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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

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_{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 ischemic stroke/transient ischemic attack. The risk of recurrent stroke was 4.26%/y (95% CI 3.43-5.09, P_{het}<0.001), with no change over time (P_{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_{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_{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.

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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 (≥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 ≥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 ≥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_{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_{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_{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)	P_{int}	N; n	Annual Risk, % (95% CI)	P_{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 $^{*}P=0.0179$, $^{\dagger}P=0.79$, $^{\ddagger}P=0.14$, $^{\S}P=0.0274$, $^{\|}P=0.0301$, $^{\#}P=0.74$.

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 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 ≥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

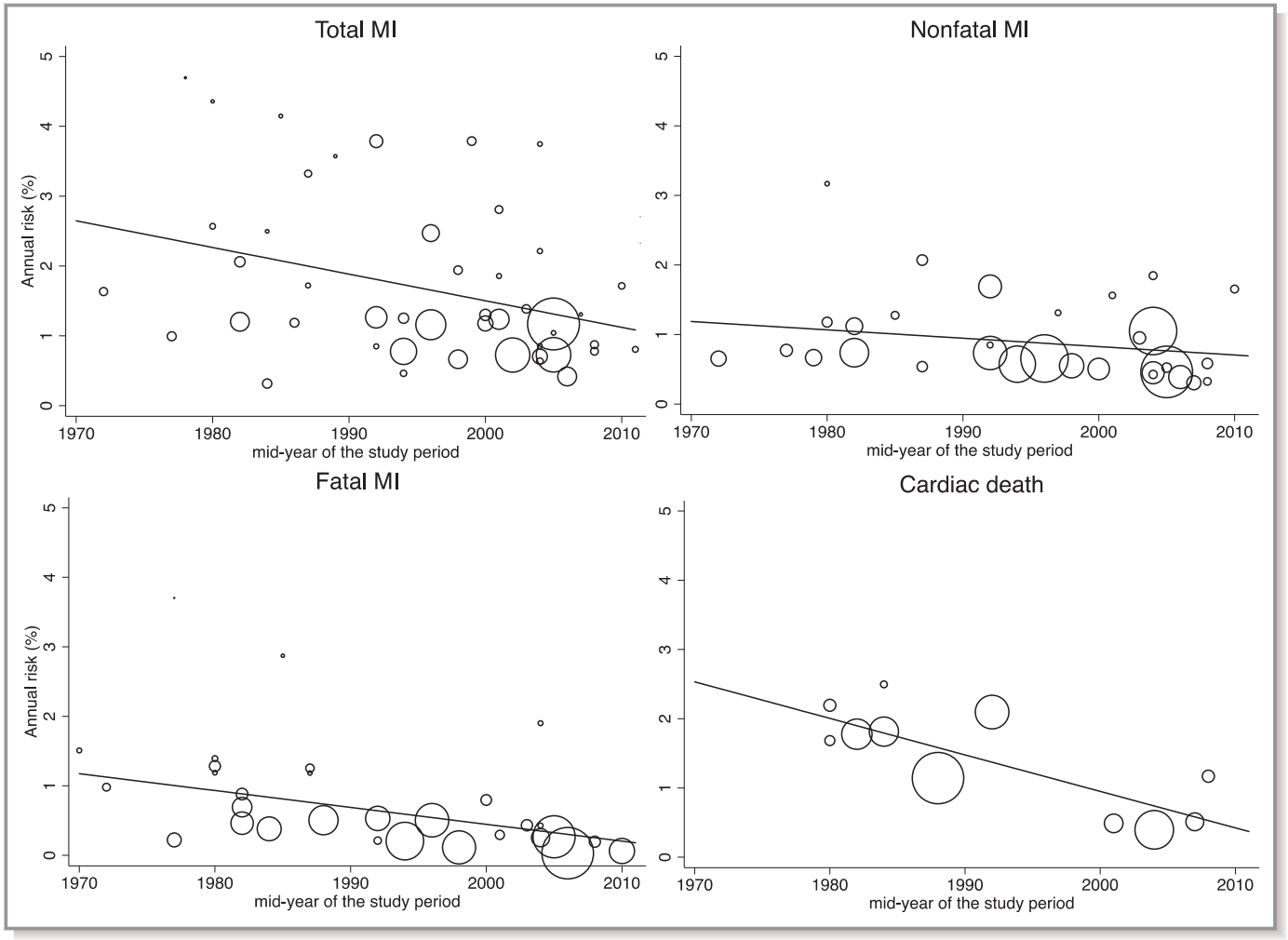

Figure 1. Evolution of the annual risks of myocardial infarction (MI) and cardiac death in IS/TIA patients over time. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

