be lower than that in TIA or IS studies (Table). The risk of recurrent stroke stratified by the presence of CAD was reported in only 1 study.¹² The sensitivity analyses restricted to studies with inclusion delay <1 month from stroke onset (5.07%, 95% CI 3.63-6.51, 14 studies, 4746 patients, $P_{\text{het}}<0.001$) and those with

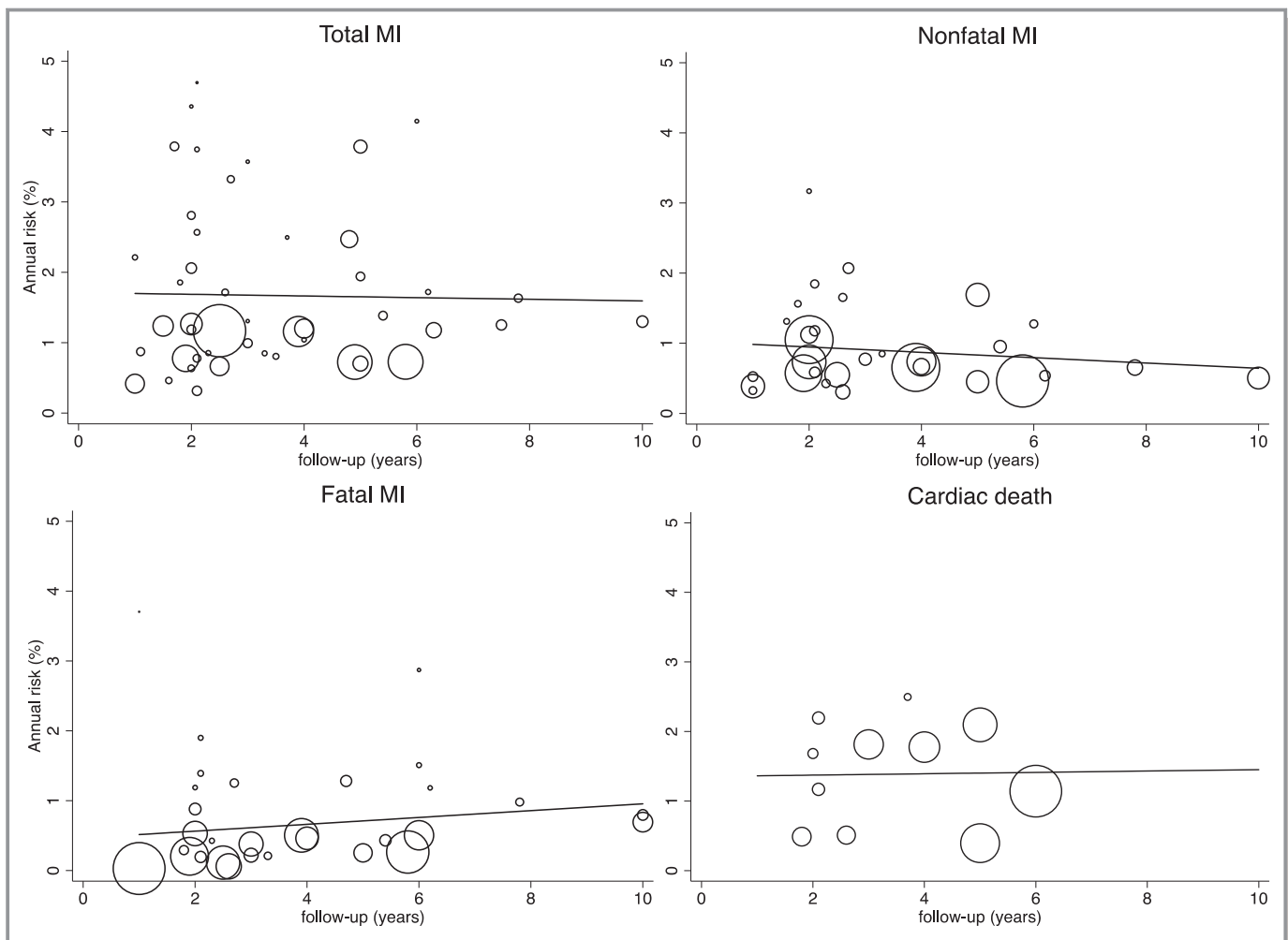


Figure 2. Evolution of the annual risks of myocardial infarction (MI) and cardiac death in IS/TIA patients with the duration of study follow-up. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

completeness of follow-up $\geq 90\%$ (4.56%, 95% CI 3.53-5.58, 21 studies, 60 310 patients, $P_{\text{het}} < 0.001$) found a risk of recurrent stroke similar to the overall risk. The risk of recurrent stroke did not differ according to whether an explicit definition of recurrent stroke was reported or not ($P_{\text{int}} = 0.28$, Tables S2 and S4).

The annual risk of fatal recurrent stroke was 0.77% (95% CI 0.45-1.10, 18 studies, 34 445 patients, $P_{\text{het}} < 0.001$). The risk did not markedly vary over time ($P_{\text{int}} = 0.55$, Figure 3) or with the duration of follow-up (range 1.0-6.2 years, $P_{\text{int}} = 0.36$, Figure 4). There was no difference in the risk of fatal recurrent stroke between types of ischemic event ($P_{\text{int}} = 0.87$) and incident versus combined or unspecified IS/TIA ($P_{\text{int}} = 0.58$), but the risk tended to be lower in RCTs (0.63%, 95% CI 0.40-0.86, 9 studies, 27 272 patients) and hospital-based studies (0.78%, 95% CI 0.02-1.57, 7 studies, 6350 patients) as compared with community-based studies (1.44%, 95% CI 0.19-2.69, 2 studies, 823 patients, $P_{\text{int}} = 0.36$, Table).

The annual risk of recurrent nonfatal stroke was 2.92% (95% CI 2.22-3.62, 20 studies, 51 568 patients, $P_{\text{het}} < 0.001$). The risk did not vary markedly over time ($P_{\text{int}} = 0.24$) and significantly decreased with the duration of follow-up (range 1.0-6.2 years, $P_{\text{int}} = 0.031$, Figure 4). There was no difference in the risk between study designs ($P_{\text{int}} = 0.51$) and incident versus combined or unspecified IS/TIA ($P_{\text{int}} = 0.83$, Table).

Risk of Vascular Death

The annual risk of cardiac death was 1.38% (95% CI 0.96-1.81, 11 studies, 15 050 patients, $P_{\text{het}} < 0.001$), and 68% of the heterogeneity among studies was explained by study design, study period, duration of follow-up, mean age, and proportion of patients on antithrombotic therapy. We could not explore the influence of incident versus combined IS/TIA on the heterogeneity across studies due to insufficient data. The risk of cardiac death significantly decreased over

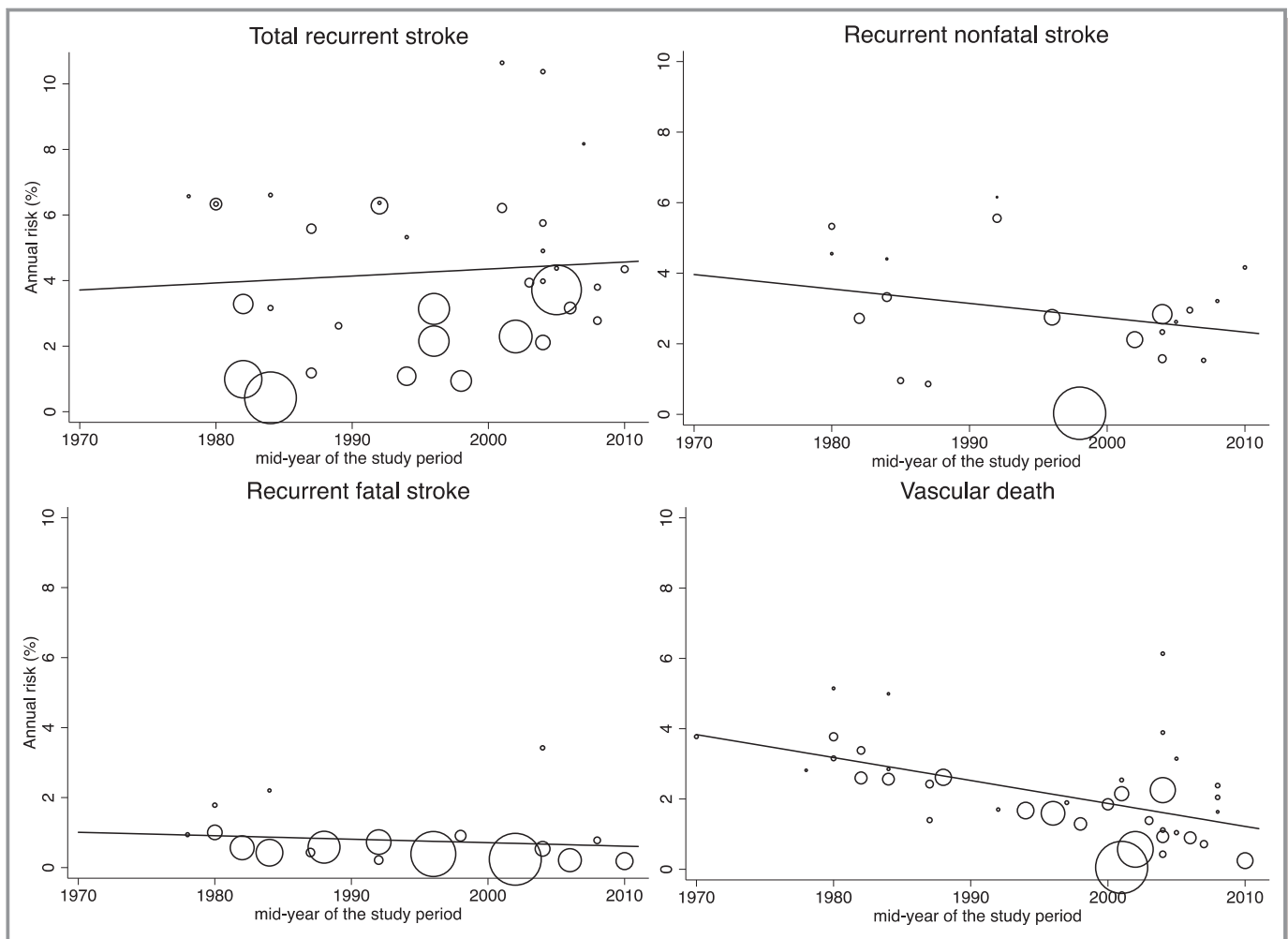


Figure 3. Evolution of the annual risks of recurrent stroke and vascular death in IS/TIA patients over time. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

time ($P_{\text{int}} < 0.001$, Figure 1) and was estimated to be 0.54% (95% CI 0.28–0.80, 4 studies, 2145 patients, $P_{\text{het}} < 0.18$) in studies that enrolled patients from 2000. That risk did not vary markedly with the duration of follow-up (range 1.0–10.0 years, $P_{\text{int}} = 0.95$, Figure 2). There was no significant difference in the risk of cardiac death among study designs ($P_{\text{int}} = 0.60$), types of ischemic event ($P_{\text{int}} = 0.51$), and incident versus combined or unspecified IS/TIA ($P_{\text{int}} = 0.71$, Table, Figures S9 through S10). None of the studies reported data on the risk of cardiac death stratified by presence of CAD. The sensitivity analyses restricted to studies with recruitment delay < 1 month from stroke onset (1.47%, 95% CI 0.33–2.60, 3 studies, 1066 patients, $P_{\text{het}} < 0.01$) and those with completeness of follow-up $\geq 90\%$ (1.43%, 95% CI 0.92–1.94, 8 studies, 11 177 patients, $P_{\text{het}} < 0.001$) found similar risk of cardiac death to the overall risk.

The annual risk of vascular death was 2.17% (95% CI 1.75–2.59, 38 studies, 76 501 patients, $P_{\text{het}} < 0.001$), and 80% of the heterogeneity among studies was explained by

study design, study period, duration of follow-up, mean age, proportion of patients on antithrombotic therapy, and incident versus combined IS/TIA. The risk of vascular death significantly decreased over time ($P_{\text{int}} < 0.001$, Figure 3) and was estimated to be 1.71% (95% CI 1.11–2.32, 20 studies, 45 060 patients, $P_{\text{het}} < 0.001$) in studies that enrolled patients from 2000. This risk did not vary markedly with the duration of follow-up (range 1.0–10.0 years, $P_{\text{int}} = 0.64$, Figure 4). There was no significant difference in the risk of vascular death among study designs ($P_{\text{int}} = 0.62$), types of ischemic event ($P_{\text{int}} = 0.65$), and incident versus combined or unspecified IS/TIA ($P_{\text{int}} = 0.91$, Table, Figures S11 through S13). The annual risk of vascular death was significantly higher in patients with a history of CAD (3.10%, 95% CI 2.78–3.43, 3 studies, 7513 patients, $P_{\text{het}} = 0.23$) than in those without (1.41%, 95% CI 0.95–1.88, 3 studies, 15 160 patients, $P_{\text{het}} = 0.001$, $P_{\text{int}} < 0.0001$). The sensitivity analyses restricted to studies with recruitment delay < 1 month from stroke onset (2.33%, 95% CI 1.14–3.51, 9 studies, 2833

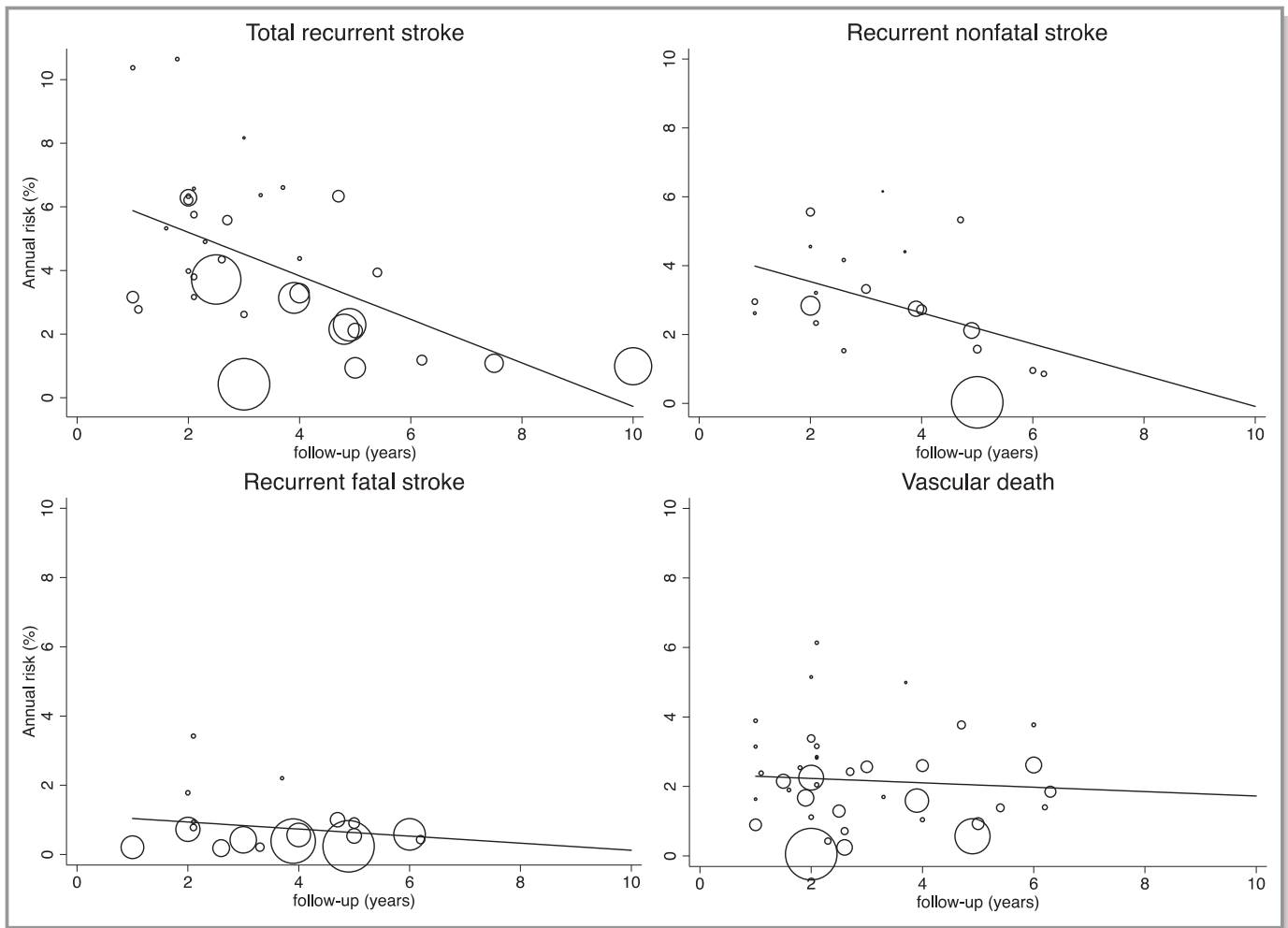


Figure 4. Evolution of the annual risks of recurrent stroke and vascular death in IS/TIA patients with the duration of study’s follow-up. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

patients, $P_{he}<0.001$) and those with completeness of follow-up $\geq 90\%$ (2.30%, 95% CI 1.82-2.78, 31 studies, 69 064 patients), $P_{het}<0.001$) found risk of vascular death to be similar to the overall risk.

Comparison of the Risk of MI and Recurrent Stroke

Numbers of fatal and nonfatal MIs and recurrent strokes along with respective incidence ratios are reported for each study in Table S2. In studies reporting both the numbers of fatal MIs and fatal recurrent strokes, the risk of fatal MI was half the risk of recurrent strokes leading to death (incidence ratio=0.51, 95% CI 0.14-0.89, 14 studies, 29 451 patients, $P_{het}=0.58$), with a decreasing trend over time ($P_{int}=0.14$, Figure 5). That ratio did not vary markedly with the duration of follow-up ($P_{int}=0.16$). IS/TIA patients were 75% less likely to develop a nonfatal MI than recurrent nonfatal strokes in studies reporting the numbers

of both nonfatal MIs and recurrent nonfatal strokes (incidence ratio=0.25, 95% CI 0.02-0.50, 15 studies, 42 330 patients, $P_{het}=0.68$), with no change over time ($P_{int}=0.73$) or with the duration of follow-up ($P_{int}=0.55$, Figure 5).

Numbers of cardiac deaths and the incidence ratio of cardiac death/fatal recurrent strokes are given for each study in Table S2. There was a nonsignificant higher risk of cardiac death than fatal recurrent strokes in studies reporting both the numbers of cardiac deaths and fatal recurrent strokes (incidence ratio=1.39, 95% CI 0.52-2.27, 7 studies, 10 399 patients, $P_{het}=0.68$), with no change over time ($P_{int}=0.60$) or with the duration of follow-up ($P_{int}=0.97$, Figure 6).

Risk Factors for MI

Pooled RRs for MI, when calculable, are presented in Figure 7. Male sex ($P<0.001$), history of hypertension ($P=0.022$), CAD ($P<0.001$), and peripheral artery disease ($P=0.0043$) were

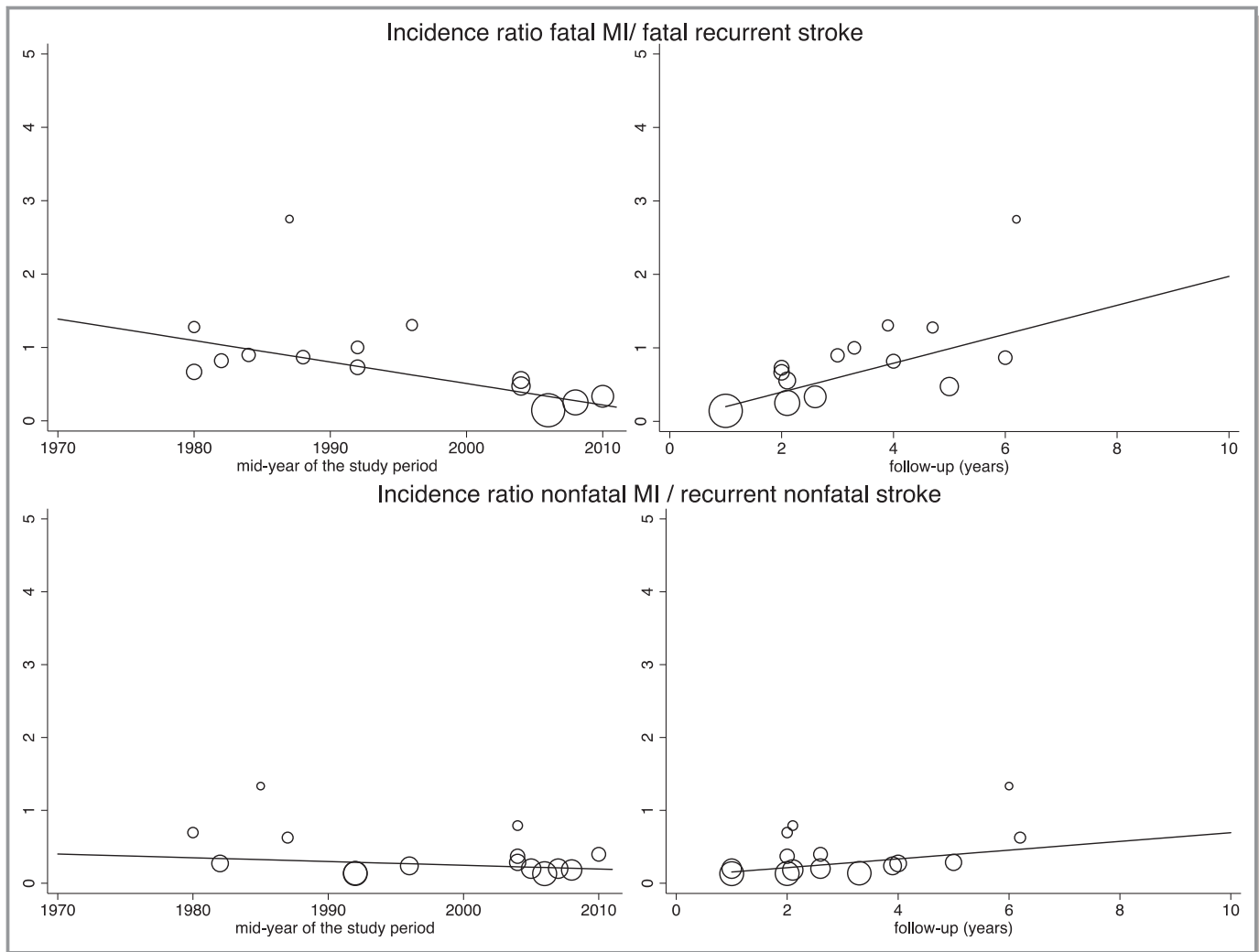


Figure 5. Evolution of the incidence ratio of fatal and nonfatal myocardial infarction (MI)/recurrent stroke over time and with the duration of study's follow-up. The size of the plot is inversely proportional to the within-study variance.

associated with a doubled risk of MI. There was no significant difference in the risk of MI in patients with a history of atrial fibrillation (RR=0.87, 95% CI=0.47-1.50), diabetes mellitus (RR=1.14, 95% CI=0.71-1.76), and current smoking (RR=1.21, 95% CI=0.83-1.73) compared to those without. Only 1 study investigated dyslipidemia as a potential risk factor for MI and found a significantly increased likelihood of MI in patients with dyslipidemia than in those without, in univariate but not in multivariate analysis.¹³ We could not assess the influence of biomarkers and genetic variants on the risk of MI because no study reported this information.

Discussion

In this meta-analysis of IS/TIA patients, the risks of MI and cardiac and vascular deaths significantly decreased over time. The risk of subsequent MI was estimated to range between 0.49%/y and 1.32%/y since 2005. On the other hand, the risk

of recurrent stroke did not markedly vary over time. IS/TIA patients were found to be more likely to have fatal recurrent strokes than a fatal MI. Unlike the risk of recurrent stroke that seemed to decrease with time after the index stroke, the risks of MI, cardiac, and vascular deaths after IS/TIA remained stable. Male sex, history of hypertension, CAD, and peripheral artery disease were associated with a doubled risk of MI.

Our review shows that, overall, the current risk of MI after IS/TIA is below 1.3%/y, that is, less than the usual threshold considered to classify high-risk patients ($\geq 20\%$ at 10 years).¹⁴ The observed decrease in the risks of total MI, fatal MI, and cardiac death over time may be partly explained by better management of acute MI. However, in such cases, an increase in the risk of nonfatal MI over time would have been expected. As that risk has not markedly varied over time, the variation in the risk of MI is likely to be due to the reduction in the prevalence of vascular risk factors. In particular, the substantial reduction in the rate of current smoking observed over

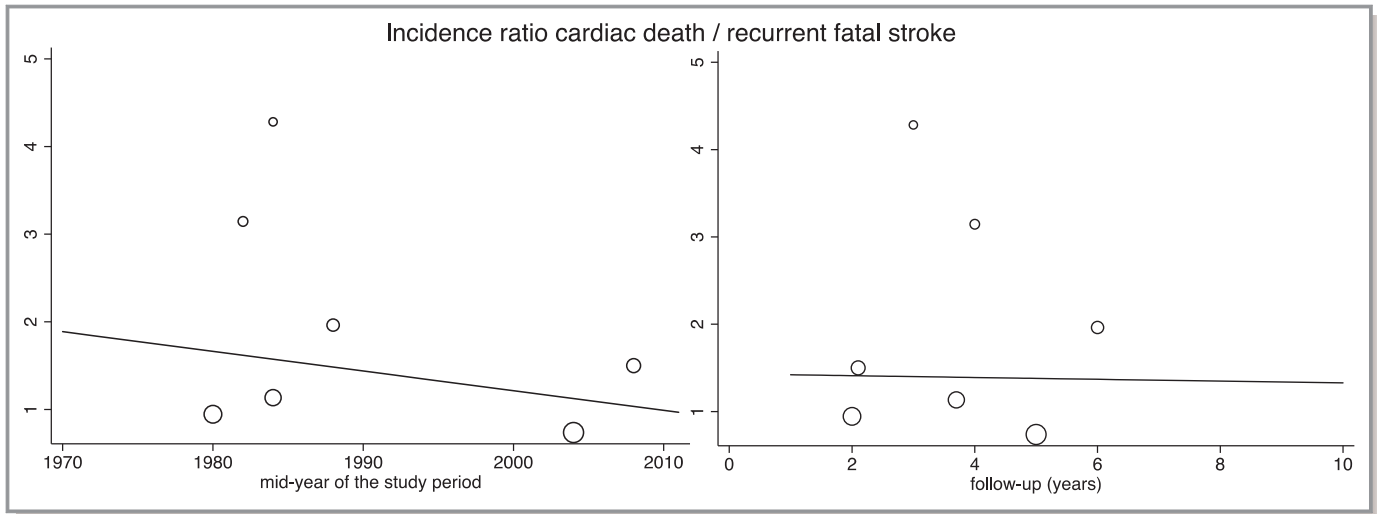


Figure 6. Evolution of the incidence ratio of cardiac death/fatal recurrent stroke against study’s duration of follow-up and over time. The size of the plot is inversely proportional to the within-study variance.

time and the improvement of secondary prevention (the decrease in BP levels observed over time as well as the use of high doses of statin drugs since 2006¹⁵) might well have contributed to this decrease. Additionally, a fall in the incidence of MI over time in the general population (not restricted to stroke patients) has been reported previously in population-based studies^{16,17} and is likely to be attributable to the treatment of modifiable risk factors.

In contrast, despite improvement in secondary prevention of stroke,¹⁸⁻²⁰ the risk of recurrent stroke did not seem to have varied significantly over time. Unlike MI, in which the

only underlying mechanism is large-artery atherosclerosis, the heterogeneity in stroke etiology may partly explain this lack of reduction in the risk of recurrent stroke over time. Findings from a nationwide register of stroke patients suggest that the reduction in the risk of stroke recurrence observed over time was mainly due to the decrease in the early risk of stroke recurrence. In contrast, temporal trends of the long-term risk of recurrence showed no significant variation over time.²¹ However, this study was subjected to selection bias in that only young patients were included. Another population-based study reporting temporal trends of recurrent stroke separately

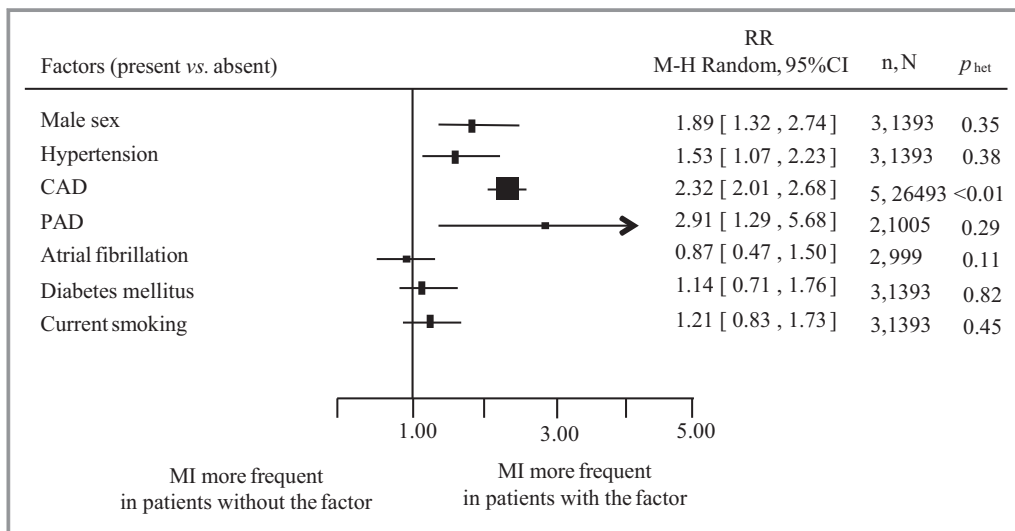


Figure 7. Forest plots of the meta-analyses of potential risk factors for myocardial infarction (MI) in IS/TIA patients. The size of the square is proportional to the sample size of the study. CAD indicates coronary artery disease; CI, confidence interval; IS, ischemic stroke; M-H, Mantel-Haenszel; MI, myocardial infarction; N, number of patients; n, number of studies; *p*_{het}, *P* value for heterogeneity; PAD, peripheral artery disease; RR, rate ratio; TIA, transient ischemic attack.

at various time points after the index stroke has not identified any significant decrease over time in the risk of stroke recurrence in patients of all age ranges.²²

This article updates the general assumption that cardiac events remained the main cause of death after stroke.^{1-3,23} The significant decrease observed over time in the risks of fatal MI and cardiac death but the relative stability of the risk of fatal recurrent strokes over time are likely to explain previous findings. In our review of studies reporting the number of MIs as well as of cardiac death and fatal recurrent strokes, the risks of cardiac death and fatal recurrent strokes were comparable. Additionally, IS/TIA patients were found to be more likely to have fatal recurrent strokes than a fatal MI. Uncertainties remain about the other causes of cardiac death not classified as attributable to MI and how to prevent them, with most of these cardiac deaths being classified as sudden deaths.

Our findings have several implications for further research on secondary prevention of IS/TIA. First, the current relatively low absolute risk of fatal MI after IS/TIA, especially in patients without history of CAD, suggests that a RCT aiming to assess effect on mortality of screening for asymptomatic CAD in IS/TIA patients would require thousands of patients to show a benefit. For instance, in a trial of IS/TIA patients aiming to show a relative risk reduction of 30% on mortality from MI between those who would benefit from a screening for asymptomatic CAD and those who would not, with 80% power and a 0.05 2-sided *P* value, and assuming an annual risk of fatal MI of 0.65%, a total of 45 000 patients would be needed. Second, although the sample size of studies reporting the risk of MI by stroke subtype was small, the risk did not seem to differ across stroke etiology, suggesting that similar intensive preventive strategies should be implemented in patients with any subtype of stroke. Additionally, the risks of MI, recurrent stroke, and cardiac and vascular deaths did not significantly differ between TIA and IS, suggesting that IS and TIA patients should benefit from equal therapy to lower these risks. Third, male sex, history of hypertension, CAD, and peripheral artery disease were associated with a doubled risk of MI after IS/TIA. However, these factors are not as helpful in clinical practice as they are highly prevalent in stroke patients, and patients after stroke receive antithrombotic and antihypertensive therapies that lower their risk. Clinically useful scores are required to risk stratify patients at high risk of MI after stroke.

Our study has some limitations. First, although we only included studies with ≥ 100 patients to minimize the risk of a chance finding due to small sample size and used a random-effect meta-analysis model, there was substantial heterogeneity across studies in the absolute risks. Substantial heterogeneity across studies, including the variability in the estimates due to clinical and/or methodological differences

among studies, is not uncommon in meta-analyses of absolute risks. Because of this heterogeneity among studies, the interpretation of our pooled estimates of absolute operative risks might not be seen as straightforward. However, the 95% CI obtained through a random-effect meta-analysis well describes uncertainty in the average risk. For instance, looking among all studies, the risk of MI was 1.67%/y, with 95% CI interval at least equal to 1.36%/y and as high as 1.98%/y. As suggested for meta-analyses in the presence of heterogeneity within studies, the use of a funnel plot and test for small-effect study is not appropriate.²⁴⁻²⁷ Heterogeneity can cause asymmetric funnel plots, even in the absence of publication bias, and may therefore lead to false-positive claims of publication bias. Therefore, we did not report funnel plots. However, we examined potential sources of heterogeneity in the overall risk of each event. This revealed that at least 60% of the heterogeneity across studies in the absolute risks was explained by the following studies' characteristics: study design, study period, duration of follow-up, incident versus combined or unspecified IS/TIA, mean age, and proportion of patients on antithrombotic therapy. However, these potential sources need to be interpreted with caution, as these analyses are exposed to ecological biases.²⁸ On the other hand, there was no significant heterogeneity in the incidence ratios of MI/recurrent stroke and of cardiac death/fatal recurrent stroke. Second, the majority of studies did not report a definition of MI or recurrent stroke. However, there was no significant difference in the risks of MI and recurrent stroke between studies that reported a specified definition and those that did not. Among studies reporting a definition of recurrent stroke, only 1 required a period of neurological stability, and the likelihood of an underestimated risk of early recurrent stroke was therefore low. Third, the average follow-up duration of studies was 2 to 4 years, and scarce information was available on the very long-term risk of MI. Aging, which is likely to increase the risk of MI, rises with the duration of follow-up, and we cannot exclude that the risk of MI rises later on. Delay from stroke onset to inclusion was several weeks or months, preventing us from assessing the early risk of MI and cardiac death, and higher early risks after stroke cannot be ruled out. However, the sensitivity analyses restricted to studies with recruitment delay < 1 month from stroke onset found similar results to the overall findings.

Author Contributions

Boulanger collected data; Boulanger, Rothwell, and Touzé participated in the study design; Boulanger performed statistical analyses; Boulanger, Béjot, Rothwell, and Touzé interpreted the results; Boulanger drafted the article; Béjot, Rothwell, and Touzé edited/reviewed the article.

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Disclosures

Touzé received honoraria for participation in advisory boards or as a symposium speaker for AstraZeneca France, Daiichi-Sankyo, BMS, Pfizer, and Boehringer-Ingelheim. Béjot received honoraria for participation in advisory boards or as a symposium speaker for AstraZeneca France, Daiichi-Sankyo, MSD, Covidem, BMS, Pfizer, and Boehringer-Ingelheim. The remaining authors have no disclosures to report.

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Supplemental Material

Data S1.

Critical appraisal of the cohort studies

The Critical Appraisal Skills Programme (CASP) checklist for cohorts includes the following questions:

- 1. Did the study address a clearly focused issue?
Studies were observational cohorts studies or randomized controlled trials that looked at the long-term prognosis after IS/TIA. IS and TIA had to be defined according to the World Health Organization as a minimum. We agree that not all studies were specifically dedicated to study the risk of MI after IS/TIA.
- 2. Was the cohort recruited in an acceptable way?
Our inclusion criteria correspond to what we can consider as “acceptable”. Studies with highly selected population (e.g. young age, specific race, patients with a rare cause of stroke) were not included. To reduce the risk of chance findings due to small sample size, we restricted our inclusion to studies involving ≥ 100 patients).
- 3. Was the exposure accurately measured to minimise bias?
Exposure corresponds to risk factors for MI in our systematic review. We only considered pre-specified traditional risk factors, which have relatively universal and reproducible definitions.
- 4. Was the outcome accurately measured to minimise bias?
Only studies with relevant methods for detecting outcomes (i.e. active or administrative follow-up) were included (table S1). In studies dedicated to the identification of predictors of MI after IS/TIA, measurement methods for MI were similar in all subgroups of patients, irrespective of exposure status.
- 5a. Have the authors identified all important confounding factors?
As in any other study-level meta-analysis, we were unable to control for confounders and reported the unadjusted pooled rate ratios for the risk of MI in patients with a potential risk factor compared with those without.
- 5b. Have they taken account of the confounding factors in the design and/or analysis?
We did not address this point as this was not our objective.
- 6a. Was the follow up of subjects complete enough?
Observational studies which did not report completeness of follow-up but described attempts to minimise loss to follow-up were not excluded.
- 6b. Was the follow up of subjects long enough?
This criteria was taken into account in our inclusion criteria. We restricted inclusion to studies with at least one year of follow-up.
- 7. What are the results of this study?
This is not relevant for this review. We only included studies in which the number of patients with a subsequent event (MI, recurrent stroke, cardiac or vascular deaths) could be extracted.
- 8. How precise are the results?

This is not relevant for this review. We only included studies in which the number of patients with a subsequent event (MI, recurrent stroke, cardiac or vascular deaths) could be extracted. Precision of estimates depends on the sample size of the study, therefore we restricted our inclusion criteria to studies involving ≥ 100 patients.

- 9. Do you believe the results?
Only studies deemed to have used robust methodologies and minimized biases (please see above) were included. Therefore, we consider our results as valid
- 10. Can the results be applied to the local population?
This criteria was taken into account in our inclusion criteria. We used large selection criteria for studies irrespective of language of publication or study setting. We also excluded highly selected population restricted to specific age ranges, race or rare cause of stroke.
- 11. Do the results of this study fit with other available evidence?
This is not relevant for this review. The objective of a systematic review is to summarize results across a number of carefully designed studies to draw high-level conclusions around a specific research question.
- 12. What are the implications of this study for practice
We did not address this point as results from one observational study rarely offer sufficiently strong evidence to provide changes to clinical practice or implications for future research. Replication in independent populations is required to support findings from one observational study. A systematic review provides therefore stronger evidence.

Data S2.

Electronic search strategies

OVID (Medline)

1. cerebrovascular event.mp.
2. myocardial infarction.mp. or Myocardial Infarction/
3. cardiac event.mp.
4. coronary event.mp.
5. vascular death.mp.
6. Brain Ischemia/ or Stroke/ or Cerebral Infarction/ or ischemic stroke.mp. or Ischemic Attack, Transient/
7. 1 or 6
8. 2 or 3 or 4 or 5
9. 7 and 8
10. limit 9 to humans

OVID (Embase)

1. cerebral infarct\$.mp. or brain infarction/
2. ischemic stroke.mp. or brain ischemia/
3. transient ischemic attack.mp. or transient ischemic attack/
4. myocardial infarction.mp. or heart infarction/
5. vascular death.mp.
6. coronary event.mp.
7. 1 or 2 or 3
8. 4 or 5 or 6
9. 7 and 8
10. limit 9 to human
11. limit 10 to conference abstract
12. 10 not 11

Table S1. Characteristics of the included studies.

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Achterberg ¹	the Netherlands	1994-2005	IS (55%), H		ND	Prospective (consecutive referrals to a university hospital) with active follow-up	62	68	49	15	8	11		22	ND	97
Agnelli ²	Italy	2005	IS (0%), H		92 (92/ND)	Prospective (hospital admissions) with active follow-up				22	7			25	ND	100
Amarenco ³	France	2005-2008	IS (0%), H		97 (84/28)	Prospective (consecutive ward admissions) with active follow-up	62	75	82	22			15	39	<10 d	99
Appelros ⁴	Sweden	1999-2000	Stroke, C		ND	Prospective (multiple search methods) with active follow-up	76	45	35	18	4	17	24	22	ND	100
Barnett ⁵	Canada, USA, Japan	1985	IS (33%), RCT	Aspirin vs. Aspirin + bybass surgery joining the superficial temporal artery and the middle cerebral artery	100 (100/0)	Prospective with active follow-up	56	82	50	18	12	10			<3 m	100
Bousser ⁶	France	1983	IS (16%), RCT	Placebo, Aspirin <i>or</i> Aspirin+ dypiridamole	66 (66/0)	Prospective with active follow-up	63	70	63	22	7	7		64	<12 m	99
Boysen ⁷	Denmark	1988	IS (49%), RCT	Aspirin vs. Placebo after carotid endarterectomy	50 (50/0)	Prospective with active follow-up	59	65	36	7	21	14		77	ND	ND
Boysen (ExSTROKE) ⁸	China, Poland, Estonia	2003-2005	IS (0%), RCT	Physiotherapist-guided physical activity vs. information on physical activity	ND	Prospective with active follow-up	69	43	54	14	8	8	13	37	<90 d	88
Brown ⁹	USA	2001	IS/TIA, H		ND	Retrospective (screening of administrative database) with administrative follow-up	77	45							ND	100
Busch ¹⁰	Germany	2003-2004	IS (25%), H		ND	Prospective (consecutive admissions to neurology ward) with active follow-up in patients who survived 1 week after stroke	64	55	70	32	12	12	18	29	ND	97

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Carolei ¹¹	Italy	1992	IS (24%), H		ND	Prospective with active follow-up	56	73	50	15	11	5			< 3 m	100
Chimowitz ¹²	North America	2005	IS (39%), RCT	Warfarin vs. Aspirin	100 (50/50)	Prospective with active follow-up	64	62	84	38		27		21	<3 m	ND
Colantonio ¹³	USA	2003-2007	IS/TIA, C		ND	Prospective (screening of administrative database and self-reported history of stroke) with active follow-up	65	38		28		0		18	ND	ND
Collins ¹⁴	UK	2004	IS (46%), RCT	Simvastatin vs. placebo	66 (63/3)	Prospective with active follow-up	66	75	50			27		14	<6 m	ND
Culebras ¹⁵	Argentina	2004	IS (19%), RCT	Triflusal vs. Aspirin	100 (100/ND)	Prospective with active follow-up	65	58	71	18	4	6		27	<6 m	100
Dennis ¹⁶	UK	1990	TIA, C		65 (57/8)	Prospective (multiple search methods) with active follow-up	69	56	34	-	-	-	-		0	99
Diener ¹⁷	Europe	1996	IS (24%), RCT	Aspirine alone, dipyridamole alone, Aspirine + dipyridamole or placebo	100 (100/0)	Prospective with active follow-up	67	58	61	15	22	14	7	24	<3 m	99
Diener (MATCH) ¹⁸	Intern.	2004	IS (21%), RCT	Aspirin + clopidogrel vs. clopidogrel	100 (100/ND)	Prospective with active follow-up	66	63	78	68	10	5			<3 m	99
Falke ¹⁹	Sweden	1994	IS (62%), H		ND	Prospective with administrative follow-up	75	64	21	8	9	9			0	100
Fang ²⁰	China	2003-2004	IS (0%), H		71 (71/ND)	Prospective (consecutive patients from community-hospitals) with active follow-up	64	51	78	30				25	ND	90
Farrel ²¹	UK	1979-1985	IS (71%), RCT	2 doses of Aspirin vs. placebo	67 (67/0)	Prospective with active follow-up	60	73	39	4	12	10	2		ND	100
Fields ²²	USA, Canada	1985	TIA, RCT	Aspirin vs. Aspirin + dypiridamole	100 (100/0)	Prospective with active follow-up	63	67	48	15	8	15		58	<3 m	92
Gates ²³	USA, Canada	2002	IS (54%), RCT	Carotid endarterectomy + BMT vs. BMT	97 (97/ND)	Prospective with active follow-up	66	70	61	21	15	18		43	<6 m	ND

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Gent (CAPRIE) ²⁴	Intern.	1996	IS (0%), RCT	Clopidogrel vs. aspirin	100 (100/0)	Prospective with active follow-up	65	64	65	25	8	12	4	30	<6 m	99
Gent (CATS) ²⁵	Canada, USA	1989	IS (22%), RCT	Ticlopidine vs. placebo	50 (50/0)	Prospective with active follow-up	65	62	67	32	11	17	1	7.3	<4 m	99
Goto ²⁶	Japan	2005-2006	Stroke, H		96 (76/20)	Prospective (consecutive outpatients) with active follow-up	68	69	74	22				22	ND	93
Has ²⁷	USA, Canada	1989	IS (50%), RCT	Ticlopidine hydrochloride vs. aspirin	100 (100/0)	Prospective with active follow-up	63	65	53	19	15	17		42	<3 m	97
Helmers ²⁸	Sweden	1987	IS (0%), RCT	Aspirin vs. placebo	50 (50/0)	Prospective with active follow-up	68	62	46	17	9	10	1	10	1-3 w	100
Howard ²⁹	USA	1987-1991	TIA, H		ND	Prospective (screening of admission and discharge records) with active follow-up, using blinded system	64	50	65	15		17		27	ND	ND
Ito ³⁰	Japan	2003	IS (14%), RCT	Ticlopidine vs. ticlopidine + aspirin	100 (100/0)	Prospective with active follow-up	67	65	47	23			3	33	1-6 m (IS) <3 m (TIA)	ND
Kim ³¹	Australia	1996-1999	Stroke, C		ND	Prospective (multiple search methods) with active follow-up in patients who survived 5 years after stroke. Patients with incomplete follow-up were excluded from analyses							19	12	ND	100
Kono ³²	Japan	2006-2007	IS (0%), H		98 (98/ND)	Prospective (consecutive ward admissions) with active follow-up	64	74	74	21				64	<2 w	ND
Li ³³	Sweden	1991-1996	Stroke, C		ND	Prospective with administrative follow-up (record linkage)	63	56	79			0		31	ND	ND
Lowenthal ³⁴	Europe	1990	IS (33%), RCT	Aspirin + dipyridamole vs. placebo	50 (50/0)	Prospective with active follow-up	64	58	37	-	-	-	-	43	<3 m	99
MacMahon ³⁵	Intern.	2001	IS (30%), RCT	Perindopril +/- indapamide vs. placebo	ND	Prospective with active follow-up	64	70	48	13				34	<5 y	99

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Man ³⁶	Hong Kong	2002-2004	IS/TIA, H		96 (ND/ND)	Prospective (ward admissions) with active follow-up. Patients with incomplete follow-up were excluded from analyses	73	58	66	33				45	<7 d	100
Manzano ³⁷	Singapour	2003-2004	IS (0%), H		ND	Prospective (consecutive ward admissions) with active follow-up. Patients with incomplete follow-up were excluded from analyses	65	88	77	40	6	23	9	26	ND	100
Matias-Guiu ³⁸	Portugal, Spain	2003	IS (26%), RCT	Triflusal vs. Aspirin	100 (100/0)	Prospective with active follow-up	65	66	61	24	4	2		31	<6 m	97
Muuronen ³⁹	Finland	1982	TIA, H		ND	Prospective with active follow-up	49	53	27	9	4				0	ND
Norrving ⁴⁰	Sweden	1991	IS (28%), RCT	Aspirin vs. placebo	50 (50/0)	Prospective with active follow-up	67	66	47	13	8	11		27	<3 m	99
Olsson ⁴¹	Sweden	1985	IS (45%), RCT	Warfarin vs. Aspirin + dipyridamole	100 (50/50)	Prospective with active follow-up	66	69	48	12		8			<2 m	81
Ovbiagele ⁴²	Intern.	1998-2005	Stroke, RCT	Atorvastatin vs. placebo	87 (87/ND)	Prospective with active follow-up	60	62	61	17					<6 m	84
Palnum ⁴³	Denmark	2003-2006	IS (0%), C		ND	Prospective with active follow-up (screening of nationwide database) in patients who survived in hospital or within 30 days after hospital discharge	53	44	13	4	9	15			ND	100
Petty ⁴⁴	USA	2003	IS (18%), C		65 (44/21)	Prospective (medical records linkage system) with active follow-up	75	42	73	17		17			0	ND
Rothwell ⁴⁵	Europe	2000	IS (50%), RCT	Carotid endarterectomy + BMT vs. BMT	85 (78/7)	Prospective with active follow-up	63	72	50	12	17	12		58	<6 m	99
Salgado ⁴⁶	Portugal	1996	IS (0%), H		ND	Prospective (consecutive ED or specialist wards or outpatient clinic attenders) with active follow-up	65	64	72	25	8	5	6	19	<1 w	99
Sander ⁴⁷	Germany	2008	IS (0%), H		ND	Prospective (consecutive admissions to neurologic rehabilitation ward) with active follow-up in patients who survived 3 months after stroke	66	58	79	35			20	18	<3 m	73

First author (study name)	Setting	Year	Population	Randomization arms	AT (AP/AC)	Ascertainment	Age	Male (%)	HTN (%)	DM (%)	PAD (%)	CAD (%)	AF (%)	Smoking (%)	Delay	FU (%)
Santos-García ⁴⁸	Spain	2005	IS (0%), H		100 (78/22)	Prospective (consecutive patients) with active follow-up. Patients with incomplete follow-up were excluded from analyses	73	58	70	25		7	25		<48 h	100
Simonsen ⁴⁹	Denmark	1981	TIA, H		ND	Retrospective (screening of hospital records) with administrative follow-up	60	68	16	6	6	7	7		<1 m	100
Sorensen ⁵⁰	Denmark	1983	IS (72%), RCT	Aspirin vs. placebo	50 (50/0)	Prospective with active follow-up	59	73	27		15	9		22	<1 m	100
Toole ⁵¹	USA, Canada, Scotland	2004	IS (0%), RCT	High vs. low dose of folic acid, pyridoxine and cobalamin	ND	Prospective with active follow-up	66	62	74	29		7		17	<4 m	93
Ueno ⁵²	Japan	2008-2014	IS (0%), H		100 (72/29)	Prospective (inpatients registry of the neurology ward) with active follow-up. Patients with incomplete follow-up were excluded from analyses	64	72						31	<7 d	100
Urbaniti ⁵³	Italy	1992	IS (82%), H		100 (100/ND)	Prospective (consecutive admissions to neurosurgical ward) with active follow-up	70	84	61	52	32	15		68	ND	100
Venkatasubramanian ⁵⁴	Intern.	2003-2004	IS (28%), H		82 (82/ND)	Prospective (consecutive outpatient/ambulatory clinics attenders) with active follow-up	66	57	80	35	4	30		14	ND	96
Vilanova ⁵⁵	Spain	2006-2013	TIA, H		100 (80/20)	Prospective (consecutive stroke patients) with active follow-up	71	58						14	<48 h	ND
Von Weitzel-Mudersbac ⁵⁶	Denmark	2007-2008	TIA, H		93 (ND/ND)	Prospective (referrals to neurology clinics) with active follow-up	66	56	70	12	18	11	8	31	ND	100
Whiteley ⁵⁷	UK	2002-2005	Stroke, H		ND	Prospective (consecutive hospital attenders) with active follow-up	71	53	53	12	8	28	20	70	ND	100
Wijnhoud ⁵⁸	the Netherlands	2008	IS (53%), H		ND	Prospective with active follow-up	60	66	53	16		11		29	<6 m	ND

Year: year of enrollment; TIA: transient ischemic attack; IS: ischemic stroke (including % of TIA if reported); Stroke: ischemic or hemorrhagic stroke; Minor: defined as non-disabling or reversible symptoms; H: hospital-based study; C: community-based study; RCT: randomized controlled trial; ED: emergency department; BMT: best medical treatment; AT: antithrombotic therapy; AP: antiplatelet

therapy; AC: oral anticoagulant therapy, numbers indicate proportion of patients under antithrombotic therapy at some point during follow-up (when only the proportion of patients under antiplatelet therapy was given, as antiplatelet therapy is the antithrombotic agent mostly used in secondary prevention of stroke, this number was reported as the proportion of patients under antithrombotic drugs ; when the proportions of patients under antiplatelet and anticoagulant drugs were reported without the total proportion of those under antithrombotic drugs, the two proportions were added to calculate the proportion under antithrombotic drugs); AP: antiplatelet therapy; NA: not applicable; ND: not defined; Intern: International; Age: mean age (years); HTN: Hypertension; DM: Diabetes Mellitus; PAD: Peripheral Arterial Disease; CAD: coronary artery disease; FU: follow-up; AF: atrial fibrillation; Smoking: current smoking; Delay: delay from IS/TIA onset to study inclusion; m: month; w: week; d: day

Table S2. Definitions of MI, recurrent stroke, cardiac and vascular deaths.

First author (study name)	MI	Recurrent stroke	Cardiac death	Vascular death
Achterberg ¹	ND	NA	NA	ND
Agnelli ²	1	NA	NA	MI, stroke, SD
Amarenco ³	ND	ND	MI, resuscitation after cardiac arrest, HF	MI, Car, HF, SD, AA
Appelros ⁴	3	NA	NA	NA
Barnett ⁵	ND	ND	NA	MI, SD, other
Bousser ⁶	ND	NA	NA	MI, PAD, PE, SD, CAr, other
Boysen ⁷	2	2	MI, SD	MI, SD
Boysen (EXSTROKE) ⁸	ND	2	NA	Stroke, MI, or other vascular causes, SD
Brown ⁹	3	6	NA	MI, stroke, SD
Busch ¹⁰	ND	7	NA	MI, stroke, SD
Carolei ¹¹	2	NA	NA	MI, HF, SD
Chimowitz ¹²	2	4	MI, SD, HF	NA
Colantonio ¹³	ND	NA	NA	NA
Collins ¹⁴	2	2	NA	NA
Culebras ¹⁵	2	NA	NA	MI, HF, SD, bleeding
Dennis ¹⁶	2	4	MI, SD	MI, Car, HF, SD, AA
Diener (ESPS2) ¹⁷	ND	ND	NA	MI, SD, HF, PE, PAD, hemorrhage
Diener (MATCH) ¹⁸	ND	NA	NA	ND
Falke ¹⁹	2	NA	NA	NA
Fang ²⁰	ND	2	MI, SD	MI, stroke, SD
Farrel ²¹	2	2	MI, SD, other IHD	Stroke, MI, SD, other IHD, AA, PE, gastrointestinal bleeding
Fields ²²	ND	NA	MI, SD	ND
Gates ²³	2	NA	MI, SD	ND
Gent (CAPRIE) ²⁴	2	NA	NA	MI, hemorrhage, others

First author (study name)	MI	Recurrent stroke	Cardiac death	Vascular death
Gent (CATS) ²⁵	ND	NA	NA	MI, HF, SD
Goto ²⁶	1	5	NA	MI, stroke, SD
Has ²⁷	ND	2	NA	ND
Helmers ²⁸	2	ND	NA	MI, chronic IHD
Howard ²⁹	ND	ND	NA	NA
Ito ³⁰	ND	ND	NA	NA
Kim ³¹	1	ND	NA	MI, stroke
Kono ³²	ND	ND	NA	NA
Li ³³	3	2	NA	NA
Lowenthal ³⁴	ND	NA	NA	MI, SD, other
MacMahon ³⁵	ND	NA	NA	MI, SD, other
Man ³⁶	ND	ND	NA	MI, stroke, AA
Manzano ³⁷	ND	ND	NA	MI, stroke
Matias-Guiu ³⁸	2	NA	NA	ND
Muuronen ³⁹	ND	NA	NA	NA
Norrving ⁴⁰	2	ND	NA	ND
Olsson ⁴¹	ND	NA	NA	NA
Ovbiagele ⁴²	ND	ND	NA	MI, stroke, PAD, revascularization
Palnum ⁴³	ND	ND	NA	NA
Petty ⁴⁴	ND	3	NA	SD, PAD, others
Rothwell ⁴⁵	2	NA	MI, SD	Heart disease, SD, AA
Salgado ⁴⁶	ND	ND	NA	ND
Sander ⁴⁷	ND	NA	NA	MI, stroke
Santos-García ⁴⁸	ND	ND	NA	MI, stroke, other cardiac diseases
Simonsen ⁴⁹	ND	NA	NA	NA

First author (study name)	MI	Recurrent stroke	Cardiac death	Vascular death
Sorensen ⁵⁰	ND	1	NA	ND
Toole ⁵¹	1	NA	NA	NA
Ueno ⁵²	ND	NA	NA	NA
Urbaniti ⁵³	ND	ND	NA	MI, stroke
Venketasubramanian ⁵⁴	ND	NA	NA	MI, stroke
Vilanova ⁵⁵	2	2	NA	MI, stroke
Weitzel-Mudersbac ⁵⁶	ND	NA	NA	MI, stroke
Whiteley ⁵⁷	ND	ND	NA	MI, stroke, PE
Wijnhoud ⁵⁸	ND	ND	MI, SD	MI, stroke, SD, PAD

MI: definition of myocardial infarction (1: Symptoms suggestive of MI with ECG changes or biological markers elevation [CK-MB or troponin] elevation; 2: Symptoms suggestive of MI and biological markers elevation and ECG changes, 3: ICD codes for MI); Recurrent stroke: definition of recurrent stroke (1: neurologic deficit lasting >72 hours, 2: neurologic deficit lasting >24 hours, 3: new neurological deficit fitting the definition for ischemic or hemorrhagic stroke occurring after a period of unequivocal neurological stability or improvement, lasting \geq 24 hours, 4: neurological deficit lasting >24 hours confirmed on brain imaging, 5: new neurological deficit confirmed on brain imaging, 6: ICD codes, 7: acute new deficit lasting >24 hours or new lesion demonstrated on brain imaging; Card.death: definition of cardiac death; Vasc.death : definition of vascular death ; HF: heart failure; SD, sudden death; CA, cardiac arrhythmia; PE, pulmonary embolism; AA, ruptured aortic aneurysm; TE: thrombo-embolic diseases; IHD: ischemic heart disease, CD: cardiac disease, S: stroke.

Table S3. Numbers and proportions of studies with definitions of myocardial infarction (MI).

Definitions of MI used in study	N studies; N patients (%)
Symptoms suggestive of MI with ECG changes or biological markers elevation	4; 8425 (6)
Symptoms suggestive of MI with ECG changes and biological markers elevation	16; 23,053 (27)
International Classification Diseases (ICD) codes	3; 2694 (5)
No explicit definition	35; 97,127 (62)

Table S4. Numbers and proportions of studies with definitions of recurrent stroke.

Definitions of recurrent stroke used in study	N studies; N patients (%)
Neurologic deficit lasting >72 hours	1; 203 (3)
Neurologic deficit lasting >24 hours	8; 11,131 (20)
Neurological deficit lasting >24 hours confirmed on brain imaging	2; 753 (5)
Acute new deficit lasting >24 hours or new lesion demonstrated on brain imaging	1; 204 (3)
New neurological deficit fitting the definition for ischemic or hemorrhagic stroke occurring after a period of unequivocal neurological stability or improvement, lasting \geq 24 hours	1; 1111 (3)
New neurological deficit confirmed on brain imaging	1; 3351 (3)
International Classification Diseases (ICD) codes	1; 1923 (3)
No explicit definition	24; 78,848 (60)

Table S5. Risks of myocardial infarction (MI), recurrent stroke, cardiac and vascular deaths in the included studies.

First author (study name)	n patients	Mean follow- up (years)	Total MI, n (%/year)	Fatal MI, n (%/year)	Nonfatal MI, n (%/year)	Total recurrent stroke, n (%/year)	Recurrent fatal stroke, n (%/year)	Recurrent nonfatal stroke, n (%/year)	Incidence ratio nonfatal MI / recurrent nonfatal stroke	Incidence ratio fatal MI / recurrent fatal stroke	Cardiac death, n (%/year)	Incidence ratio cardiac death / recurrent fatal stroke	Vascular Death, n (%/year)
Achterberg ¹	971	6.3	72 (1.2)										113 (1.8)
Agnelli ²	755	1							0.2				24 (3.1)
Amarenco ³	377	2.6			3 (0.3)				0.2		5 (0.5)		7 (0.7)
Appelros ⁴	377	10	49 (1.3)	30 (0.8)	19 (0.5)								
Barnett ⁵	1377	4.7		83 (1.3)		410 (6.3)				1.28			244 (3.8)
Bousser ⁶	604	3	18 (1)	4 (0.2)	14 (0.8)								
Boysen ⁷	301	2.1	2 (0.3)			20 (3.2)							18 (2.8)
Boysen (EXSTROKE) ⁸	314	2	4 (0.6)			25 (4.0)							7 (1.1)
Brown ⁹	1923	2	108 (2.8)			239 (6.2)							2 (0.6)
Busch ¹⁰	204	2.3	4 (0.9)	2 (0.4)		23 (4.9)							2 (0.4)
Carolei ¹¹	712	4			19 (0.7)								
Chimowitz ¹²	569	1.8	19 (1.9)	3 (0.3)	16 (1.6)	109 (10.6)					5 (0.5)		26 (2.5)
Colantonio ¹³	3432	5.8	145 (0.7)	53 (0.3)									
Collins ¹⁴	3280	4.8	389 (2.5)			339 (2.2)							
Culebras ¹⁵	429	1.6			9 (1.3)								13 (1.9)
Dennis ¹⁶	184	3.7	17 (2.5)			45 (6.6)					17 (2.5)	1.13	34 (5)
Diener (ESPS2) ¹⁷	6602	2	167 (1.3)	70 (0.5)	97 (0.7)	830 (6.3)			0.13	0.73			
Diener (MATCH) ¹⁸	7599	1.5	141 (1.2)										245 (2.1)
Falke ¹⁹	209	6	52 (4.1)	36 (2.9)	16 (1.3)				1.33				
Fang ²⁰	710	5	25 (0.7)	9 (0.3)		75 (2.1)			0.29	0.47	14 (0.4)	0.74	33 (0.9)
Farrel ²¹	2435	4	117 (1.2)	45 (0.5)	72 (0.7)	320 (3.3)	55 (0.6)	265 (2.7)	0.27	0.82	173 (1.8)	0.65	253 (2.6)
Fields ²²	890	2.1	48 (2.6)	26 (1.4)	22 (1.2)						41 (2.2)		59 (3.2)
Gates ²³	2815	5	533 (3.8)		238 (1.7)						295 (2.1)		

Sorensen ⁵⁰	203	2.1	20 (4.7)			28 (6.6)							12 (2.8)
Toole ⁵¹	3680	1.7	237 (3.8)										
First author (study name)	n patients	Mean follow-up (years)	Total MI, n (%/year)	Fatal MI, n (%/year)	Nonfatal MI, n (%/year)	Total recurrent stroke, n (%/year)	Recurrent fatal stroke, n (%/year)	Recurrent nonfatal stroke, n (%/year)	Incidence ratio nonfatal MI / recurrent nonfatal stroke	Incidence ratio fatal MI / recurrent fatal stroke	Cardiac death, n (%/year)	Incidence ratio cardiac death / recurrent fatal stroke	Vascular Death, n (%/year)
Ueno ⁵²	177	3.5	5 (0.8)										
Urbaniti ⁵³	150	6.2	16 (1.7)	11 (1.2)	5 (0.5)	11 (1.2)			0.63	2.75			13 (1.4)
Venketasubramanian ⁵⁴	18992	2			399 (1.1)				0.37				855 (2.3)
Vilanova ⁵⁵	628	2.6	28 (1.7)	1 (0.1)		71 (4.3)			0.4	0.33			4 (0.2)
Weitzel-Mudersbac ⁵⁶	306	1			0 (0)								5 (1.6)
Whiteley ⁵⁷	877	2.1	69 (3.7)	35 (1.9)		106 (5.8)			0.79	0.56			113 (6.1)
Wijnhoud ⁵⁸	489	2.1	8 (0.8)	2 (0.2)		39 (3.8)			0.18	0.25	12 (1.2)	1.5	21 (2)

N: number, MI: myocardial infarction, TIA: transient ischemic attack; IS: ischemic stroke

Figure S1. PRISMA Flow diagram describing identification, screening, eligibility, and inclusion of studies in the systematic review

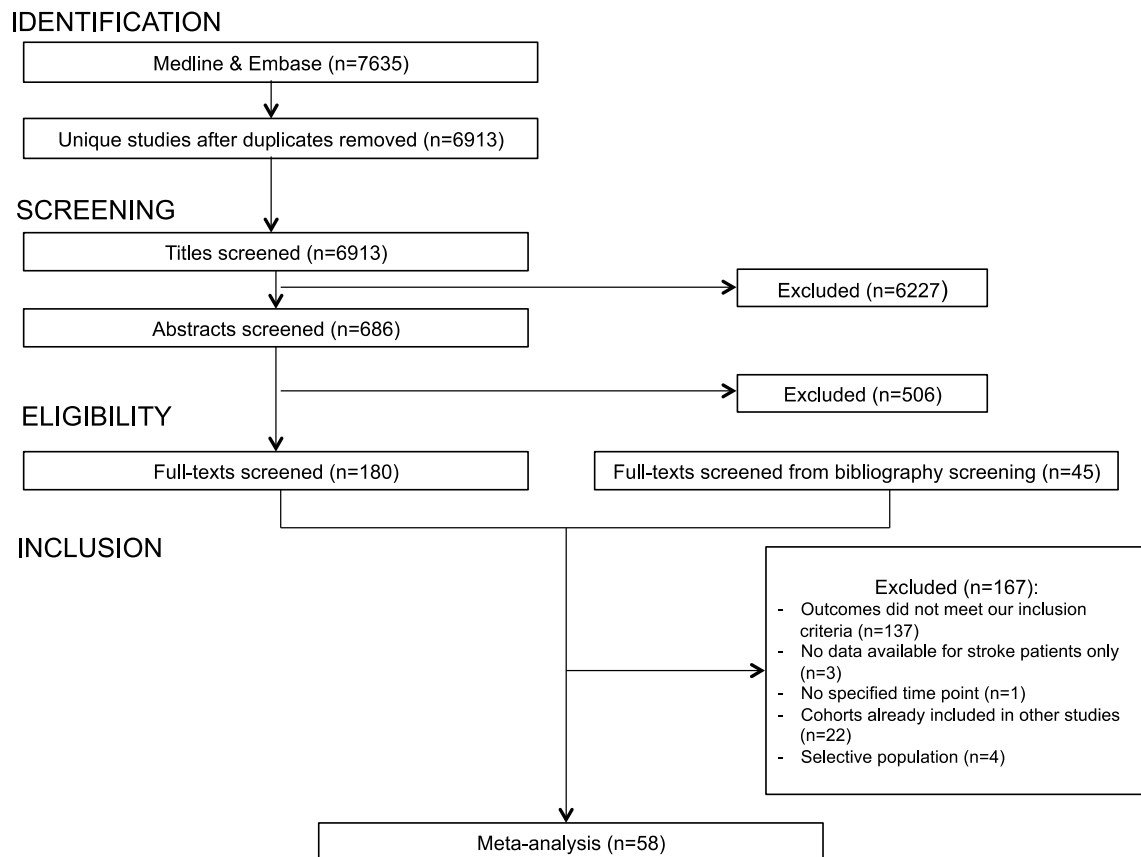
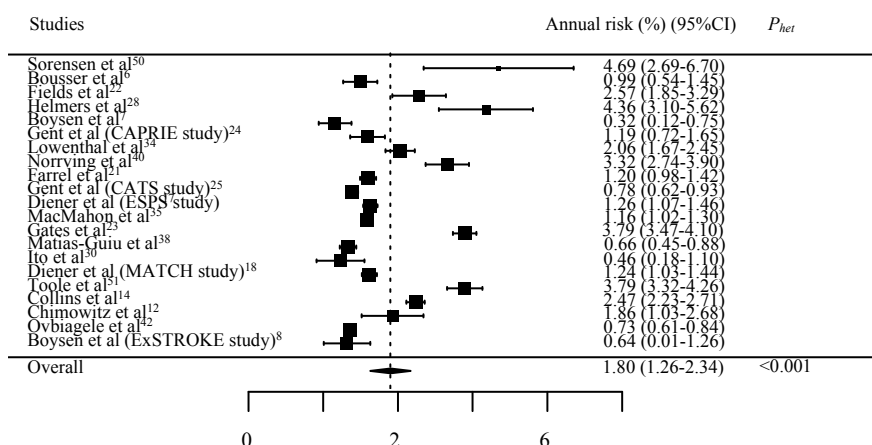
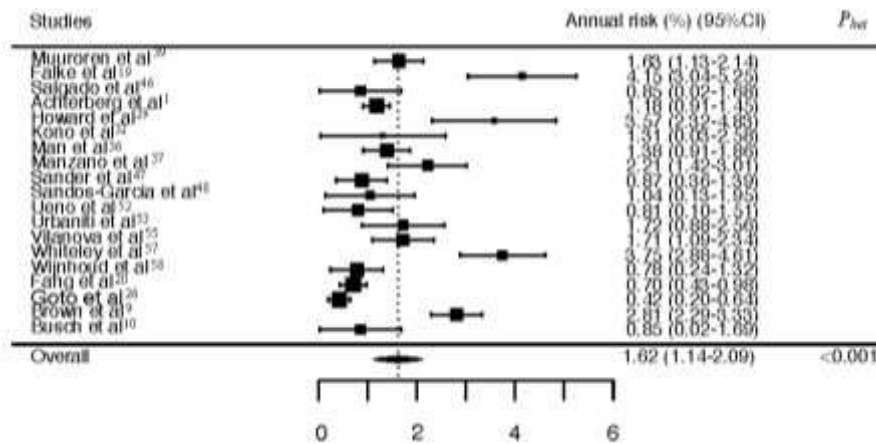


Figure S2. Forest plot of the meta-analysis of the risk of MI after TIA/IS in randomized controlled trials (RCTs).



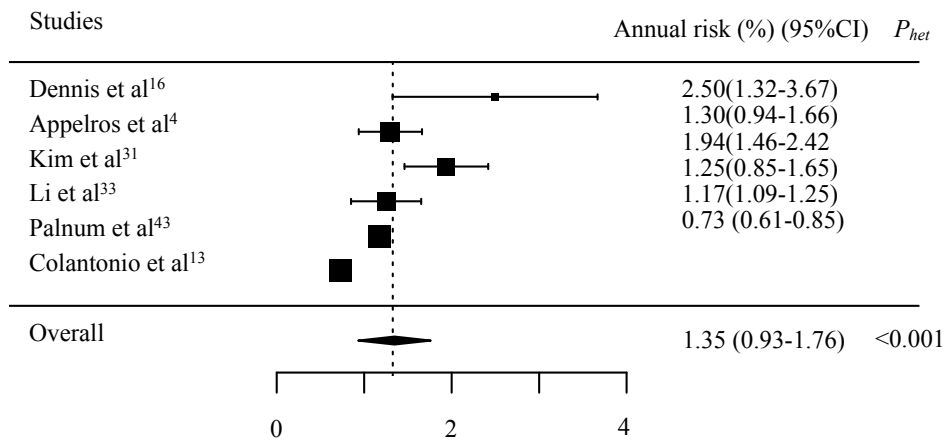
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S3. Forest plot of the meta-analysis of the risk of MI after TIA/IS in hospital-based studies.



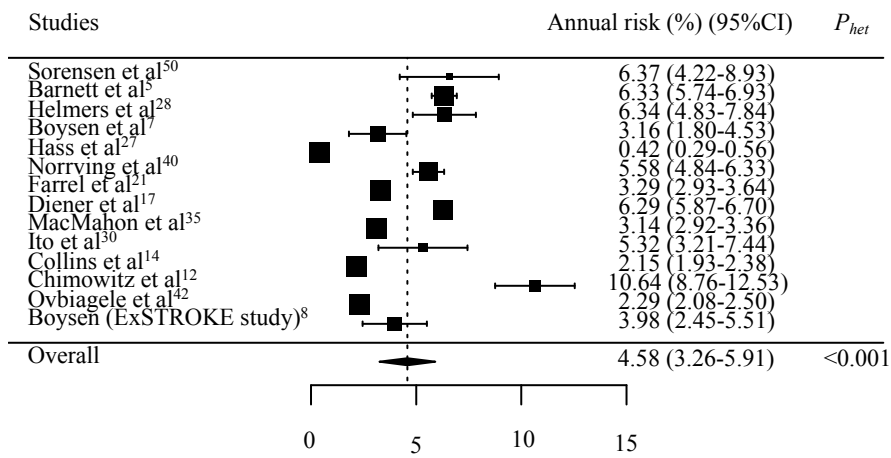
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S4. Forest plot of the meta-analysis of the risk of MI after TIA/IS in community-based studies.



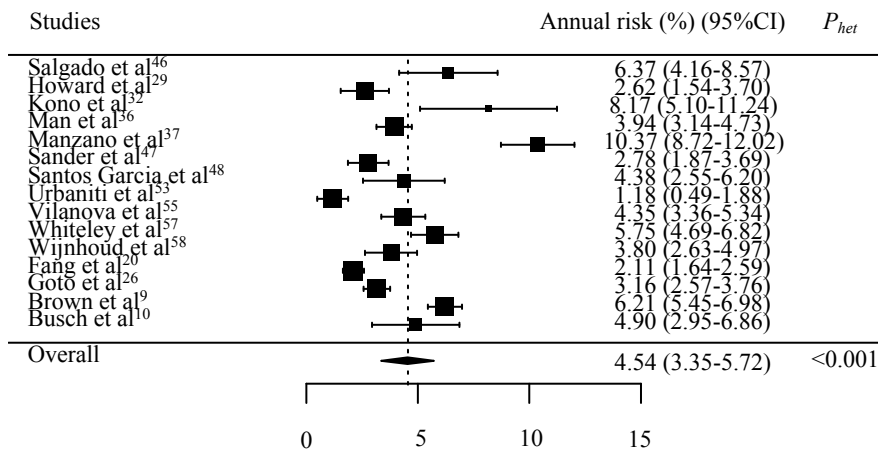
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S5. Forest plot of the meta-analysis of the risk of recurrent stroke after TIA/IS in randomized controlled trials (RCTs).



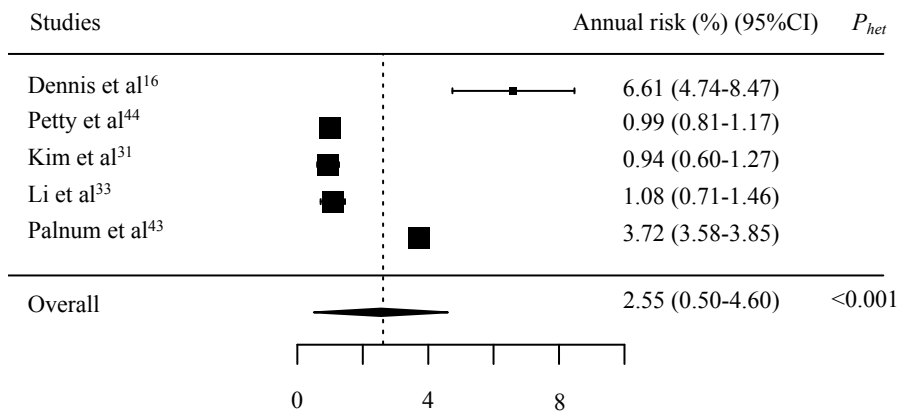
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S6. Forest plot of the meta-analysis of the risk of recurrent stroke after TIA/IS in hospital-based studies.



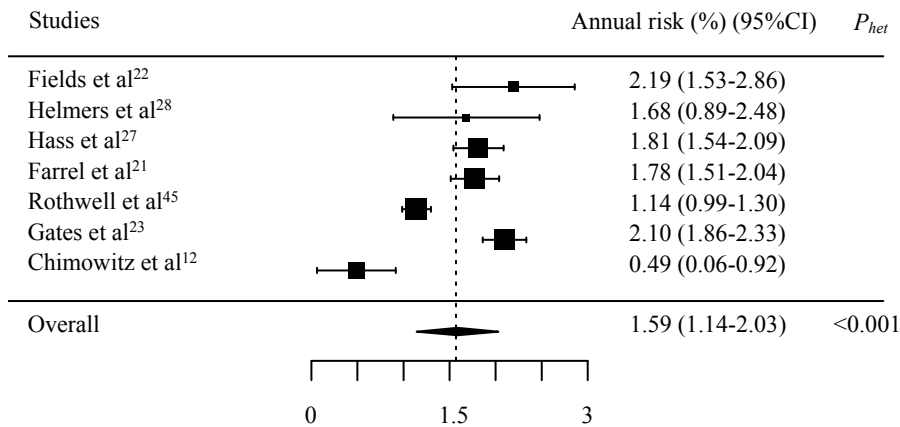
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S7. Forest plot of the meta-analysis of the risk of recurrent stroke after TIA/IS in community-based studies.



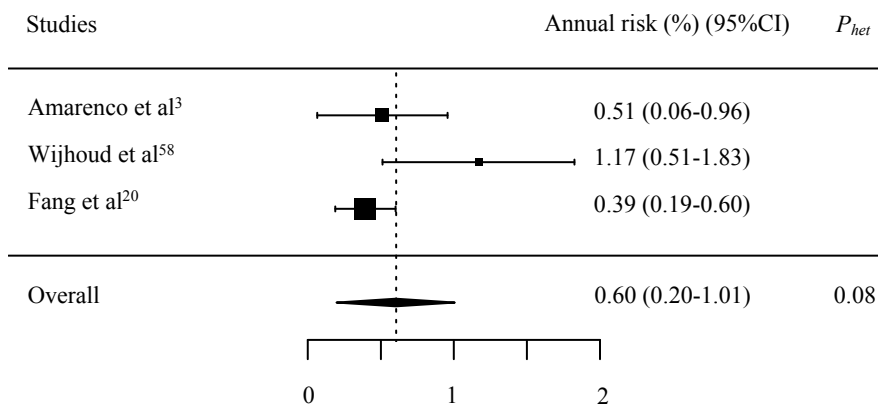
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S8. Forest plot of the meta-analysis of the risk of cardiac death after TIA/IS in randomized controlled trials (RCTs).



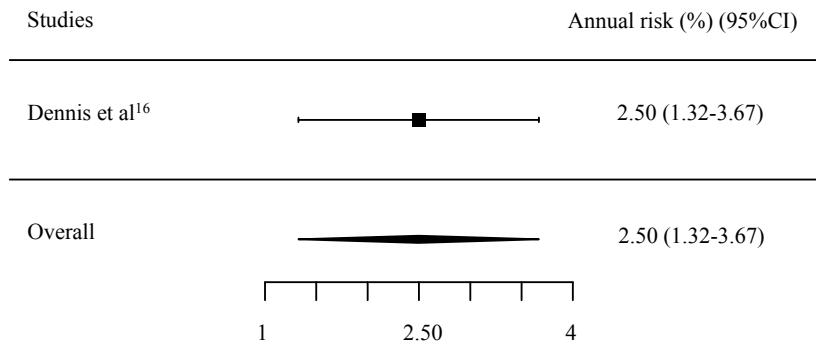
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S9. Forest plot of the meta-analysis of the risk of cardiac death after TIA/IS in hospital-based studies.



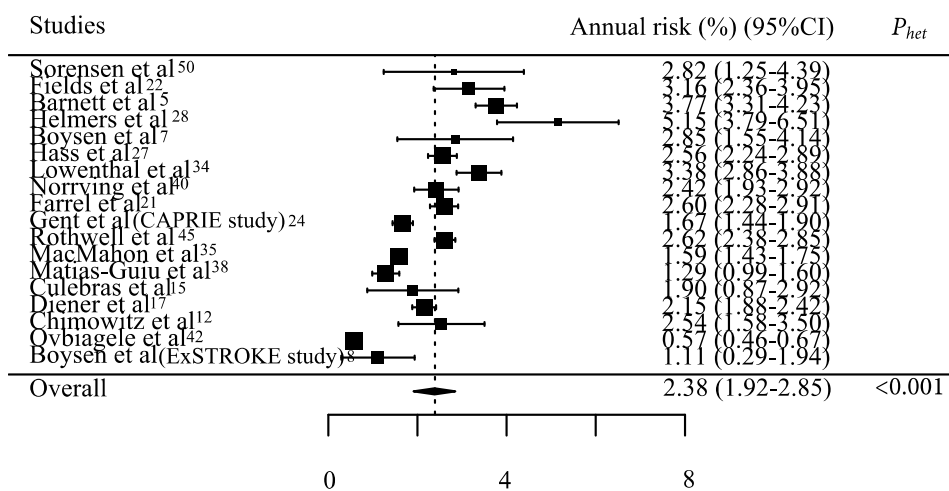
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S10. Forest plot of the meta-analysis of the risk of cardiac death after TIA/IS in community-based studies.



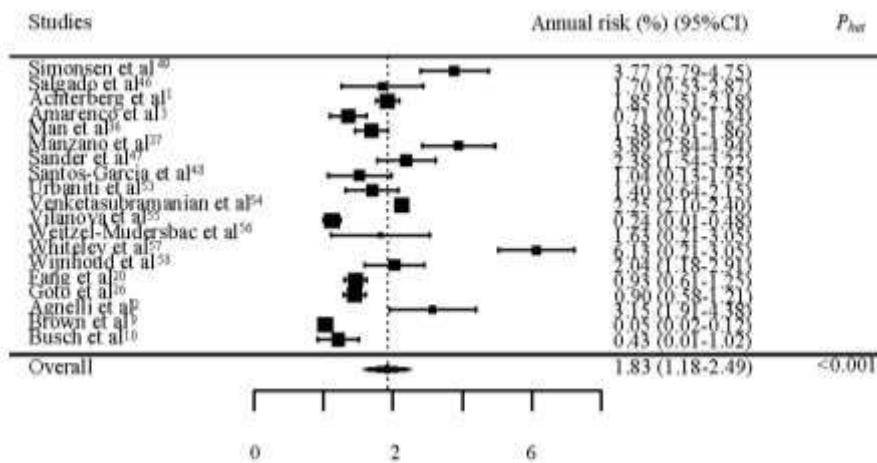
Bars indicate 95% confidence intervals (CI).

Figure S11. Forest plot of the meta-analysis of the risk of vascular death after TIA/IS in randomized controlled trials (RCTs).



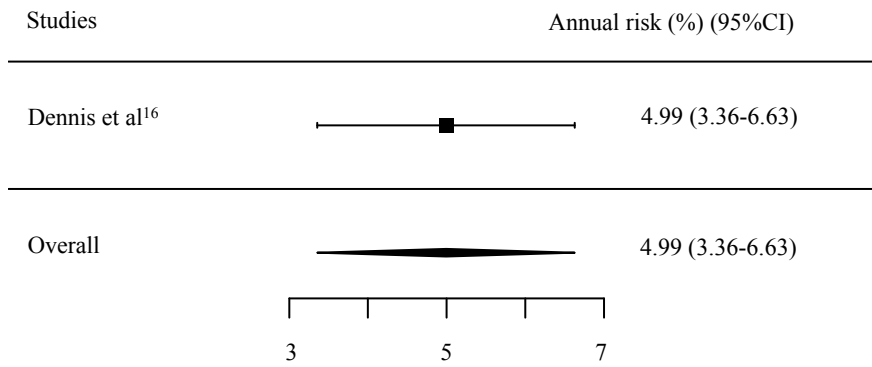
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S12. Forest plot of the meta-analysis of the risk of vascular death after TIA/IS in hospital-based studies.



The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het} : Heterogeneity across studies.

Figure S13. Forest plot of the meta-analysis of the risk of vascular death after TIA/IS in community-based studies. Bars indicate 95% confidence intervals (CI).



Bars indicate 95% confidence intervals (CI)

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Long-Term Risk of Myocardial Infarction Compared to Recurrent Stroke After Transient Ischemic Attack and Ischemic Stroke: Systematic Review and Meta-Analysis

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Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke

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Abstract

Objective

To determine whether TIA or ischemic stroke patients with coexisting cardiovascular disease (i.e., history of coronary or peripheral artery disease) are still at high risk of recurrent ischemic events despite current secondary prevention guidelines.

Methods

In a population-based study in Oxfordshire, UK (Oxford Vascular Study), we studied consecutive patients with TIA or ischemic stroke for 2002–2014. Patients were treated according to current secondary prevention guidelines and we determined risks of coronary events, recurrent ischemic stroke, and major bleeding stratified by the presence of coexisting cardiovascular disease.

Results

Among 2,555 patients (9,148 patient-years of follow-up), those ($n = 640$; 25.0%) with coexisting cardiovascular disease (449 coronary only; 103 peripheral only; 88 both) were at higher 10-year risk of coronary events than those without (22.8%, 95% confidence interval 17.4–27.9; vs 7.1%, 5.3–8.8; $p < 0.001$; age- and sex-adjusted hazard ratio [HR] 3.07, 2.24–4.21) and of recurrent ischemic stroke (31.5%, 25.1–37.4; vs 23.4%, 20.5–26.2; $p = 0.0049$; age- and sex-adjusted HR 1.23, 0.99–1.53), despite similar rates of use of antithrombotic and lipid-lowering medication. However, in patients with noncardioembolic TIA/stroke, risk of extracranial bleeds was also higher in those with coexisting cardiovascular disease, particularly in patients aged <75 years (8.1%, 2.8–13.0; vs 3.4%, 1.6–5.3; $p = 0.0050$; age- and sex-adjusted HR 2.71, 1.16–6.30), although risk of intracerebral hemorrhage was not increased (age- and sex-adjusted HR 0.36, 0.04–2.99).

Conclusions

As in older studies, TIA/stroke patients with coexisting cardiovascular disease remain at high risk of recurrent ischemic events despite current management. More intensive lipid-lowering might therefore be justified, but benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding.

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OXVASC study coinvestigators are listed in appendix 2 at the end of the article.

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Glossary

DWI = diffusion-weighted imaging; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **MI** = myocardial infarction; **N-STEMI** = non-ST-elevation; **OXVASC** = Oxford Vascular Study; **PCSK-9** = proprotein convertase subtilisin/kexin type 9; **STEMI** = ST-elevation; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Risk of recurrent vascular events in patients with TIA and stroke remains substantial, and there is a need for improved secondary prevention of stroke and also prevention of coronary events.^{1,2} Antiplatelet monotherapy is currently standard for long-term secondary prevention, and there is evidence in certain subsets of patients that anticoagulation is associated with a high risk of intracerebral hemorrhage.^{3,4} TIA/stroke patients with coexisting stable atherosclerotic cardiovascular disease (coronary or peripheral artery disease) have been shown previously to be at high absolute risk of recurrent stroke and coronary events.^{5–7} However, the absolute risk of coronary events after TIA/stroke has decreased over the last few decades,² and there are relatively few recent data on the overall residual vascular risk in TIA/stroke patients on current guideline-based management, particularly on long-term follow-up. Moreover, data on the long-term risk of major bleeding with antithrombotic therapies based on the presence of coexisting cardiovascular disease are scarce. If TIA/stroke patients with coexisting stable atherosclerotic cardiovascular disease still have a high absolute risk of recurrent ischemic stroke or coronary events, then more intensive secondary prevention might result in a sufficient reduction in ischemic events to counterbalance any increased risk of bleeding or increased cost of more intensive treatment.

In patients with stable atherosclerotic cardiovascular disease, the COMPASS trial reported a 50% relative reduction in risk of ischemic stroke on rivaroxaban plus aspirin vs aspirin alone, albeit with a 70% increased risk of major bleeding.⁸ COMPASS excluded patients with recent TIA or stroke, but the subgroup of patients with carotid artery disease did benefit from combination treatment.⁹ Moreover, the annual risk of stroke was <1% in the aspirin-alone group, which is lower than reported after TIA and ischemic stroke in routine practice,¹⁰ particularly in patients with coexisting coronary or peripheral artery disease.⁶ In patients with recent cryptogenic stroke, the NAVIGATE ESUS trial reported no reduction in risk of recurrent ischemic stroke on rivaroxaban vs aspirin, but a higher risk of intracerebral hemorrhage.³ However, cryptogenic TIA/stroke patients have a low prevalence of coexisting cardiovascular disease, have a relatively low absolute risk of recurrent ischemic stroke,¹¹ and may be at higher risk of intracerebral hemorrhage.^{12–14}

Patients with TIA and ischemic stroke also have a substantial long-term risk of myocardial infarction (MI) and cardiac death,¹⁵ and there is also increasing evidence that tighter control of cholesterol levels than the current guideline target (low-density lipoprotein [LDL] <2.6 mmol/L) may be

necessary,¹⁶ with randomized controlled trials of LDL reduction to <1.8 mmol/L ongoing.¹⁷ Trials of new cholesterol-lowering therapies, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors,^{18–20} also focused on populations with stable cardiovascular disease and reported significant reductions in LDL cholesterol and in MI, as compared with placebo, in patients on high-dose statins with LDL level >1.8 mmol/L. There was less evidence for a reduction in risk of ischemic stroke with PCSK-9 inhibitors,^{19,20} but dyslipidemia is estimated to account for a higher proportion of the risk of coronary events than of the risk of ischemic stroke.^{21,22} However, although PCSK-9 inhibitors reduced the relative risk of MI by 27% in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial¹⁹ and by 13% in the Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial,²⁰ the drugs are very costly²³ and may only be cost-effective in high-risk subgroups. The annual risk of MI was only 1%–2% in the trials, which is again lower than reported after TIA and ischemic stroke in patients with coexisting coronary or peripheral artery disease.⁶

Given the potential that more intensive antithrombotic treatment or lipid-lowering might reduce the long-term risk of recurrent stroke and coronary events in TIA or stroke patients with coexisting stable cardiovascular disease, we aimed to determine the prognosis of this subgroup on current standard preventive treatment for both recurrent ischemic events and for major bleeding. Up-to-date estimates of event rates will help clinicians assess potential benefits of more intensive treatment and facilitate the planning of future trials.

Methods

Study population

The Oxford Vascular Study (OXVASC) is an ongoing population-based study of the incidence and outcome of all acute vascular events.²⁴ The study population comprised all 92,728 individuals, irrespective of age, registered with 100 family physicians in 9 general practices in Oxfordshire, UK. In Oxfordshire, it is estimated that 97.1% of the true residential population is registered with a primary care practice, the majority of nonregistered individuals being young adults. The analysis reported here included consecutive cases, irrespective of age, with a first TIA or ischemic stroke from April 1, 2002, to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was only available in cases recruited from April 1, 2002, to March 31, 2012, with follow-up until March 31, 2013.

The OXVASC study design has been described in detail previously.²⁴ Briefly, multiple overlapping methods of hot and cold pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke.^{25,26} These include the following: (1) a daily, rapid access TIA and stroke clinic to which participating general practitioners and the local emergency department refer individuals with suspected TIA or minor stroke; (2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; (3) daily searches of the local emergency department attendance register; (4) daily searches of in-hospital death records via the Bereavement Office; (5) monthly searches of all death certificates and coroner's reports for out-of-hospital deaths; (6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; (7) monthly searches of all brain and vascular imaging referrals. Patients gave written informed consent after an event or assent was obtained from a relative for patients who were unable to provide consent. OXVASC was approved by our local research ethics committee.

Standard WHO definitions were used for TIA and stroke, which have been reported previously.^{24,25} All cases were investigated according to current guidelines and reviewed by a senior neurologist with stroke expertise (P.M.R.) in order to ensure consistency over time. Differentiation between TIA and stroke was based on the WHO 24-hour cutoff for symptom duration (i.e., events were classified as TIA even if diffusion-weighted imaging [DWI] was positive if symptoms resolved within 24 hours) and we have kept the same definition over time. TIA/stroke etiology was categorized by P.M.R. according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (table e-1, doi.org/10.5061/dryad.t4r1n64).²⁷ Patients were prescribed standard secondary prevention medication according to contemporary guidelines, including antiplatelet or anticoagulant treatment, as appropriate, blood pressure-lowering medication, and statin treatment to achieve a target of blood pressure <140/90 mm Hg and LDL <2.6 mmol/L, both at baseline and at the time of study follow-up visits. It was our policy in patients with coexisting cardiovascular disease who were on antiplatelet treatment before the TIA/stroke to continue dual therapy if already on dual (e.g., after recent stent) for as long as previously indicated and to add clopidogrel for 1 month only if on monotherapy beforehand, but revert to monotherapy after 1 month. Anticoagulation was also continued or started when clinically indicated, but was not used preferentially in patients with coexisting cardiovascular disease.

Demographic data, atherosclerotic risk factors (male sex, history of hypertension, diabetes mellitus, hypercholesterolemia, smoking [i.e., ex or current smoker], family history of premature MI [defined as MI occurring in a first-degree relative, siblings, or parents, aged ≤55 years if male or aged ≤65 years if female]), previous atrial fibrillation, prior coronary artery disease, prior peripheral artery disease, and

medication were collected from face-to-face interviews and cross-referenced with primary care records. Renal insufficiency was defined as glomerular filtration rate <30 mL/min, calculated by the MDRD equation,²⁸ using the creatinine level closest to the date of TIA/stroke. Patients were classified as having a prior coronary artery disease if they had at least one of the following: previous MI, unstable angina, angina, previous percutaneous coronary intervention, or coronary artery bypass graft surgery. Prior peripheral artery disease was defined as having at least one of the following: previous acute limb ischemia, critical limb ischemia, intermittent claudication, previous angioplasty or stenting, peripheral arterial bypass graft, or amputation. For intermittent claudication, the diagnosis was based on the judgement of the study clinician based on both prior medical records and symptoms.

All patients were followed up face-to-face at 1, 6, 12, 60, and 120 months by a study nurse or physician and subsequent vascular events identified and risk factor control evaluated and treatment revised as necessary. For patients who had moved out of the study area, telephone follow-up was done, and patients with dementia were followed up via a carer or by assessment in a nursing home. All recurrent events that presented to medical attention would also be identified by ongoing daily case ascertainment of all acute vascular events in the study population. All study patients were also notified to the UK Office of National Statistics such that all deaths were reported back to the study with causes. Deaths were also identified by regular review of primary care records and by regular contact with the Coroner's Office to ascertain out-of-hospital deaths. If a recurrent nonfatal vascular event was suspected, the patient was reassessed face-to-face by a study physician.

MI was defined using standard criteria.²⁹ Sudden cardiac death was defined using recommendations in Epidemiology and Clinical Research Studies and required a definite history of preceding symptoms consistent with acute coronary ischemia, or postmortem evidence of either substantial coronary atherosclerosis or acute thrombosis, or a documented MI during the previous 28 days.³⁰ Fatal MI was defined as any death within 30 days of a documented MI. Definitions of MI and sudden cardiac death remained unchanged over the period. We collected information on MI subtype (ST-elevation [STEMI] and non-ST-elevation MI [N-STEMI]). Recurrent ischemic stroke was defined as new neurologic deficit fitting the definition for ischemic stroke occurring after a period of neurologic stability or improvement. Major bleeds were defined according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) criteria and were bleeds that were fatal or substantially disabling with persistent sequelae, symptomatic intracranial, intraocular bleeds leading to significant loss of vision, or bleeds requiring transfusion of ≥2 units of blood, use of IV inotropic agents, or necessitating a surgical intervention (appendix e-1, doi.org/10.5061/dryad.t4r1n64).³¹

Statistical analysis

We determined the 10-year risk of follow-up coronary events (defined as MI or sudden cardiac deaths), recurrent ischemic stroke, major ischemic vascular events (defined as coronary event or recurrent ischemic stroke, whichever happens first), and major bleeds (extracranial and intracerebral hemorrhage) from Kaplan-Meier analyses, stratified by history of coexisting cardiovascular disease, and assessed any difference with log-rank test. We used similar analyses for the 10-year risk stratified by stroke subtype. We also compared risks of follow-up events between patients with and without coexisting cardiovascular disease using logistic regression analysis adjusted for age and sex. All analyses were done using R version 3.1.3.

Data availability

Requests for anonymized data will be considered by the corresponding author.

Results

Of 2,555 patients (949 TIA and 1,606 ischemic stroke; mean age 74 years; 21% aged ≥ 85 years), 443 (17.3%) had a previous TIA or stroke before their index event and 640 (25.0%) had history of coexisting stable cardiovascular disease (449 coronary artery disease only; 103 peripheral artery disease only; 88 both [tables 1 and 2]). At baseline, the mean total cholesterol level was 5.05 (± 1.27) mmol/L, ranging from 4.86 (± 1.30) mmol/L in patients on statin treatment prior to the TIA/stroke to 5.12 (± 1.25) mmol/L in those with no statin ($p < 0.001$).

Patients with coexisting cardiovascular disease were older (mean age 78 vs 73 years, $p < 0.001$), had more atherosclerotic risk factors, and were more likely to be on antithrombotics, antihypertensives, and statins before the TIA/stroke than those without (table 1 and table e-2, doi.org/10.5061/dryad.t4r1n64). Rates of use of secondary preventive therapies were high at 1-year follow-up, with similar rates of use of antithrombotics and statins in patients with and without coexisting cardiovascular disease, but rate of use of antihypertensives remained higher in those with coexisting cardiovascular disease (table 1 and table e-2, doi.org/10.5061/dryad.t4r1n64). Patients with TIA/stroke due to large artery disease (TOAST classification) and cardioembolism had the highest prevalence of coexisting cardiovascular disease ($p < 0.001$, table 2).

During 9,148 patient-years of follow-up, there were 158 coronary events (29 STEMI; 89 N-STEMI; 40 sudden cardiac deaths), 413 recurrent ischemic strokes, and 1,118 deaths. Patients with coexisting cardiovascular disease comprised 25% of all patients but accounted for 51% of coronary events and 28% of recurrent ischemic stroke during follow-up. In patients with noncardioembolic TIA/ischemic stroke and after exclusion of those on anticoagulants, 82 extracranial bleeds and 20 intracerebral hemorrhages occurred.

The 10-year risk of coronary events (10.6%, 95% confidence interval 8.8–12.4 overall) was higher in patients with coexisting cardiovascular disease than in those without (22.8%, 17.4–27.9; vs 7.1%, 5.3–8.8; $p < 0.001$; age- and sex-adjusted hazard ratio [HR] 3.07, 2.24–4.21, table 3, figure 1, and figures e-1 and e-2, doi.org/10.5061/dryad.t4r1n64), particularly in patients aged < 75 years (16.69%, 9.65–23.19; vs 3.78%, 2.09–5.44; $p < 0.001$; age- and sex-adjusted HR 4.33, 2.42–7.73, table 3).

The 10-year risk of recurrent ischemic stroke (25.3%, 22.6–27.8 overall) was also higher in patients with coexisting cardiovascular disease than those without (31.5%, 25.1–37.4; vs 23.4%, 20.5–26.3; $p = 0.0049$; age- and sex-adjusted HR 1.23, 0.99–1.53, table 3, figure 1, and figure e-3, doi.org/10.5061/dryad.t4r1n64), particularly in patients aged < 75 years (30.3%, 21.4–38.3; vs 17.6%, 14.3–20.7; $p < 0.001$; adjusted HR 1.74, 1.23–2.46, table 3). Patients with coexisting cardiovascular disease also had a higher 10-year risk of all major ischemic vascular events than those without (45.1%, 38.4–51.1; vs 28.7%, 25.3–31.9; $p < 0.001$; age- and sex-adjusted HR 1.56, 1.30–1.88, table 3, figure 1).

In patients with noncardioembolic TIA/stroke and after exclusion of those on anticoagulants, the 10-year risk of major extracranial bleeds was higher in those with coexisting cardiovascular disease (table 3), particularly in patients aged < 75 years (8.1%, 2.8–13.0; vs 3.5%, 1.6–5.3; $p = 0.0050$; age- and sex-adjusted HR 2.71, 1.16–6.30). The excess risk of major extracranial bleeds in those with coexisting cardiovascular disease was not limited only to the very early follow-up period (figure 1). In contrast, patients with coexisting cardiovascular disease were not at increased risk of intracerebral hemorrhage (1.5%, 0–4.3; vs 2.5%, 1.0–4.0; $p = 0.09$; age- and sex-adjusted HR 0.17, 0.02–1.26, table 3).

The subgroup of patients with (TOAST) large artery disease had the highest 10-year risk of coronary events compared to the other stroke subtypes (16.1%, 10.3–21.6, $p < 0.001$) and among the highest 10-year risk of recurrent ischemic stroke (26.3%, 18.9–33.1, $p < 0.001$, table 4, figure 2). However, in patients with (TOAST) large artery disease, risk of coronary events remained increased in those with coexisting cardiovascular disease compared to those without (10-year risk 33.5%, 15.9–47.4; vs 9.5%, 4.2–14.6; $p < 0.001$; age- and sex-adjusted HR 3.39, 1.65–6.96) while risk of recurrent ischemic stroke was high irrespective of presence of coexisting cardiovascular disease (10-year risk 26.4%, 12.6–38.1; vs 26.3%, 17.3–34.4; $p = 0.79$; age- and sex-adjusted HR 1.02, 0.57–1.83, figure 3 and table e-3, doi.org/10.5061/dryad.t4r1n64). Patients with (TOAST) large artery disease also had a high 10-year risk of major extracranial bleeds (11.1%, 1.8–19.5, $p = 0.85$) but a relatively low risk of intracerebral hemorrhage (0.4%, 0.0–1.1, $p = 0.26$, table 4 and table e-3, doi.org/10.5061/dryad.t4r1n64). In contrast, the subgroup of patients with

Table 1 Baseline characteristics in TIA or ischemic stroke patients, stratified by history of coexisting cardiovascular disease

Baseline characteristics	Total (n = 2,555)	Coexisting cardiovascular disease		p Value
		Yes (n = 640)	No (n = 1915)	
Demographics				
Mean age (SD), y	73.9 (13.0)	78.0 (10.0)	72.6 (13.6)	<0.001
Age ≥75 years	1,404 (55.0)	444 (69.4)	960 (50.1)	<0.001
Men	1,262 (49.4)	354 (55.3)	908 (47.4)	<0.001
Prior comorbidities				
Previous TIA	231 (9.0)	93 (14.5)	138 (7.2)	<0.001
Previous stroke	264 (10.3)	95 (14.8)	169 (8.8)	<0.001
Atrial fibrillation	522 (20.4)	204 (31.9)	318 (16.6)	<0.001
Hypertension	1,537 (60.1)	492 (76.9)	1,045 (54.6)	<0.001
Diabetes mellitus	357 (14.0)	156 (24.4)	201 (10.5)	<0.001
Hypercholesterolemia	782 (30.6)	334 (52.2)	448 (23.4)	<0.001
History of smoking ^a	1,416 (55.4)	403 (63.0)	1,013 (52.9)	<0.001
Current smoker ^a	361 (14.1)	64 (10.0)	297 (15.5)	<0.001
Family history of premature myocardial infarction ^b	224 (8.8)	86 (16.5)	138 (8.9)	<0.001
Renal insufficiency ^c	132 (5.2)	56 (8.8)	76 (4.0)	<0.001
TIA/stroke subtypes (TOAST classification)				
Large artery disease	280 (11.0)	85 (13.3)	195 (10.2)	0.03
Cardioembolic	669 (26.2)	226 (35.3)	443 (23.1)	<0.001
Small vessel disease	317 (12.4)	48 (7.5)	269 (14.0)	<0.001
Cryptogenic	811 (31.7)	140 (21.9)	671 (35.0)	<0.001
More than one cause	90 (3.5)	45 (7.0)	45 (2.3)	<0.001
Unknown	331 (13.0)	88 (13.8)	242 (12.6)	0.47
Other causes	57 (2.2)	8 (1.3)	49 (2.6)	0.05
Baseline therapies				
Antithrombotics	1,100 (43.1)	496 (77.5)	603 (31.5)	<0.001
Antihypertensives	1,486 (58.2)	530 (82.8)	956 (49.9)	<0.001
Statins	684 (26.8)	358 (55.9)	326 (17.0)	<0.001
Secondary prevention medication at 1-month follow-up^d				
Antithrombotics	n = 2,339	n = 559	n = 1,780	
Antithrombotics	2,196 (93.9)	522 (93.4)	1,673 (94.0)	0.60
Antihypertensives	1,771 (75.7)	482 (86.2)	1,288 (72.4)	<0.001
Statins	1,755 (75.0)	451 (80.7)	1,304 (73.3)	<0.001
Secondary prevention medication at 1-year follow-up^d				
Antithrombotics	n = 1,976	n = 458	n = 1,518	
Antithrombotics	1,884 (95.3)	437 (95.4)	1,447 (95.3)	0.85
Antihypertensives	1,572 (79.6)	398 (86.9)	1,174 (77.3)	<0.001

Continued

Table 1 Baseline characteristics in TIA or ischemic stroke patients, stratified by history of coexisting cardiovascular disease (continued)

Baseline characteristics	Total (n = 2,555)	Coexisting cardiovascular disease		p Value
		Yes (n = 640)	No (n = 1915)	
Statins	1,589 (80.4)	370 (80.8)	1,219 (80.3)	0.87

Abbreviation: TOAST = Trial of Org 10172 in Acute Stroke Treatment.

Data are n (%), unless otherwise specified. *p* For comparison between patients with and without coexisting cardiovascular disease (χ^2 test for categorical variables and *t* test for continuous variable).

^a Data missing for 7 patients.

^b Data missing for 476 patients.

^c Data missing for 13 patients.

^d Patients who died before the follow-up were not included.

cryptogenic stroke had the lowest 10-year risk of recurrent ischemic stroke (19.5%, 15.6–23.3, *p* < 0.001) and of coronary events compared to the other stroke subtypes (8.3%,

5.4–11.1, table 4, figure 2), but a relatively high 10-year risk of intracerebral hemorrhage (2.5%, 0.76–4.2, *p* = 0.26, table 4).

Table 2 Baseline characteristics in TIA or ischemic stroke patients stratified by TIA/stroke subtypes (Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification)

Baseline characteristics	Large artery disease (n = 280)	Cardioembolic (n = 669)	Small vessel disease (n = 317)	Cryptogenic (n = 811)	p Value
Demographics					
Mean (SD) age, y	73.3 (10.3)	77.9 (11.9)	69.7 (12.6)	70.3 (12.8)	<0.001
Age ≥75 years	137 (48.9)	469 (70.1)	121 (38.2)	346 (42.7)	<0.001
Men	172 (61.4)	306 (45.7)	182 (57.4)	402 (49.6)	<0.001
Prior comorbidities					
Coexisting cardiovascular disease	85 (30.6)	226 (33.8)	48 (15.1)	140 (17.3)	<0.001
Hypertension	198 (70.7)	454 (67.9)	183 (57.7)	419 (51.7)	<0.001
Diabetes mellitus	52 (18.6)	81 (12.1)	51 (16.1)	99 (12.2)	0.0172
Hypercholesterolemia	121 (43.2)	205 (30.6)	94 (29.7)	228 (28.1)	<0.001
History of smoking	183 (65.3)	348 (52.0)	197 (62.1)	443 (54.6)	<0.001
Baseline therapies					
Antithrombotics	106 (37.9)	427 (63.8)	101 (31.9)	273 (33.7)	<0.001
Antihypertensives	187 (66.8)	482 (72.0)	151 (47.6)	394 (48.6)	<0.001
Statins	102 (36.4)	191 (28.6)	70 (22.1)	205 (25.3)	0.03
Secondary prevention medication at 1-month follow-up^a					
Antithrombotics	263 (96.3)	520 (93.5)	307 (96.8)	769 (95.2)	0.22
Antihypertensives	224 (82.1)	446 (80.2)	258 (81.4)	589 (72.9)	<0.001
Statins	232 (85.0)	380 (68.3)	266 (83.9)	649 (80.3)	<0.001
Secondary prevention medication at 1-year follow-up^a					
Antithrombotics	239 (96.8)	411 (94.3)	292 (94.2)	719 (94.0)	0.53
Antihypertensives	213 (86.2)	359 (82.3)	246 (79.4)	573 (74.9)	<0.001
Statins	221 (78.9)	315 (72.2)	256 (82.6)	627 (82.0)	0.0011

Data are number (%), unless otherwise specified. *p* For comparison among all stroke subtypes (χ^2 test for categorical variables and one-way analysis of variance test for continuous variable).

^a Patients who died before the follow-up were not included.

Table 3 Ten-year risk of coronary events, recurrent ischemic stroke, major ischemic vascular events, intracerebral hemorrhage, and major extracranial bleeds after TIA/ischemic stroke in patients with vs without coexisting cardiovascular disease, stratified by age

Coexisting cardiovascular disease	Events, n/N		10-year risk, % (95% CI)		p Value	Crude HR (95% CI)	Age- and sex-adjusted HR (95% CI)	p Value
	Yes	No	Yes	No				
All patients								
Coronary events	80/640	78/1,915	22.83 (17.40–27.91)	7.06 (5.30–8.79)	<0.001	3.83 (2.81–5.21)	3.07 (2.24–4.21)	<0.001
Recurrent ischemic stroke	118/640	295/1,915	31.51 (25.10–37.37)	23.43 (20.49–26.25)	0.0049	1.36 (1.10–1.68)	1.23 (0.99–1.53)	0.06
Major ischemic vascular events	175/640	345/640	45.12 (38.44–51.07)	28.65 (25.28–31.86)	<0.001	1.76 (1.47–2.11)	1.56 (1.30–1.88)	<0.001
Intracerebral hemorrhage ^a	1/414	19/1,472	1.47 (0.00–4.29)	2.49 (0.97–3.99)	0.09	0.21 (0.03–1.54)	0.17 (0.02–1.26)	0.08
Major extracranial bleeds ^a	27/351	55/1,226	11.14 (6.56–15.50)	7.44 (5.09–9.74)	0.0050	1.91 (1.21–3.03)	1.58 (0.99–2.52)	0.06
Age <75 years								
Coronary events	23/196	23/955	16.69 (9.65–23.19)	3.78 (2.09–5.44)	<0.001	5.38 (3.06–9.48)	4.33 (2.42–7.73)	<0.001
Recurrent ischemic stroke	44/196	127/955	30.34 (21.43–38.25)	17.61 (14.34–20.74)	<0.001	1.87 (1.33–2.62)	1.74 (1.23–2.46)	0.0012
Major ischemic vascular events	59/196	141/955	39.68 (30.39–47.73)	20.96 (17.11–24.62)	<0.001	2.28 (1.69–3.09)	2.10 (1.54–2.87)	<0.001
Intracerebral hemorrhage ^a	1/150	8/801	2.27 (0.00–6.58)	2.23 (0.31–4.12)	0.66	0.63 (0.08–5.03)	0.36 (0.04–2.99)	0.41
Major extracranial bleeds ^a	9/126	16/653	8.07 (2.81–13.04)	3.45 (1.61–5.26)	0.0050	3.04 (1.34–6.88)	2.71 (1.16–6.30)	0.0209
Age ≥75 years								
Coronary events	57/444	55/960	27.99 (19.05–35.94)	12.44 (8.38–16.31)	<0.001	2.64 (1.83–3.82)	2.59 (1.79–3.77)	<0.001
Recurrent ischemic stroke	74/444	168/960	33.81 (23.47–42.76)	32.19 (26.42–37.51)	0.89	1.02 (0.78–1.34)	1.05 (0.80–1.38)	0.79
Major ischemic vascular events	116/444	204/960	50.66 (39.87–59.51)	39.69 (33.37–45.41)	0.0096	1.35 (1.08–1.70)	1.37 (1.09–1.73)	0.0063
Intracerebral hemorrhage ^a	0/264	11/671	0	2.49 (0.76–4.20)	0.0443	0.01 (0.00–100)	0.01 (0.00–100)	0.59
Major extracranial bleeds ^a	18/225	39/573	19.21 (3.88–32.10)	14.15 (8.01–19.87)	0.34	1.31 (0.75–2.29)	1.28 (0.73–2.56)	0.39

Abbreviations: CI = confidence interval; HR = hazard ratio.

Major ischemic vascular event was a component of coronary event or recurrent ischemic stroke. Information on coronary events, recurrent ischemic stroke, and intracerebral hemorrhage was available in cases recruited from April 1, 2002, to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was available in cases recruited from April 1, 2002, to March 31, 2012, with follow-up until March 31, 2013.

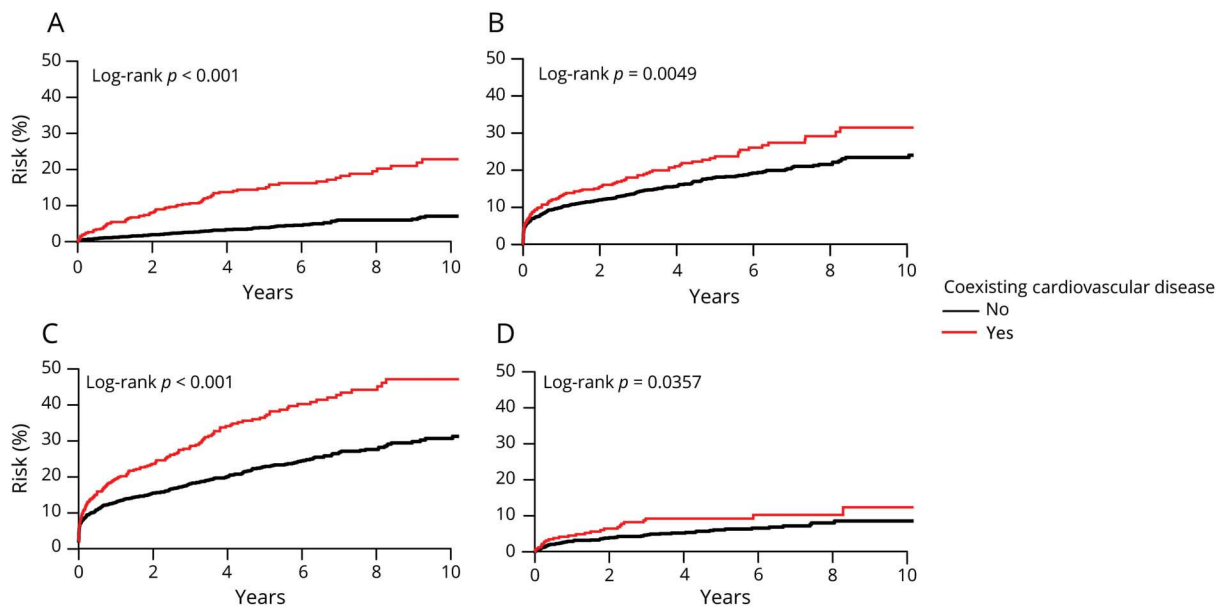
^a Patients with cardioembolic TIA/ischemic stroke and those on anticoagulants were excluded.

Discussion

In this population-based cohort of consecutive TIA/stroke patients on current standard management, those with coexisting cardiovascular disease were at significantly higher 10-year risk of coronary events and recurrent ischemic stroke than those without, particularly at age <75 years (16.7% vs 3.8% and 30.3% vs 17.6%, respectively). However, in younger patients with noncardioembolic TIA/

stroke (i.e., on antiplatelet therapy for secondary prevention), 10-year risk of major extracranial bleeds was also higher in those with coexisting cardiovascular disease (8.1% vs 3.5%), although there was no increased risk of intracerebral hemorrhage. More intensive lipid-lowering therefore might be justified in patients with coexisting cardiovascular disease, although economic evaluation of PCSK9 inhibitors in addition to statin therapy in similar patient populations suggests that treatment might still exceed the generally accepted cost-effectiveness

Figure 1 Risks of coronary events, recurrent ischemic stroke, major ischemic vascular events, and major bleeds after TIA or ischemic stroke, stratified by history of coexisting cardiovascular disease



(A) Coronary events. (B) Recurrent ischemic stroke. (C) Major ischemic vascular events. (D) Major bleeds. Major ischemic vascular event was a component of coronary event or recurrent ischemic stroke. Risk of major bleeds was calculated in noncardioembolic TIA or ischemic stroke patients and after exclusion of those on anticoagulants.

threshold,³² and there is probably still potential for more intensive treatment with statins and other lipid-lowering drugs. Benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding, particularly in older patients, in whom bleeds are more likely to be disabling or fatal.³³

We found that the subgroup of patients with large artery disease (TOAST classification) were at high risk of ischemic events, consistent with previous findings.^{34,35} However, the current absolute risk of ischemic events (10-year risk of coronary events of 16.1% and 10-year risk of recurrent ischemic stroke of 26.3%) was lower than previously reported (10-year

Table 4 Ten-year risk of coronary events, recurrent ischemic stroke, major ischemic vascular events, intracerebral hemorrhage, and major extracranial bleeds after TIA or ischemic stroke, stratified by stroke subtype

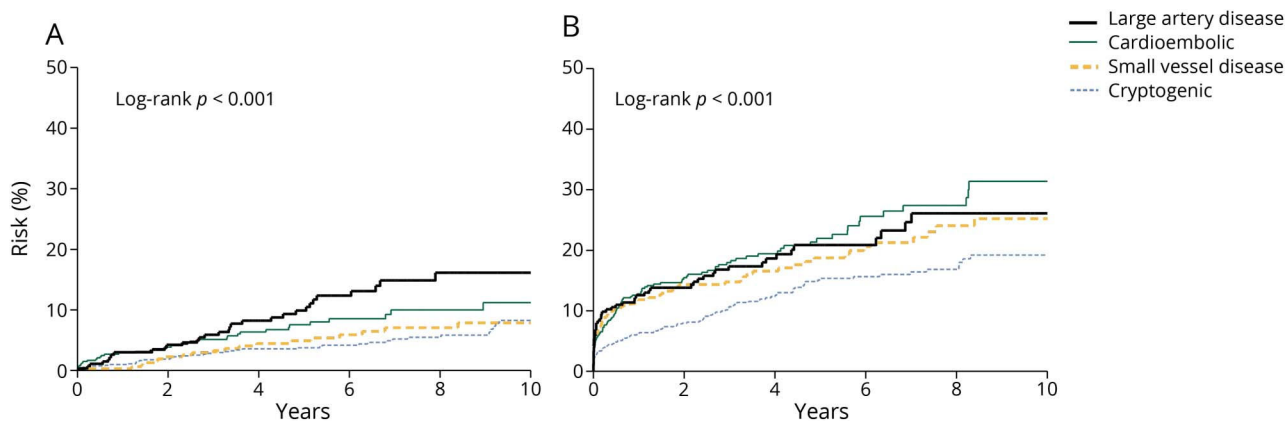
	Large artery disease (n = 280)		Cardioembolic (n = 669)		Small vessel disease (n = 317)		Cryptogenic (n = 811)		p Value
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
Coronary events	40	16.13 (10.28–21.60)	37	11.19 (6.91–15.27)	19	7.87 (4.22–11.38)	41	8.29 (5.38–11.11)	<0.001
Recurrent ischemic stroke	54	26.34 (18.89–33.11)	114	31.91 (24.76–38.38)	64	25.91 (19.47–31.84)	111	19.50 (15.57–23.25)	<0.001
Major ischemic vascular events	71	36.73 (28.18–44.26)	140	39.02 (31.35–45.84)	78	31.58 (24.82–37.74)	139	25.70 (20.87–30.23)	<0.001
Intracerebral hemorrhage^a	1	0.37 (0.00–1.09)	NA	NA	2	1.90 (0.00–4.85)	11	2.50 (0.76–4.21)	0.26
Major extracranial bleeds^a	11	11.09 (1.84–19.48)	NA	NA	16	7.65 (3.57–11.56)	31	7.31 (4.27–10.27)	0.85

Abbreviation: CI = confidence interval.

p Values are log-rank values. Major ischemic vascular event was a composite of recurrent ischemic stroke or coronary event. Information on coronary events, recurrent ischemic stroke, and intracerebral hemorrhage was available in cases recruited from April 1, 2002, to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was available in cases recruited from April 1, 2002, to March 31, 2012, with follow-up until March 31, 2013, including 235 patients with large artery disease, 277 with small vessel disease, and 669 with cryptogenic TIA/stroke.

^a Patients with cardioembolic TIA/ischemic stroke and those on anticoagulants were excluded.

Figure 2 Risks of coronary events and recurrent ischemic stroke after TIA or ischemic stroke, stratified by stroke subtype (Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification)

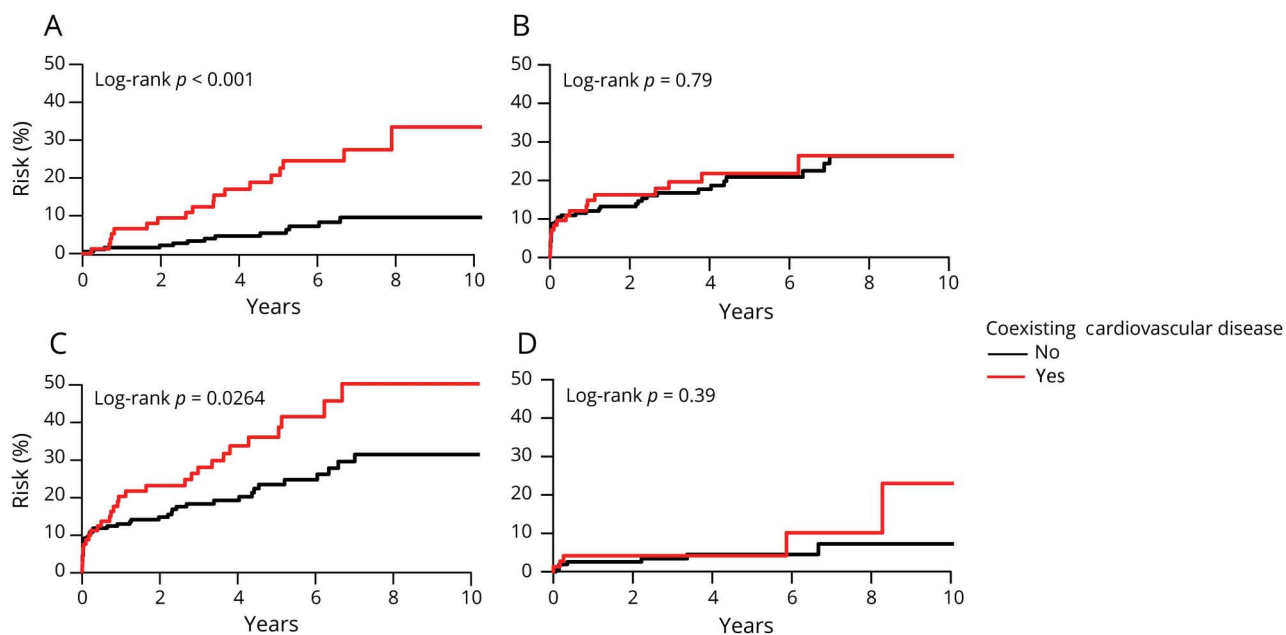


(A) Coronary events. (B) Recurrent ischemic stroke.

risk >20% and >30%, respectively).^{34,35} We also found that stratification by presence of coexisting cardiovascular disease identified individuals at higher risk of coronary events, with 10-year risk ranging from 9.5% in patients without coexisting cardiovascular disease to 33.5% in those with. The suggestion that carotid stenosis should be considered as a coronary heart disease equivalent (defined as 10-year risk $\geq 20\%$)³⁶³⁷ was based mainly on data from trials of endarterectomy performed in the 1980s and early 1990s, which reported risks of coronary

events of more than 20% over 10 years.^{34,35} The risk of MI after TIA/stroke has declined over time,² but only one recent study reported the risk in patients with TIA/stroke due to large artery disease, with an annual risk of 0.8%,³⁸ although prevalence of coronary artery disease was lower (11%) than in our cohort (30%) and mean follow-up was only 2.1 years. We found that most coronary events occurred in the subset of patients with large artery disease who had prior coexisting cardiovascular disease.

Figure 3 Risks of coronary events, recurrent ischemic stroke, major ischemic vascular events, and major bleeds after TIA or ischemic stroke due to large artery disease (Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification), stratified by history of coexisting cardiovascular disease



(A) Coronary events. (B) Recurrent ischemic stroke. (C) Major ischemic vascular events. (D) Major bleeds. Major ischemic vascular event was a component of coronary event or recurrent ischemic stroke. Risk of major bleeds was calculated in noncardioembolic TIA or ischemic stroke patients and after exclusion of those on anticoagulants.

We also found that patients with cryptogenic TIA/stroke, in whom the prevalence of coexisting cardiovascular disease was relatively low, had the lowest risk of coronary events or recurrent ischemic stroke, but a relatively high risk of intracerebral hemorrhage compared to the other non-cardioembolic subtypes. Patients with cryptogenic TIA/stroke were younger than those with other subtypes and had less hypertension and diabetes, which are known risk factors for intracerebral hemorrhage,^{21,39} and their higher risk of intracerebral hemorrhage remains difficult to explain. Notwithstanding the results of ongoing trials of anticoagulation vs antiplatelet treatment in patients with cryptogenic stroke,⁴⁰ future trials on more intensive antithrombotic management might focus on subgroups of TIA/stroke patients with a high risk of recurrent ischemic events and a lower risk of bleeding.

Hypertension is a strong predictor of intracerebral hemorrhage²¹ and blood pressure management in TIA/stroke patients significantly reduces the risk of intracerebral hemorrhage, with benefit increasing over time.⁴¹ The prevalence of history of hypertension was higher in patients with coexisting cardiovascular disease than in those without and the rates of use of antihypertensives at both baseline and 1 year were also higher, which might at least partly explain the relatively low risk of intracerebral hemorrhage in patients with coexisting cardiovascular disease.

Although we consider our findings to be valid, our study has limitations. First, our population consisted of a predominantly white British population, which will limit generalizability. Second, rates of use of secondary prevention medication were high, but were not 100%. However, our population-based cohort includes many frail and very elderly patients, often with dementia, prior gastrointestinal bleeding, or terminal illness, and some patients refuse medication for other reasons. Nevertheless, rates of medication use at 1 month and 1 year were higher than in the majority of other similar cohorts,^{42–45} and can be regarded as being based closely on current guidelines for secondary prevention. Third, although all hospital admissions for chest pain were reviewed, details were only collected for MI and we did not report information on angina pectoris. Indeed, data on angina are considered to be less reliable than those on MI because underdiagnosed angina is estimated to be common and not all patients with angina symptoms seek medical attention.⁴⁶ Finally, diagnosis of MI has evolved over the last 2 decades^{29,47} and so our findings may not be fully generalizable to future clinical practice. Similarly, those centers that use a DWI-based definition of TIA vs ischemic stroke may obtain higher estimate of recurrent stroke risk.

TIA/ischemic stroke patients with coexisting cardiovascular disease have a high risk of recurrent ischemic events on current standard management. More intensive lipid-lowering therefore might be justified, but benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding, particularly in older patients.

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Disclosure

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Nicola G. Lovett, MBBS	Centre for Prevention of Stroke and Dementia, University of Oxford, UK	Author	Collected the data
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Appendix 1 (continued)

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Appendix 2 Coinvestigators of the OXVASC study

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Appendix 2 (continued)

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Continued

Appendix 2 (continued)

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Appendix 2 (continued)

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Maria Drummond	Centre for Prevention of Stroke and Dementia, University of Oxford, UK	Administrative assistant	Involved in the follow-up of patients

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Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke

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SUPPLEMENTARY FILE**Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke**

Marion Boulanger, Linxin Li, Shane Lyons, Nicola G. Lovett, Magdalena M. Kubiak, Louise Silver, Emmanuel Touzé, Peter M. Rothwell, on behalf of the Oxford Vascular Study

Table e-1: Criteria for the modified TOAST classification for TIA or ischemic stroke etiology

Table e-2: Baseline characteristics of patients with non-cardioembolic TIA or ischemic stroke and after exclusion of those on anticoagulants, stratified by history of co-existing cardiovascular disease

Table e-3: 10-year risk of coronary events, recurrent ischemic stroke, major ischemic vascular events, intracerebral hemorrhage and major extracranial bleeds in the subgroup of patients with TIA or ischemic stroke due to large artery disease (TOAST classification), stratified by baseline history of co-existing cardiovascular disease

Figure e-1: Risk of coronary events in TIA or ischemic stroke patients stratified by history of coronary (CAD), peripheral artery disease (PAD) or age

Figure e-2: 5 year-risk of coronary events in TIA or ischemic stroke patients with and without history of coronary artery disease, stratified by number of atherosclerotic risk factors, history of peripheral artery disease (PAD) or TOAST subtypes

Figure e-3: Risk of recurrent ischemic strokes in TIA or ischemic stroke patients stratified by history of coronary (CAD), peripheral artery disease (PAD) or age

Appendix: Definition of major bleeding according to the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) criteria

Table e-1: Criteria for the modified TOAST classification for stroke etiology¹

TOAST subtypes	Definition
Large artery disease (LAD)	Imaging abnormality of atherosclerosis of intra or extracranial artery supplying the ischaemic field with either occlusive or stenosis ($\geq 50\%$ diameter reduction).
Small vessel disease (SVD)	Clinical lacunar syndromes with no cerebral cortical dysfunction and normal imaging; OR Imaging evidence of a relevant acute infarction < 20 mm within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery.
Cardioembolic (CE)	Major-risk cardioembolic source of embolism <ul style="list-style-type: none"> • Prosthetic cardiac valve • Mitral stenosis • Permanent or paroxysmal AF (> 30s) • Sustained atrial flutter • Intracardiac thrombus • Sick sinus syndrome • Recent myocardial infarction (< 4 weeks) • Atrial myxoma or other cardiac tumors • Infective endocarditis • Valvular vegetations • Congestive heart failure (Ejection fraction $< 30\%$) • PFO and concomitant PE or DVT or long-haul flight preceding the cerebrovascular event with clinical presentation of an embolic event
Unknown causes	The absence of diagnostic tests that, under the examiner's judgment, their presence would have been essential to uncover the underlying aetiology.
Other determined causes	The presence of a specific disease process that involves clinically appropriate brain arteries and disorders that bear a clear and close temporal or spatial relationship with the acute event. <ul style="list-style-type: none"> • Abnormalities of thrombosis and haemostasis • Arterial dissection • Acute disseminated intravascular coagulation • Clinically relevant aneurysm • Drug-induced event • Fibromuscular dysplasia • Hyperviscosity syndromes • Hypoperfusion syndromes • Iatrogenic causes • Meningitis • Migraine-induced event • Mitochondrial myopathy encephalopathy with lactic acidosis and stroke-like episodes • Moyamoya disease • Primary antiphospholipid antibody syndrome • Primary infection of the arterial wall • Segmental vasoconstriction or vasospasm • Sickle cell disease • Sneddon syndrome • Thrombotic thrombocytopenic purpura • Other
Severale causes	The presence of > 1 evident mechanism in which there is either probable evidence for each.
Cryptogenic	Patient who has had at least one type of brain imaging (CT/MR/autopsy), ECG and at least one type of vascular imaging (Carotid Doppler/MRA/CTA/DSA/TCD/autopsy) but no aetiology was identified.

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Table e-2: Baseline characteristics of patients with non-cardioembolic TIA or ischemic stroke and after exclusion of those on anticoagulants, stratified by history of co-existing cardiovascular disease

Baseline characteristics	Total (n=1886)	Co-existing cardiovascular disease		p
		Yes (n=414)	No (n=1472)	
Demographics				
Mean age (SD),years	72.5 (13.1)	76.9 (10.1)	71.2 (13.5)	<0.001
Age ≥ 75years	935 (49.6)	264 (63.8)	671 (45.6)	<0.001
Men	956 (50.7)	249 (60.1)	707 (48.0)	<0.001
Known comorbidities				
Previous TIA	158 (8.4)	60 (14.5)	98 (6.7)	<0.001
Previous stroke	173 (9.2)	58 (14.0)	115 (7.8)	<0.001
Atrial fibrillation	91 (4.8)	45 (10.9)	46 (3.1)	<0.001
Hypertension	1082 (57.4)	319 (77.1)	763 (51.8)	<0.001
Diabetes mellitus	276 (14.6)	163 (39.4)	113 (7.7)	<0.001
Hypercholesterolemia	577 (30.6)	231 (55.8)	346 (23.5)	<0.001
History of smoking*	1068 (56.6)	271 (65.5)	797 (54.1)	<0.001
Current smoker*	316 (16.8)	48 (11.6)	268 (18.2)	0.0019
Renal insufficiency‡	85 (4.5)	32 (7.7)	53 (3.6)	<0.001
TIA/stroke subtypes (TOAST classification)				
Large artery disease	280 (11.0)	85 (13.3)	195 (10.2)	0.03
Small vessel disease	317 (12.4)	48 (7.5)	269 (14.0)	<0.001
Cryptogenic	811 (31.7)	140 (21.9)	671 (35.0)	<0.001
More than one cause	90 (3.5)	45 (7.0)	45 (2.3)	<0.001
Unknown	331 (13.0)	88 (13.8)	242 (12.6)	0.47
Other causes	57 (2.2)	8 (1.3)	49 (2.6)	0.05
Baseline therapies				
Antithrombotics	673 (35.7)	310 (74.9)	363 (24.7)	<0.001
Antihypertensives	1004 (53.2)	333 (80.4)	671 (45.6)	<0.001
Statins	493 (26.1)	246 (59.4)	247 (16.8)	<0.001
Secondary prevention at 1-month follow-up§				
	n=1783	n=379	n=1404	
Antithrombotics	1676 (94.0)	356 (93.9)	1319 (93.9)	0.99
Antihypertensives	1325 (74.3)	325 (85.8)	999 (71.2)	<0.001
Statins	1375 (77.1)	308 (81.3)	1067 (76.0)	0.0359
Secondary prevention at 1-year follow-up§				
	n=1595	n=318	n=1277	
Antithrombotics	1474 (92.4)	299 (94.0)	1175 (92.0)	0.27
Antihypertensives	1213 (76.1)	274 (86.1)	939 (73.5)	<0.001
Statins	1274 (79.9)	258 (81.1)	1016 (79.6)	0.58

Data are numbers (%), unless otherwise specified. p for comparison between patients with and without stable cardiovascular disease (χ^2 test for categorical variables and t-test for continuous variable)

*data missing for 4 patients, ‡ data missing for 10 patients, § patients who died before the follow-up were not include

Table e-3: 10-year risk of coronary events, recurrent ischemic stroke, major ischemic vascular events, intracerebral hemorrhage and major extracranial bleeds in the subgroup of patients with TIA or ischemic stroke due to large artery disease (TOAST classification), stratified by baseline history of co-existing cardiovascular disease

Co-existing cardiovascular disease	Events, n/N		10-year risk, % (95%CI)		p	Crude HR (95%CI)	Age-and sex-adjusted HR (95%CI)	p
	Yes	No	Yes	No				
Coronary events	18/85	13/195	33.49 (15.91-47.39)	9.53 (4.18-14.57)	<0.001	3.98 (1.97-8.09)	3.39 (1.65-6.96)	<0.001
Recurrent ischemic stroke	17/85	37/195	26.4 (12.6-38.1)	26.3 (17.3-34.4)	0.79	1.08 (0.61-1.91)	1.02 (0.57-1.83)	0.94
Major ischemic vascular events	29/85	48/195	49.90 (31.39-63.41)	31.07 (21.30-39.62)	0.0264	1.70 (1.06-2.72)	1.53 (0.95-2.48)	0.08
Intracerebral hemorrhage*	0/85	1/195	0	0.53 (0.00-1.55)	0.51	0.01 (0.00-100)	0.01 (0.00-100)	0.59
Major extracranial bleeds*	5/75	6/160	22.98 (0.00-44.70)	6.61 (0.14-12.67)	0.27	1.94 (0.59-6.37)	1.66 (0.49-5.60)	0.41

HR: Hazard ratio. Major ischemic vascular event was a component of coronary event or recurrent ischemic stroke. *Patients with cardioembolic TIA/ischemic stroke and those on anticoagulants were excluded

Information on coronary events, recurrent ischemic stroke and intracerebral hemorrhage was available in cases recruited from April 1, 2002 to March 31, 2014, with follow-up until September 30, 2014. Information on major extracranial bleeds was only available in cases recruited from April 1, 2002 to March 31, 2012, with follow-up until March 31, 2013.

Figure e-1: Risk of coronary events in TIA or ischemic stroke patients stratified by history of coronary (CAD), peripheral artery disease (PAD) or age

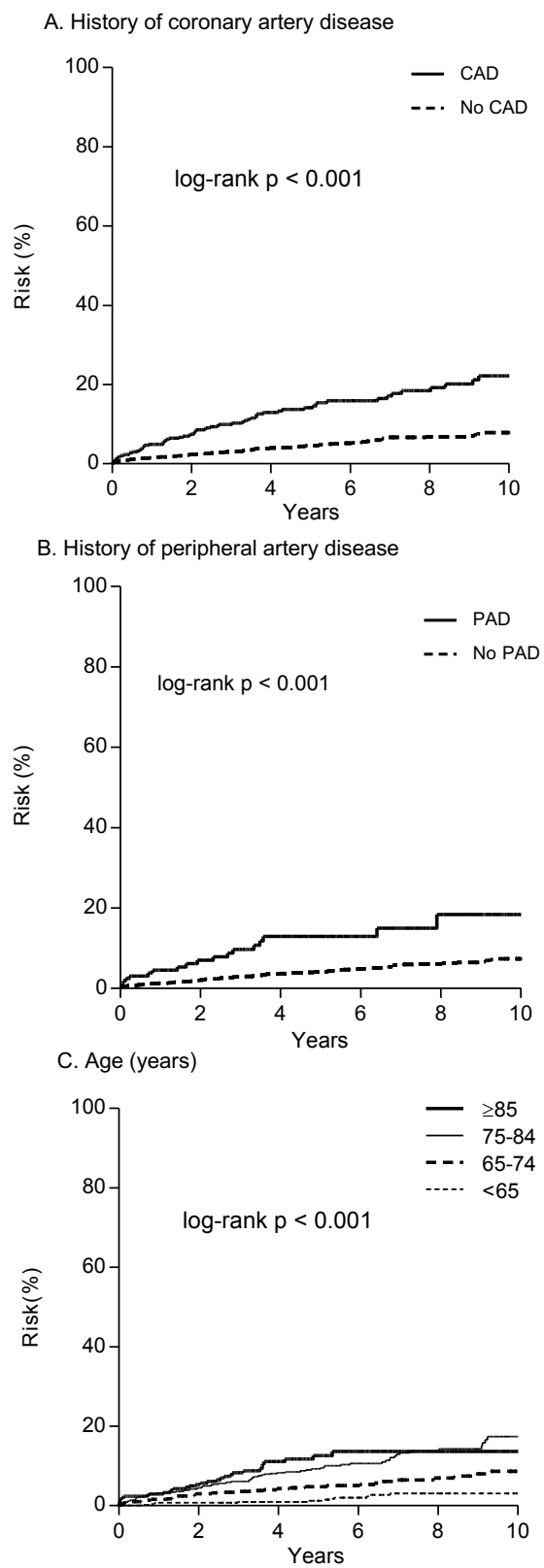
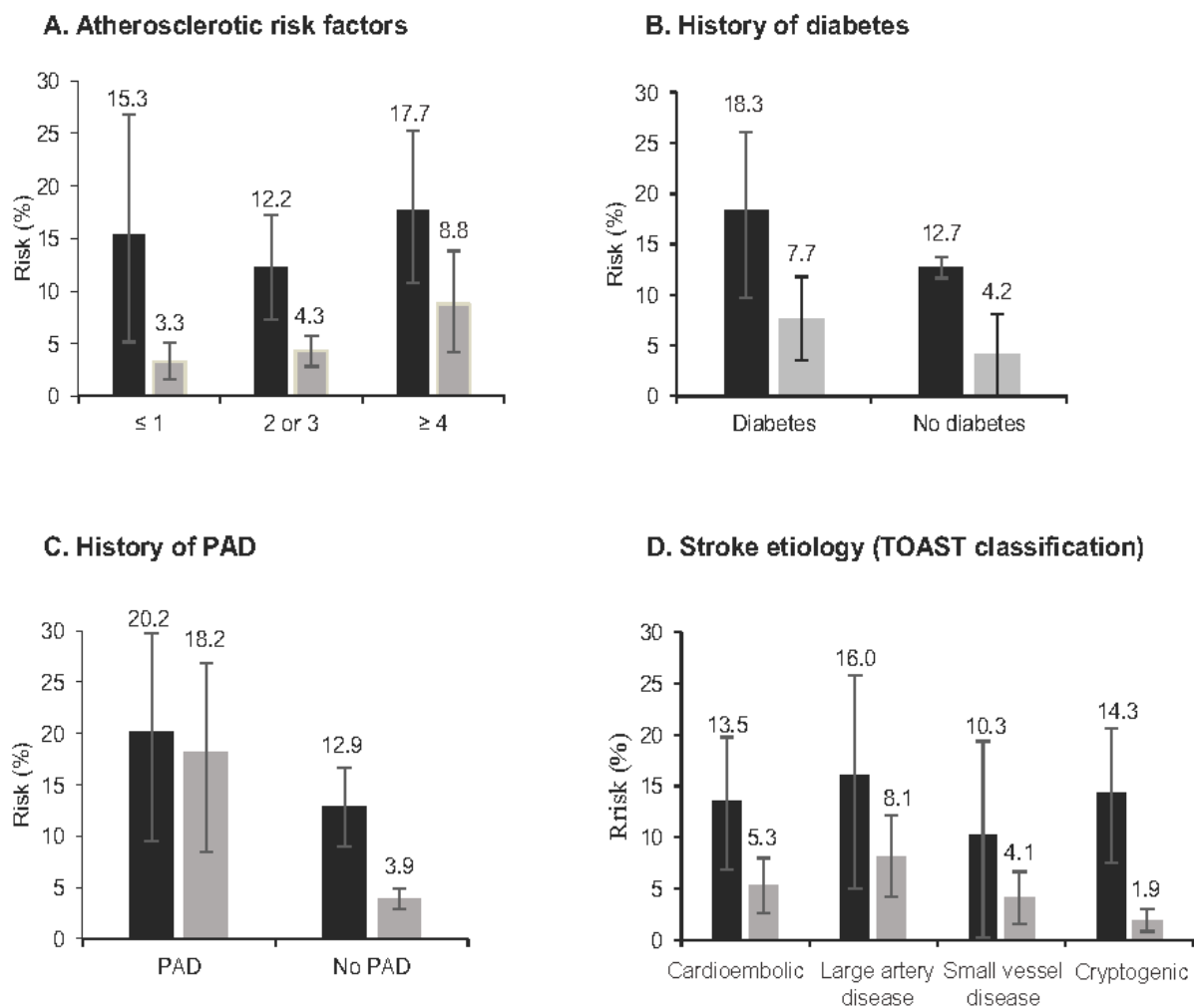


Figure e-2: 5 year-risk of coronary events in TIA or ischemic stroke patients with and without history of coronary artery disease, stratified by number of atherosclerotic risk factors, history of diabetes, history of peripheral artery disease (PAD) or TIA/stroke subtype

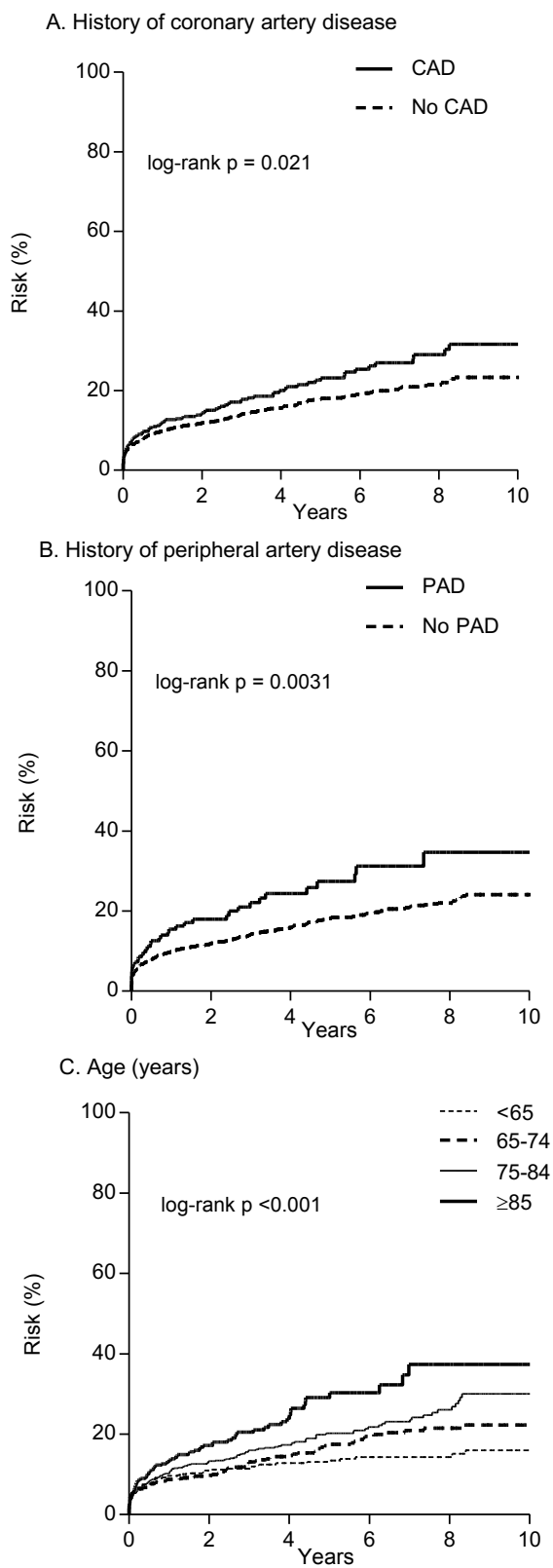
- History of coronary artery disease
- No history of coronary artery disease



Bars indicate 95% confidence intervals.

Atherosclerotic risk factors were male sex, history of hypertension, diabetes mellitus, hypercholesterolemia, smoking (i.e. ex or current smoker) and family history of premature myocardial infarction (defined as myocardial infarction occurring in a first-degree relative, siblings or parents, aged ≤55 years if male or aged ≤65 years if female). Data missing for number of atherosclerotic risk factors for 479 patients.

Figure e-3: Risk of recurrent ischemic strokes in TIA or ischemic stroke patients stratified by history of coronary artery disease (CAD), peripheral artery disease (PAD) or age



Appendix: Definition of major bleeding according to the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) criteria²

Major bleeding:

--Life-threatening:

-fatal

-symptomatic intracranial

-requiring surgical intervention

-resulting in substantial hypotension requiring the use of intravenous inotropic agents

-Hemoglobin decrease ≥ 5 g/dL or required ≥ 4 units of blood

--Other major bleeding: Transfusion of 2–3 units, intraocular

Non-major bleeding: Led to discontinuation of study drug

2. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494-502.

OPEN

Essen Risk Score in Prediction of Myocardial Infarction After Transient Ischemic Attack or Ischemic Stroke Without Prior Coronary Artery Disease

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Background and Purpose—More intensive secondary prevention with newer drugs may be cost-effective in patients with coronary artery disease (CAD). Whether some subgroups of patients who had a transient ischemic attack (TIA) or ischemic stroke, but no prior CAD are at similar high risk of myocardial infarction as those with prior CAD remains unclear. We determined whether the Essen score identified a subset of TIA/stroke patients without known prior CAD who, nevertheless, had a high risk of myocardial infarction on current secondary prevention management.

Methods—In a population-based cohort (Oxford Vascular Study) of consecutive TIA or ischemic stroke patients recruited from 2002 to 2014, 10-year actuarial risks of myocardial infarction and of recurrent ischemic stroke were determined by face-to-face follow-up in patients with and without prior CAD using Kaplan-Meier analyses. Predictive value of the Essen score was assessed with C statistic.

Results—Of 2555 patients with TIA/stroke (13 070 patient-years of follow-up), 10-year risk of myocardial infarction in those without prior CAD (n=2017, 78.9%) ranged from 0.9% (95% CI, 0–1.9) at Essen score ≤ 1 to 29.8% (95% CI, 7.7–46.6) in those with a score ≥ 5 (C statistic =0.64 [95% CI, 0.57–0.71] $P < 0.001$). The score tended to be less predictive (difference: $P = 0.0460$) for the risk of recurrent ischemic stroke (C statistic =0.57 [95% CI, 0.54–0.60]). Compared with patients with prior CAD (n=538, 21.1%), an Essen risk score of ≥ 4 (n=294, 11.5%) in those without prior CAD identified a subgroup at similar high 10-year risks of myocardial infarction (17.2% [95% CI, 6.9–26.3]; versus 16.9% [95% CI, 11.5–22.0]) and of recurrent stroke (40.4% [95% CI, 26.7–51.6]; versus 32.4% [95% CI, 25.2–38.8]).

Conclusions—The Essen score is a simple clinical score to risk-stratify patients with TIA/stroke without prior CAD and to identify subsets who may be at sufficiently high risk of myocardial infarction and recurrent stroke to justify more intensive treatment or inclusion in trials. (*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.119.025831.)

Key Words: coronary artery disease ■ myocardial infarction ■ risk ■ secondary prevention ■ transient ischemic attack

See related article, p XXX

The long-term risk of myocardial infarction (MI) and recurrent ischemic stroke after a transient ischemic attack (TIA) or ischemic stroke is particularly high in patients with prior coronary artery disease (CAD).^{1,2} Recent trials of more intensive secondary prevention, such as those of lipid-lowering with the PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitors^{3–5} or those combining antithrombotic treatments,⁶ focused on patients with prior CAD. However, whether some subgroups of patients with TIA/stroke without prior CAD have a similar high long-term risk of MI or recurrent ischemic stroke remains uncertain. Although the SPARCL trial⁷ showed

that higher dose of statin should be standard of care in patients with TIA/stroke, it is uncertain whether more intensive treatment might be justified in certain subgroups.

Long-term follow-up of patients with TIA/stroke has shown that the risks of death due to recurrent stroke and death due to coronary events are similar.¹ However, risk stratification schemes tend to focus on risk of recurrent stroke.^{8–13} Nevertheless, since risk scores to predict the risk of recurrent ischemic stroke are mostly based on risk factors for, or clinical manifestations of, atherosclerosis they may also predict coronary events. Therefore, rather than attempting to derive and validate a new score to predict coronary events after

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TIA/stroke, we determined the predictive value of the Essen stroke risk score for risk of MI after TIA/stroke. The Essen risk score is a simple clinical score that was derived to predict the 1-year risk of recurrent ischemic stroke after ischemic stroke based on the presence of prior vascular comorbidities, including current smoking, previous TIA or ischemic stroke, prior CAD, peripheral artery disease, hypertension, diabetes mellitus, and age and is one of the most established scores for patients with stroke.^{11,13}

The Essen score has been validated previously, but further validation would be helpful for several reasons. First, previous validations have looked only at short-term risk, predicting the 1-year risk of recurrent stroke,^{11,13–19} or the 1-year risk of the combined outcome of recurrent stroke, MI, and cardiovascular death^{14,17,19} or the 1-year risk of combined outcome of recurrent stroke or cardiovascular death.¹⁸ Second, the score was derived on patients recruited into a trial cohort in the early 1990s, and the validation cohorts involved patients recruited in trials or hospital-based registries, mostly in the early 2000s before the widespread use of higher-dose statins.⁷ The absolute risk of MI after TIA/stroke has decreased over the past few decades,¹ and there are relatively few recent data on the overall residual vascular risk in patients with TIA/stroke on current guideline-based management, particularly on long-term follow-up. Third, previous validation studies have focused mainly on patients with stroke due to large artery disease, have excluded patients with TIA, and have suggested that the score might perform less well in those with stroke due to small vessel disease.¹⁹ Finally, no study has looked at whether the score predicts risk of MI as well as stroke, and none have assessed predictive value in patients with no prior CAD.

We aimed to determine whether the Essen score identified a subset of patients with TIA/stroke without known prior CAD who nevertheless had a high risk of MI on current secondary prevention management and might, therefore, benefit from more intensive treatment or might be included in future trials.

Methods

Requests for anonymized data will be considered by the corresponding author.

The OXVASC (Oxford Vascular Study) is an ongoing population-based study of the incidence and outcome of all acute vascular events in 92 728 individuals, irrespective of age, registered with 100 family physicians in 9 general practices in Oxfordshire, United Kingdom.²⁰ The analysis reported here included consecutive cases, irrespective of age, with a TIA or ischemic stroke from 2002 to 2014, with follow-up until 2016. The OXVASC study design has been described in detail previously.²⁰ Briefly, multiple overlapping methods of hot and cold pursuit were used to achieve near-complete ascertainment of all individuals with TIA or stroke.^{21,22} These include (1) a daily, rapid access TIA and stroke clinic to which participating general practitioners and the local emergency department refer individuals with suspected TIA or minor stroke; (2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; (3) daily searches of the local emergency department attendance register; (4) daily searches of in-hospital death records via the Bereavement Office; (5) monthly searches of all death certificates and coroner's reports for out-of-hospital deaths; (6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; and (7) monthly searches of all brain and vascular imaging referrals.

Demographic data, prior comorbidities, and medication were collected from face-to-face interviews and cross-referenced with primary care records. All cases were investigated and treated according to current guidelines. Patients were classified as having a prior CAD if they had at least one of the following: previous MI; unstable angina; angina; previous percutaneous coronary intervention; or coronary artery bypass graft surgery. Written informed consent or assent from relatives was obtained in all patients. OXVASC was approved by our local research ethics committee.

Standard World Health Organization definitions were used for TIA and stroke, which have been reported previously.^{20,21} All cases were investigated according to current guidelines and reviewed by a senior neurologist with stroke expertise (P.M. Rothwell) to ensure consistency over time and TIA/stroke cause was categorized according to the modified TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria (Table 1 in the [online-only Data Supplement](#)).²³ Differentiation between TIA and stroke was based on the WHO 24-hour cutoff for symptom duration (ie, events were classified as TIA even if diffusion-weighted imaging was positive if symptoms resolved within 24 hours), and we have kept the same definition over time. Patients were prescribed standard secondary prevention medication according to contemporary guidelines, including antiplatelet or anticoagulant treatment, as appropriate, blood pressure-lowering medication and statin treatment to achieve a target of blood pressure <140/90 and LDL (low-density lipoprotein) <2.6 mmol/L, both at baseline and at the time of study follow-up visits.

All patients were followed up face-to-face at 1, 6, 12, 60, and 120 months by a study nurse or physician and subsequent vascular events identified and risk factor control evaluated and treatment revised as necessary. For patients who had moved out of the study area, telephone follow-up was done, and patients with dementia were followed up via a carer or by assessment in a nursing home. All MIs that presented to medical attention would also be identified by ongoing daily case-ascertainment of all acute vascular events in the study population. All study patients were also notified to the UK Office of National Statistics such that all deaths were reported back to the study with causes. Deaths were also identified by regular review of primary care records and by regular contact with the Coroner's Office to ascertain out-of-hospital deaths.

MI was defined using standard criteria and remained unchanged over the study period.²⁴ Recurrent ischemic stroke was defined as new neurological deficit fitting the definition for ischemic stroke occurring after a period of neurological stability or improvement.

Statistical Analysis

We determined the 10-year actuarial risk of MI and of recurrent ischemic stroke from Kaplan-Meier analyses in patients with TIA/stroke with and without prior CAD. Among the latter subgroup, we stratified risk by the Essen score but excluded the history of other cardiac disease (ie, cardiac disease other than MI or atrial fibrillation; Table 1) because this variable was not fully defined in previous reports.^{11,14,15} Essen scores in patients without prior CAD, therefore, ranged from 0 to 7: 1 point is attributed for age 65 to 75 years; 2 for age >75 years and 1 for each history of prior hypertension, diabetes mellitus, peripheral artery disease, current smoking, or previous TIA or ischemic stroke. A small number of patients with missing value on the Essen score were excluded from the analyses. Discrimination (ie, how well the score distinguished between people with the outcome and those without) was assessed with the C statistic. Difference in the discrimination of the score for the risk of MI and for the risk of recurrent ischemic stroke was assessed by a Z-test. Age- and sex-adjusted risk associations between variables of the Essen score and MI were determined by Cox regression. In additional analyses in patients without prior CAD, we determined the 10-year risk of MI or recurrent ischemic stroke based on the Essen score and stratified by presence of large artery disease (TOAST) subtype, which have been shown to carry one of the highest risks of MI and recurrent ischemic stroke,² and difference was assessed by log-rank *P*. Also, we determined the predictive value of adding the variable presence of large artery disease (TOAST) subtype as a categorical variable to the Essen

Table 1. The Essen Risk Score^{11,13}

Variables of the Essen Score	Points
Age, y	
<65	0
65–75	1
>75	2
History of hypertension	1
History of diabetes mellitus	1
History of peripheral artery disease	1
History of previous myocardial infarction	1
History of other cardiovascular disease (except myocardial infarction and atrial fibrillation)	1
Current smoking	1
Additional TIA or ischemic stroke in addition to the qualifying event (ie, previous TIA/ischemic stroke)	1

TIA indicates transient ischemic attack.

score for the risk of MI and of recurrent ischemic stroke, with 1 point being attributed for the presence of large artery disease subtype and 0 point for any other subtypes than large artery disease. All analyses were done using R version 3.1.3.

Results

Of 2555 patients with TIA/stroke, those without prior CAD (n=2017; 78.9%) were younger, had less prior vascular comorbidities, except for current smoking, and were less likely to be on antithrombotics, antihypertensives and statins before the TIA/stroke than those with prior CAD (P<0.001, Table 2). Rates of secondary preventive therapies use were high at 1-year follow-up, but rates of antithrombotics and antihypertensives use remained lower in patients without CAD than in those with (Table 2). The prevalence of TIA/stroke due to large artery disease was similar in patients with and without prior CAD, but TIA/stroke was less often due to cardioembolism in patients without CAD (Table 2).

During 13 070 patient-years of follow-up, there were 118 MIs after a median (range) of 5.6 (0–14.6) years, of which 70 (59.3%) occurred in patients without prior CAD. Five (0.2% of patients) had a missing value for one of the Essen score variables and were excluded from subsequent analyses. Among patients without prior CAD, those with an Essen score ≤1 comprised 565 (28.1%) of all patients but accounted for 3 (4.3%) of follow-up MI, whereas those with a score ≥4 comprised 14.6% (n=294) of all patients but accounted for 31.4% (n=22) of MI (Table 3). There were also 413 recurrent ischemic strokes during follow-up, of which 313 (75.7%) occurred among patients without prior CAD.

In patients without prior CAD, variables of the Essen score were all associated with an increased risk of MI after adjustment for age and sex (Table 4). The 10-year risk of MI in patients without prior CAD (overall risk =6.0% [95% CI, 4.4–7.5]) ranged from 0.9% (0–1.9) in those with an Essen score ≤1 to 29.8% (7.7–46.6) in those with a score ≥5 (Figure, Table 3), with a C statistic of 0.64 (0.57–0.71, P<0.001). Compared with patients with prior CAD (n=538, 21.1%), an Essen risk score of ≥4 (n=294, 11.5%) in those without prior CAD identified a

Table 2. Baseline Characteristics of OxVasc Patients With TIA or Stroke Included in the Analysis and Medication at Baseline and on Follow-Up

	Prior Coronary Artery Disease		P Value
	No (n=2017)	Yes (n=538)	
Mean (SD) age, y	72.7 (13.5)	78.4 (9.8)	<0.001
Men	971 (48.1)	291 (54.1)	0.0162
Prior comorbidities			
Previous TIA or ischemic stroke	248 (12.3)	101 (18.8)	<0.001
Atrial fibrillation	339 (16.8)	183 (34.0)	<0.001
Peripheral artery disease	103 (5.1)	88 (16.4)	<0.001
Hypertension	1128 (55.9)	409 (76.0)	<0.001
Diabetes mellitus	225 (11.2)	132 (24.5)	<0.001
Hypercholesterolemia	493 (24.4)	289 (53.7)	<0.001
Smoking status			
Present*	321 (15.9)	40 (7.4)	<0.001
Past†	771 (38.2)	282 (52.4)	<0.001
TIA/stroke subtype			
Cardioembolic	471 (23.3)	198 (36.8)	<0.001
Large artery disease	216 (10.7)	64 (11.9)	0.48
Small vessel disease	276 (13.7)	41 (7.6)	<0.001
Cryptogenic	689 (34.1)	122 (22.7)	<0.001
More than one cause	54 (2.7)	36 (6.7)	<0.001
Unknown	261 (12.9)	70 (13.0)	0.99
Other causes	50 (2.5)	7 (1.3)	0.14
Baseline medication			
Antithrombotics	659 (32.7)	441 (82.0)	<0.001
Antihypertensives	1027 (50.9)	459 (85.3)	<0.001
Statins	367 (18.2)	317 (58.9)	<0.001
Secondary prevention medication at 1-year follow-up‡			
Antithrombotics	1511 (92.2)	374 (95.4)	0.035
Antihypertensives	1228 (74.9)	344 (87.8)	<0.001
Statins	1279 (78.0)	310 (79.1)	0.70

Data are numbers (%), unless otherwise specified. P for comparison between patients with and without coronary artery disease (χ^2 test for categorical variables and t test for continuous variable). OxVasc indicates Oxford Vascular Study; and TIA, transient ischemic attack.

*Missing data for 7 patients (5 patients without prior CAD and 2 with prior CAD).

†Missing data for 9 patients (6 patients without prior CAD and 3 with prior CAD).

‡Patients who died before follow-up were not included.

subgroup at similarly high 10-year risk of MI (17.2%, 6.9–26.3; versus 16.9%, 11.5–22.0). The subgroup of patients without prior CAD with an Essen risk score of ≥4 were also at significantly higher 10-year risk of MI than those with a score of <3 (17.2%, 6.9–26.3 versus 4.7%, 3.2–6.2; P<0.001, age-and sex-adjusted hazard ratio =2.23, 1.32–3.76, Table 5, Table II in the [online-only Data Supplement](#)), with no interaction by TIA/

Table 3. Ten-Year Risks of Myocardial Infarction and Recurrent Ischemic Stroke After Transient Ischemic Attack or Ischemic Stroke in Patients Without Prior CAD, Stratified by the Essen Risk Score, and in Those With Prior CAD

Prior CAD Status	Myocardial Infarction		Recurrent Ischemic Stroke	
	Cumulative Events, n/N	10-Year Risk, % (95% CI)	Cumulative Events, n/N	10-Year Risk, % (95% CI)
All patients	118/2555	8.01 (6.38–9.61)	413/2555	25.25 (22.58–27.83)
Prior CAD	48/538	16.89 (11.49–21.96)	100/538	32.34 (25.20–38.80)
No prior CAD				
Essen score*				
≤1	3/565	0.89 (0–1.93)	52/565	11.15 (7.91–14.27)
2	18/577	5.60 (2.72–8.39)	98/577	24.10 (18.99–28.89)
3	27/576	9.25 (5.00–13.31)	107/576	32.12 (25.12–38.47)
4	14/240	15.59 (2.70–26.78)	43/240	40.95 (23.94–54.16)
≥5	8/54	29.82 (7.72–46.63)	13/54	39.51 (17.20–55.82)
Total	70/2012	5.97 (4.39–7.53)	313/2012	23.60 (20.73–26.37)

CAD indicates coronary artery disease.

*Data missing for 5 patients.

stroke subtype (P interaction =0.93). The risk of MI was approximately linear with time in patients with prior CAD and in those without (Figure I in the [online-only Data Supplement](#)).

The 10-year risk of recurrent ischemic stroke was 23.6% (20.7–26.4) overall in patients without prior CAD, ranging from 11.2% (7.9–14.3) in those with an Essen score ≤1 to 39.5% (17.2–55.8) in those with a score ≥5 (Figure, Table 3). The score tended to be less predictive (difference: $P=0.0460$) for the risk of recurrent ischemic stroke (C statistic =0.57, 0.54–0.60) than for the risk of MI.

An Essen risk score of ≥4 also identified a subgroup at similarly high 10-year risk of recurrent ischemic stroke to those with prior CAD (40.4%, 26.7–51.6; versus 32.4%, 25.2–38; Table 3). Although the risk of recurrent ischemic stroke increased with an increasing Essen score (Figure), the subgroup with an Essen risk score of ≥4 were not at significantly higher 10-year risk than those with an Essen risk score of <3 (40.4%, 26.7–51.6 versus 21.6%, 18.7–24.3, $P=0.0063$, age- and sex-adjusted hazard ratio =1.21, 0.90–1.63), with no interaction observed by TIA/stroke subtype (P -interaction=0.91, Table 5, Table II in the [online-only Data Supplement](#)). After

the early high risk-period, the risk of recurrent ischemic stroke was approximately linear with time in patients with prior CAD and in those without (Figure II in the [online-only Data Supplement](#)).

In patients without prior CAD, 10-year risk of MI or recurrent ischemic stroke increased with an increasing Essen score in patients with large artery disease (TOAST) subtype and in those without (Table III in the [online-only Data Supplement](#)). Ten-year risk of MI or recurrent ischemic stroke in the subgroup of patients with large artery disease subtype (overall risk =27.5%, 2.37–34.1) ranged from 15.6% (5.1–25.0) in those with an Essen score ≤1 to 74.6% (16.2–92.3) in those with a score ≥5 while 10-year risk in the subgroup of patients with other TIA/stroke subtypes than large artery disease (overall risk =24.3%, 21.5–26.9) ranged from 10.5% (7.5–13.4) in those with an Essen score ≤1 to 50.0% (23.8–67.1) in those with a score ≥5.

Compared with cryptogenic subtype, cardioembolism, large artery disease, and small vessel disease subtypes were all associated with a higher risk of MI and of recurrent ischemic stroke after adjustment for age and sex, and

Table 4. Variables of the Essen Score and Risk of Myocardial Infarction in Patients With TIA/Stroke Without Prior Coronary Artery Disease

Variables of the Essen Score	Events, n/N	Crude HR, (95% CI)	Age- and Sex-Adjusted, HR (95% CI)	P Value
Age (vs <65 y)				
65–75	20/544	4.08 (1.53–10.86)	4.08 (1.53–10.86)	0.0049
>75	45/977	7.63 (3.02–19.26)	7.66 (3.01–19.47)	<0.001
Hypertension	50/1128 vs 20/889	2.14 (1.28–3.60)	1.66 (1.00–2.80)	0.05
Diabetes mellitus	13/225 vs 57/1792	1.91 (1.05–3.49)	2.00 (1.09–3.66)	0.025
Peripheral artery disease	11/103 vs 59/1914	4.49 (2.36–8.55)	3.93 (2.05–7.52)	<0.001
Current smoking*	17/321 vs 53/1691	1.48 (0.86–2.55)	3.27 (1.82–5.88)	<0.001
Prior TIA/ischemic stroke	15/248 vs 55/1769	2.13 (1.20–3.77)	1.66 (0.94–2.96)	0.08

HR indicates hazard ratio; and TIA, transient ischemic attack.

*Data missing for 5 patients.

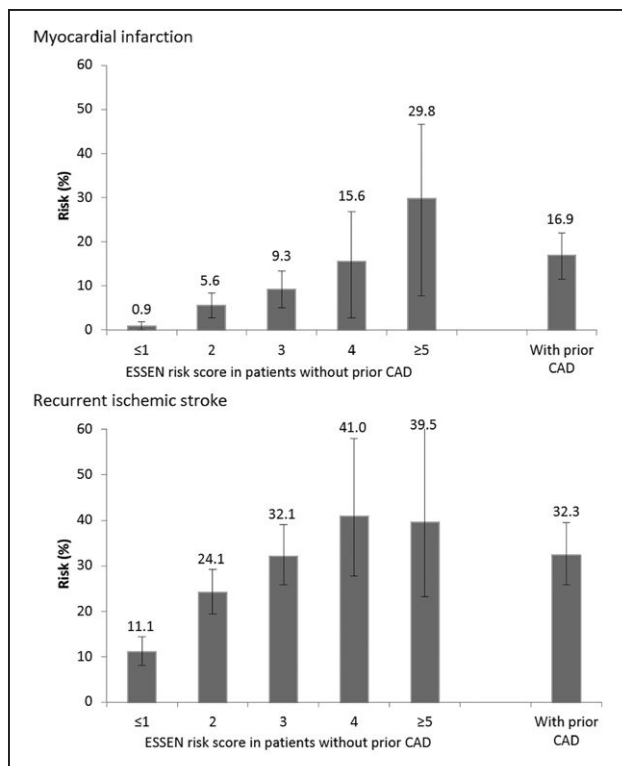


Figure. Ten-year actuarial risk of myocardial infarction and of recurrent ischemic stroke in transient ischemic attack/stroke patients based on the presence of prior coronary artery disease (CAD) and the Essen score.

the associations remained unchanged after further adjustment for the Essen score (Table IV in the [online-only Data Supplement](#)).

Adding the variable presence of large artery disease (TOAST) subtype as a categorical variable to the Essen score did not significantly increase the predictive value of the score for the risk of MI (C statistic =0.74, 0.57–0.71, Tables V and VI in the [online-only Data Supplement](#)) and of recurrent ischemic stroke (C statistic =0.58, 0.54–0.60).

Information on antithrombotic therapy at the time of the follow-up MI was available for 102 of the 118 patients with MI (87 on antiplatelet therapy only and 15 on anticoagulant therapy). Antithrombotic therapy had been withdrawn within 30 days of the MI in 7 (7%) patients (3 for bleeding and 4 for surgery, Table VII in the [online-only Data Supplement](#)). None of these 7 patients had prior CAD, but the MI was fatal in 5 cases.

Discussion

In this population-based cohort of consecutive patients with TIA or ischemic stroke on current secondary prevention management, the Essen score risk-stratified individuals without prior CAD for the risk of follow-up MI and of recurrent ischemic stroke. An Essen score of ≥ 4 in those without prior CAD identified a subgroup at similarly high 10-year risk of MI to those with prior CAD and of recurrent ischemic stroke. Thus, in addition to the 538 patients with known prior CAD, an Essen risk score of ≥ 4 identified a further 257 patients with high-risk TIA/stroke. Since trials of more intensive secondary prevention have reported significant reductions in the risk of recurrent ischemic events in patients with prior CAD,^{3–6} trials of such treatment might also be justified in high-risk patients without prior CAD.

The Essen score was previously shown to predict the 1-year risk of recurrent ischemic stroke in patients with TIA/stroke due to large artery disease,^{10,12–15} but we have shown predictive value in a broader range of patients with longer follow-up. We also showed that the score predicted risk of MI better than recurrent stroke, perhaps because all patients already had established cerebrovascular disease, and so discrimination for stroke risk was more difficult. We found a 2-fold increase in the risk of MI and a 20% rise in the risk of recurrent ischemic stroke in patients with Essen score of ≥ 4 compared with those with a score of < 4 . We also found that the predictive value of the score was similar for patients with different TIA/stroke TOAST subtypes, although larger studies would be required to confirm this finding. In patients with TIA/stroke without prior CAD, a few scores have been shown to predict the presence of asymptomatic coronary lesions (PRECORIS score [Predicting Asymptomatic Coronary Artery Disease in Patients With Ischemic Stroke and Transient Ischemic Attack])^{25,26} or the risk of MI (Framingham score).²⁷ However, these scores involved patients recruited in trials or hospital-based cohorts, with more potential selective biases than population-based cohorts, and only looked at the short-term risk and their clinical utility for predicting the long-term risk is unknown. A high Essen risk score in patients with TIA/stroke without prior CAD identified subgroups at substantially high risk of follow-up MI. However, whether these individuals should be screened for asymptomatic coronary lesions is unclear.

No study has assessed whether coronary revascularisation in patients with TIA/stroke screened for asymptomatic CAD might reduce future cardiac events.

Table 5. Stratification by Essen Score of ≥ 4 Versus < 4 and Risk of Myocardial Infarction and of Recurrent Ischemic Stroke in Patients With TIA/Stroke Without Prior Coronary Artery Disease

Essen Score*	Events, n/N		10-Year Risk, % (95% CI)		P Value	Crude HR, (95% CI)	Age- and Sex-Adjusted HR, (95% CI)	P Value
	< 4	≥ 4	< 4	≥ 4				
Follow-up events								
Myocardial infarction	48/1718	22/294	4.71 (3.22–6.17)	17.19 (6.92–26.32)	< 0.001	3.60 (2.17–5.97)	2.23 (1.32–3.76)	0.0028
Recurrent ischemic stroke	257/1718	56/294	21.55 (18.70–24.30)	40.42 (26.67–51.59)	0.0063	1.49 (1.12–1.98)	1.21 (0.90–1.63)	0.21

HR indicates hazard ratio; and TIA, transient ischemic attack. P for comparison between Essen Score ≥ 4 versus < 4 .

*Data missing for 5 patients.

Although we consider our findings to be valid, our study has limitations. First, our cohort was predominantly made up of white patients, which might limit generalisability. Second, although we aimed for very high rates of secondary prevention, our population-based cohort included many frail and very elderly patients, often with dementia, prior bleeding, or terminal illness, and some patients refused medication, or it was contraindicated for other reasons. However, 1-year medication rates were higher than in other similar cohorts,^{28–31} and can be regarded as being based closely on current guidelines for secondary prevention. We also showed that very few MIs were accounted for by discontinuation of antithrombotic therapy. Third, in our cohort, baseline characteristics were well-defined, and although we make recommendations to primary care physicians about changes to risk factors and medication at study follow-up visits, we have limited information on the control of vascular risk factors during the whole follow-up. Fourth, we excluded the other cardiovascular disease variable from our analysis of the Essen score due to a lack of clarity of what conditions and what severity of disease are required to satisfy the definition.¹⁰ However, this omission is likely to have reduced predictive value, and so our findings are probably somewhat conservative. The C statistics of the score were of moderate predictive value for the risk of MI and of recurrent ischemic stroke, however, in certain clinical situations, the score would still provide clinically important information. In the subgroups of patients with TIA/stroke without prior CAD and with a score of ≥ 4 , 10-year risk of MI was 17%, and 10-year risk of recurrent ischemic stroke was 40%, which was as high as in patients with prior CAD.

In conclusion, the Essen score is a simple clinical score to risk-stratify patients with TIA/stroke without prior CAD, and to identify patients who may be at sufficiently high risk of MI and recurrent stroke to justify more intensive treatment or inclusion in trials.

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Disclosures

None.

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Stroke

Essen risk score in prediction of myocardial infarction after TIA or ischemic stroke without prior coronary artery disease

SUPPLEMENTAL MATERIAL

Supplemental Table I: Criteria for the modified TOAST classification for stroke

Supplemental Table II: Stratification by Essen score of ≥ 4 versus < 4 and risk of myocardial infarction and of recurrent ischemic stroke in TIA/stroke patients without prior coronary artery disease, stratified by TIA/stroke subtype (TOAST classification)

Supplemental Table III: 10-year risk of myocardial infarction or recurrent ischemic stroke after TIA or ischemic stroke based on presence of large artery disease (TOAST) subtype in patients without prior coronary artery disease (CAD), stratified by the Essen risk score, and in those with prior CAD

Supplemental Table IV: Association between TIA/stroke subtype (TOAST classification) and risk of myocardial infarction and of recurrent ischemic stroke in TIA or recurrent ischemic stroke patients without prior coronary artery disease

Supplemental Table V: 10-year risk of myocardial infarction and of recurrent ischemic stroke after TIA or ischemic stroke in patients without prior coronary artery disease (CAD), stratified by the modified Essen risk score (after adding the variable "presence of large artery disease TIA/Stroke subtype" to the score), and in those with prior CAD

Supplemental Table VI: Stratification by modified Essen score (after adding the variable "presence of large artery disease subtype" to the score) of ≥ 4 versus < 4 and risk of myocardial infarction and of recurrent ischemic stroke in TIA/stroke patients without prior coronary artery disease

Supplemental Table VII: Characteristics of the seven TIA or ischemic stroke patients who experienced a myocardial infarction (MI) during follow-up after withdrawal of antithrombotic therapy

Supplemental Figure I: Risk of follow-up myocardial infarction in TIA or ischemic stroke patients stratified by presence of prior coronary artery disease (CAD)

Supplemental Figure II: Risk of recurrent ischemic strokes in TIA or ischemic stroke patients stratified by presence of prior coronary artery disease (CAD)

Supplemental Table I: Criteria for the modified TOAST classification for stroke etiology¹

TOAST subtypes	Definition
Large artery disease (LAD)	Imaging abnormality of atherosclerosis of intra or extracranial artery supplying the ischemic field with either occlusive or stenosis ($\geq 50\%$ diameter reduction).
Small vessel disease (SVD)	Clinical lacunar syndromes with no cerebral cortical dysfunction and normal imaging; OR Imaging evidence of a relevant acute infarction < 20 mm within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery.
Cardioembolic (CE)	Major-risk cardioembolic source of embolism <ul style="list-style-type: none"> • Prosthetic cardiac valve • Mitral stenosis • Permanent or paroxysmal AF (> 30s) • Sustained atrial flutter • Intracardiac thrombus • Sick sinus syndrome • Recent myocardial infarction (< 4 weeks) • Atrial myxoma or other cardiac tumors • Infective endocarditis • Valvular vegetations • Congestive heart failure (Ejection fraction $< 30\%$) • PFO and concomitant PE or DVT or long-haul flight preceding the cerebrovascular event with clinical presentation of an embolic event
Unknown causes	The absence of diagnostic tests that, under the examiner's judgment, their presence would have been essential to uncover the underlying etiology.
Other determined causes	The presence of a specific disease process that involves clinically appropriate brain arteries and disorders that bear a clear and close temporal or spatial relationship with the acute event. <ul style="list-style-type: none"> • Abnormalities of thrombosis and hemostasis • Arterial dissection • Acute disseminated intravascular coagulation • Clinically relevant aneurysm • Drug-induced event • Fibromuscular dysplasia • Hyperviscosity syndromes • Hypoperfusion syndromes • Iatrogenic causes • Meningitis • Migraine-induced event • Mitochondrial myopathy encephalopathy with lactic acidosis and stroke-like episodes • Moyamoya disease • Primary antiphospholipid antibody syndrome • Primary infection of the arterial wall • Segmental vasoconstriction or vasospasm • Sickle cell disease • Sneddon syndrome • Thrombotic thrombocytopenic purpura • Other
Several causes	The presence of > 1 evident mechanism in which there is either probable evidence for each.
Cryptogenic	Patient who has had at least one type of brain imaging (CT/MR/autopsy), ECG and at least one type of vascular imaging (Carotid Doppler/MRA/CTA/DSA/TCD/autopsy) but no etiology was identified.

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Supplemental Table II: Stratification by Essen score of ≥ 4 versus < 4 and risk of myocardial infarction and of recurrent ischemic stroke in TIA/stroke patients without prior coronary artery disease, stratified by TIA/stroke subtype (TOAST classification)

Essen score*	10-year risk, % (95% CI)		p	Crude Hazard Ratio (95%CI)	Age- and sex-adjusted Hazard Ratio (95%CI)	p
	<4	≥ 4				
All patients						
Myocardial infarction	4.71 (3.22-6.17)	17.19 (6.92-26.32)	<0.001	3.60 (2.17-5.97)	2.23 (1.32-3.76)	0.0028
Recurrent ischemic stroke	21.55 (18.70-24.30)	40.42 (26.67-51.59)	0.0063	1.49 (1.12-1.98)	1.21 (0.90-1.63)	0.21
Stroke subtypes				<i>p</i> -interaction=0.93 for myocardial infarction <i>p</i> -interaction=0.91 for recurrent ischemic stroke		
Cardioembolic						
Myocardial infarction	7.10 (1.88-12.04)	8.23 (0-18.60)	0.45	1.61 (0.45-5.73)	1.09 (0.30-3.98)	0.90
Recurrent ischemic stroke	29.10 (20.26-36.97)	35.65 (13.31-52.23)	0.22	1.42 (0.81-2.50)	1.07 (0.60-1.89)	0.81
Large artery disease						
Myocardial infarction	7.39 (1.90-12.57)	28.56 (10.29-43.10)	<0.001	7.55 (2.87-19.86)	5.69 (1.81-17.88)	0.0029
Recurrent ischemic stroke	21.61 (12.81-29.52)	47.97 (22.74-64.96)	0.0014	2.74 (1.44-5.23)	2.90 (1.40-60.2)	0.0043
Small vessel disease						
Myocardial infarction	4.36 (1.24-7.39)	19.72 (0-35.91)	0.0014	5.72 (1.71-19.19)	3.57 (0.92-13.92)	0.06
Recurrent ischemic stroke	22.18 (15.43-28.39)	51.73 (0-79.95)	0.93	0.96 (0.38-2.41)	1.01 (0.38-2.66)	0.90
Cryptogenic						
Myocardial infarction	2.78 (0.92-4.61)	11.10 (0-24.14)	0.17	2.38 (0.66-8.54)	1.16 (0.32-4.20)	0.82
Recurrent ischemic stroke	15.40 (11.78-18.87)	37.51 (15.38-53.86)	0.0440	1.73 (1.01-2.97)	1.31 (0.74-2.29)	0.35

*Data on Essen score missing in 5 patients. *p*-interaction between the TIA/stroke subtypes

Supplemental Table III: 10-year risk of myocardial infarction or recurrent ischemic stroke after TIA or ischemic stroke based on presence of large artery disease (TOAST) subtype in patients without prior coronary artery disease (CAD), stratified by the Essen risk score, and in those with prior CAD

Prior CAD status	Large artery disease TIA/stroke subtype		All other TIA/stroke subtypes	
	Cumulative events, n/N	10-year risk, % (95% CI)	Cumulative events, n/N	10-year risk, % (95% CI)
No prior CAD				
Essen score*:				
≤1	8/52	15.62 (5.06-25.00)	47/513	10.48 (7.45-13.42)
2	13/62	25.20 (11.50-36.79)	97/514	24.91 (19.85-29.65)
3	11/62	23.46 (8.68-35.86)	116/514	35.50 (28.62-41.72)
4	13/31	48.09 (22.66-65.16)	39/209	41.60 (24.71-54.70)
≥5	6/9	74.60 (16.20-92.30)	14/45	49.97 (23.80-67.15)
Total	51/216	27.54 (20.37-34.08)	313/1795	24.27 (21.52-26.94)
Prior CAD	19/64	39.50 (22.41-52.82)	116/473	38.25 (31.28-44.50)

CI: confidence interval, *data missing for 5 patients

All other TIA/stroke subtypes include cardioembolism, small vessel disease, cryptogenic, more than one cause, unknown and other causes

Supplemental Table IV: Association between TIA/stroke subtype (TOAST classification) and risk of myocardial infarction and of recurrent ischemic stroke in TIA or recurrent ischemic stroke patients without prior coronary artery disease

TIA/stroke subtype	Crude Hazard Ratio (95%CI)	Age-and sex-adjusted Hazard Ratio (95%CI)	Age-, sex- and Essen score-adjusted Hazard Ratio (95%CI)	p
Cardioembolic				
Myocardial infarction	2.52 (1.21-5.24)	1.95 (0.93-4.08)	1.97 (0.94-4.13)	0.07
Recurrent ischemic stroke	1.97 (0.94-4.13)	1.64 (1.20-2.23)	1.60 (1.18-2.18)	0.0028
Large artery disease				
Myocardial infarction	4.37 (2.15-8.87)	4.07 (2.00-8.29)	3.58 (1.76-7.30)	<0.001
Recurrent ischemic stroke	3.58 (1.76-7.30)	1.66 (1.15-2.40)	1.55 (1.08-2.24)	0.0186
Small vessel disease				
Myocardial infarction	2.11 (0.98-5.46)	2.19 (1.01-4.75)	2.13 (1.00-4.61)	0.05
Recurrent ischemic stroke	2.13 (0.98-4.61)	1.43 (1.01-2.02)	1.38 (0.98-1.95)	0.06
Cryptogenic	1 (reference)	1 (reference)	1 (reference)	-

CI: confidence interval

Supplemental Table V: 10-year risk of myocardial infarction and of recurrent ischemic stroke after TIA or ischemic stroke in patients without prior coronary artery disease (CAD), stratified by the modified Essen risk score (after adding the variable “presence of large artery disease TIA/Stroke subtype” to the score), and in those with prior CAD

Prior CAD status	Myocardial infarction		Recurrent ischemic stroke	
	Cumulative events, n/N	10-year risk, % (95% CI)	Cumulative events, n/N	10-year risk, % (95% CI)
No prior CAD				
Modified Essen score*:				
≤1	3/522	0.96 (0-2.08)	44/522	10.46 (7.12-13.68)
2	14/557	4.45 (1.77-7.06)	95/557	23.58 (18.55-28.31)
3	27/576	9.16 (5.12-13.04)	109/576	32.18 (25.24-38.47)
4	13/271	12.75 (3.41-21.19)	40/271	33.19 (20.26-44.02)
≥5	13/86	24.62 (10.74-36.34)	25/86	45.04 (27.02-58.62)
Total	70/2012	5.97 (4.39-7.53)	313/2012	23.60 (20.73-26.37)
Prior CAD	48/538	16.89 (11.49-21.96)	100/538	32.34 (25.20-38.80)

CI: confidence interval, *data missing for 5 patients.

Modified Essen score in patients without prior CAD ranged from 0 to 8: 1 point is attributed for age 65-75 years; 2 for age >75 years and 1 for each history of prior hypertension, diabetes mellitus, peripheral artery disease, current smoking or previous TIA or ischemic stroke; and 1 point for presence of large artery disease (TOAST) subtype.

In TIA/stroke patients without prior CAD, the c-statistic score of the modified Essen score was 0.74 (95%CI 0.68-0.79) for the risk of myocardial infarction and 0.58 (95%CI 0.54-0.60) for the risk of recurrent ischemic stroke.

Supplemental Table VI: Stratification by modified Essen score (after adding the variable “presence of large artery disease subtype” to the score) of ≥ 4 versus < 4 and risk of myocardial infarction and of recurrent ischemic stroke in TIA/stroke patients without prior coronary artery disease

Modified Essen score*	Events, n/N		10-year risk, % (95% CI)		p	Crude HR (95%CI)	Age- and sex-adjusted HR (95%CI)	p
	<4	≥ 4	<4	≥ 4				
Follow-up events:								
Myocardial infarction	44/1655	26/357	4.46 (2.99-5.90)	15.67 (7.75-22.92)	<0.001	3.49 (2.15-5.68)	2.21 (1.33-3.65)	0.0020
Recurrent ischemic stroke	248/1655	65/357	21.50 (18.60-24.29)	36.37 (25.59-45.60)	0.0146	1.40 (1.07-1.83)	1.44 (0.87-1.51)	0.34

CI: confidence interval, *data missing for 5 patients. HR: hazard ratio, p for comparison between modified Essen score ≥ 4 versus < 4 .

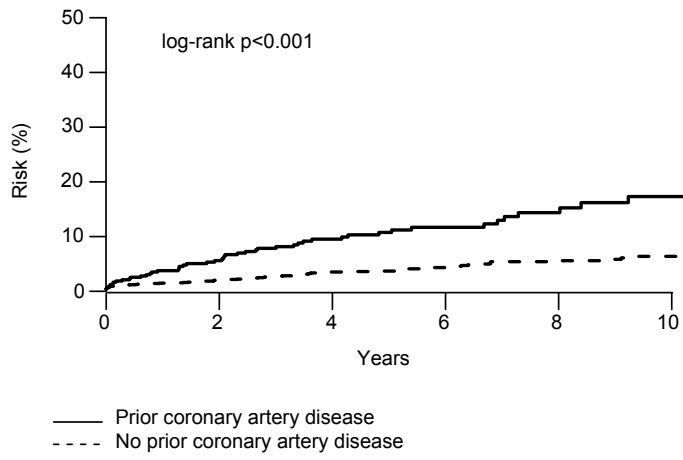
Modified Essen scores in patients without prior CAD ranged from 0 to 8: 1 point is attributed for age 65-75 years; 2 for age > 75 years and 1 for each history of prior hypertension, diabetes mellitus, peripheral artery disease, current smoking or previous TIA or ischaemic stroke; and 1 point for presence of large artery disease (TOAST) subtype.

Supplemental Table VII: Characteristics of the seven TIA or ischemic stroke patients who experienced a myocardial infarction (MI) during follow-up after withdrawal of antithrombotic therapy

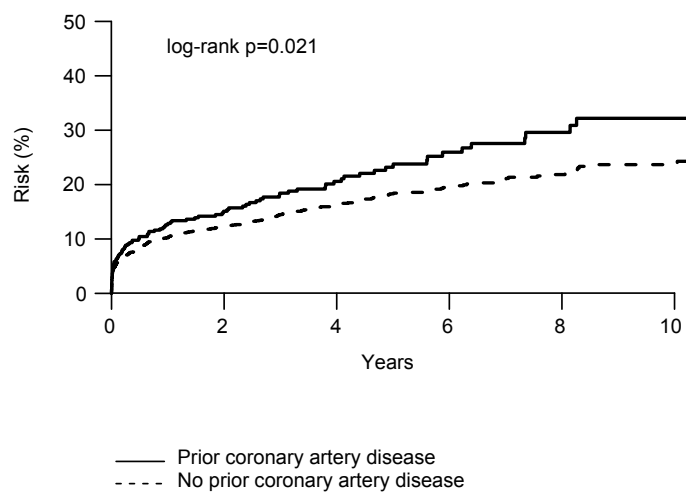
Sex	Age (years)	CAD	PAD	HTN	DM	Previous TIA/IS	Current smoking	Essen score	TIA/stroke subtype	Antithrombotic drug used prior to the MI	Reason for withdrawal of antithrombotic drug	Date (type) of stroke	Date (type) of MI	Date (cause) of death
F	71	No	No	Yes	No	Yes	No	3	CE	Aspirin	Surgery	10/08/02 (TIA)	12/08/02 (N-STEMI)	No
F	92	No	No	Yes	Yes	Yes	No	5	SVD	Aspirin	Bleeding	27/08/02 (IS)	09/03/05 (STEMI)	09/03/05 (cardiac)
F	84	No	Yes	Yes	No	Yes	Yes	6	LAD	Clopidogrel	Bleeding	04/03/03 (IS)	23/05/03 (N-STEMI)	06/06/03 (non-cardiac)
F	88	No	No	Yes	No	No	No	3	Crypt.	Aspirin + Clopidogrel	Surgery	08/09/03 (TIA)	02/10/03 (N-STEMI)	21/12/05 (cardiac)
M	91	No	No	Yes	No	Yes	No	4	Crypt.	Clopidogrel	Surgery	17/08/05 (TIA)	30/10/07 (N-STEMI)	30/10/07 (cardiac)
M	92	No	No	No	No	Yes	No	3	Crypt.	Aspirin	Surgery	25/12/05 (TIA)	28/10/08 (N-STEMI)	10/11/08 (cardiac)
M	68	No	No	Yes	No	No	No	2	SVD	Rivaroxaban	Bleeding	11/10/10 (IS)	25/09/14 (STEMI)	No

Discontinuation was recommended by a physician-based for 5 patients (2 for surgery and 3 for bleeding) and the reason was not documented for the other 2 patients M: male, F: female, CAD: coronary artery disease, PAD: peripheral artery disease, HTN: hypertension, DM: diabetes mellitus, IS: ischemic stroke, CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, Crypt.: cryptogenic, STEMI: ST-elevation myocardial infarction, N-STEMI: Non-ST-elevation myocardial infarction, cardiac: cardiac death, non-cardiac: death not attributable to cardiac cause

Supplemental Figure I: Risk of follow-up myocardial infarction in TIA or ischemic stroke patients stratified by history of presence of prior coronary artery disease



Supplemental Figure II: Risk of recurrent ischemic strokes in TIA or ischemic stroke patients stratified by presence of prior coronary artery disease



Titre: Improving secondary prevention after transient ischaemic attack (TIA) or ischaemic stroke

RESUME GENERAL

Le pronostic à long-terme actuel après un accident ischémique transitoire (AIT) ou un infarctus cérébral reste mal connu. Ainsi, j'ai déterminé les risques absolus à long-terme de récurrence d'infarctus cérébral et d'évènement coronarien aigu après un AIT ou un infarctus cérébral et identifié les individus qui restent à haut risque absolu de récurrence ischémique malgré la prévention secondaire actuelle.

Dans une cohorte populationnelle contemporaine de patients ayant eu un AIT ou un infarctus cérébral (OXVASC study, 2002-2014), les risques absolus de récurrence d'infarctus cérébral et d'infarctus du myocarde après un AIT/infarctus cérébral ont significativement diminué au cours de la période d'étude, très probablement du fait de l'amélioration de la prévention secondaire avec le temps. Cependant, malgré la prévention secondaire actuelle les sous-groupes de patients avec un antécédent de pathologie coronarienne et ceux sans antécédent coronaire mais avec un score Essen ≥ 4 sont exposés à un risque absolu de récurrence d'évènement ischémique suffisamment élevé pour justifier d'une intensification du traitement. Néanmoins, les thérapeutiques de prévention secondaire futures nécessitent de permettre d'obtenir une réduction absolue du risque de récurrence d'évènement ischémique importante pour compenser un risque augmenté d'effets indésirables ou de surcoût par rapport aux thérapeutiques actuelles. En effet, chez ces sous-groupes de patients à haut risque de récurrence ischémique, une réduction plus intensive du taux de cholestérol avec les inhibiteurs des PCSK-9 paraît tout à fait justifiée, cependant nous avons montré que le coût de ces traitements excède la limite du rapport coût-efficacité généralement accepté tandis que le bénéfice d'une majoration du traitement antithrombotique semble contrebalancé par l'augmentation du risque hémorragique extracrânien.

Mots clés: infarctus cérébral, infarctus du myocarde, prédiction, prévention secondaire

GENERAL ABSTRACT

The current long-term prognosis after transient ischaemic attack (TIA) or ischaemic stroke is not well known. I aimed to determine the long-term absolute residual risks of recurrent stroke and coronary events after TIA or ischaemic stroke and identify individuals who remain at high absolute risk of recurrent ischaemic events despite current secondary prevention management.

In a population-based cohort of consecutive TIA or ischaemic stroke patients (OXVASC study, 2002-2014), the overall absolute risks of recurrent ischaemic stroke and coronary events after TIA/ischaemic stroke have decreased over the study period, and are likely to be explained by the improvement of secondary prevention over time. However, despite current secondary prevention, the subgroups of patients with prior coronary artery disease and those without prior coronary artery disease but with an Essen score of ≥ 4 remain at sufficiently high absolute risk of recurrent ischaemic events to justify more intensive treatment. Nevertheless, future secondary prevention therapies would need to achieve a substantial absolute risk reduction to outweigh increased side effects or cost compared to current therapies. Indeed, in these high-risk subgroups, more intensive lipid-lowering therapies might be justified, but we showed that the total cost of PCSK-9 inhibitors seems to exceed the generally accepted cost-effectiveness threshold while benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding.

Keywords: secondary prevention, ischaemic stroke, myocardial infarction, prediction