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_{int}=0.020). There was no evidence for a variation over time (P_{int}=0.14, Figure 1) or with the duration of follow-up (range 1.0-10.0 years, P_{int}=0.45, Figure 2). There was no difference in the risk between types of ischemic event (P_{int}=0.84) and incident versus combined or unspecified IS/TIA (P_{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_{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_{int}=0.63, Figure 3) and significantly decreased with the duration of follow-up (range 1.0-10.0 years, P_{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_{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_{int}=0.95) and types of ischemic event (P_{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_{het}<0.001) and those with

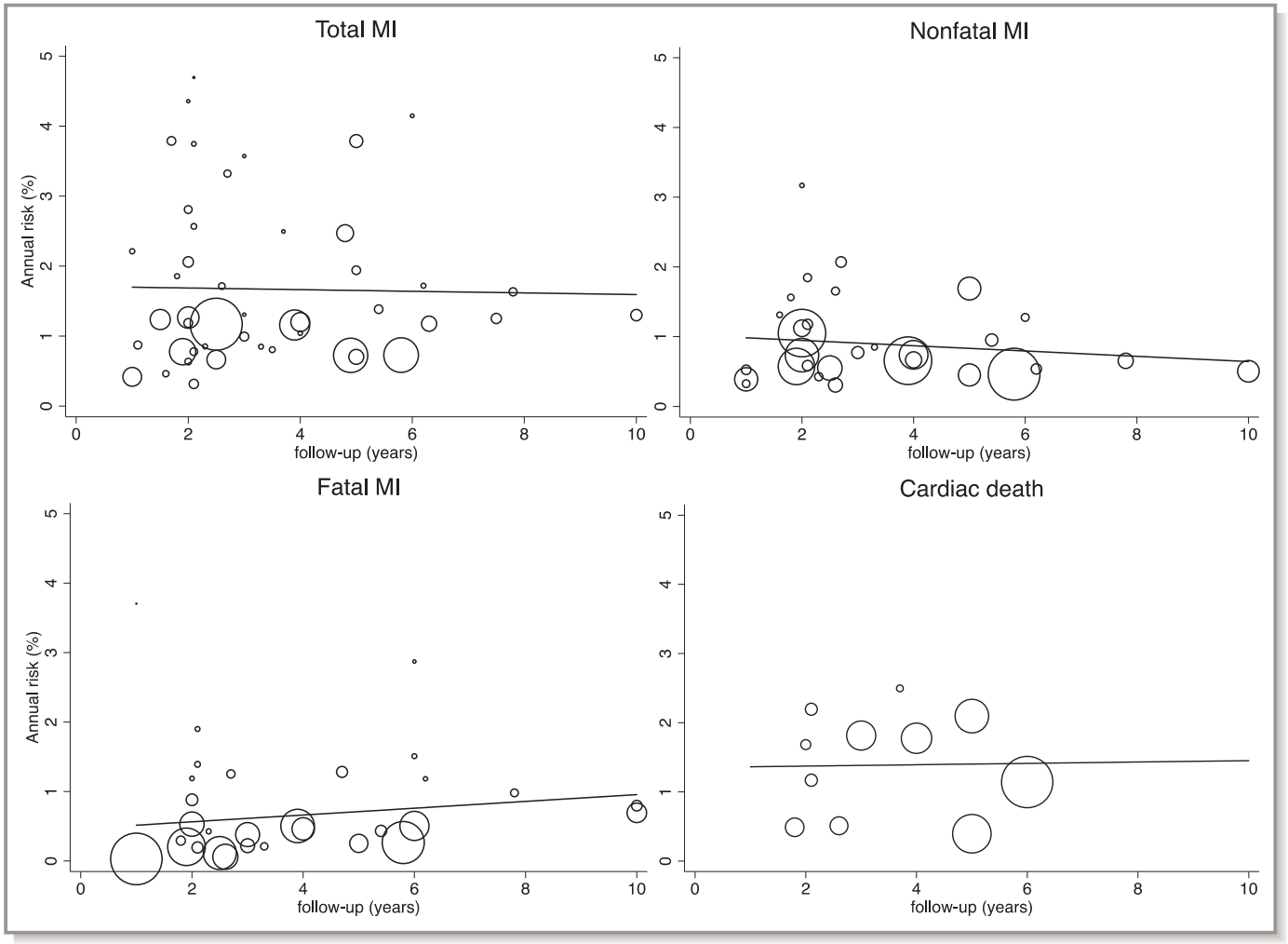

Figure 2. Evolution of the annual risks of myocardial infarction (MI) and cardiac death in IS/TIA patients with the duration of study follow-up. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

completeness of follow-up ≥90% (4.56%, 95% CI 3.53-5.58, 21 studies, 60 310 patients, P_{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_{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_{het}<0.001). The risk did not markedly vary over time (P_{int}=0.55, Figure 3) or with the duration of follow-up (range 1.0-6.2 years, P_{int}=0.36, Figure 4). There was no difference in the risk of fatal recurrent stroke between types of ischemic event (P_{int}=0.87) and incident versus combined or unspecified IS/TIA (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 with community-based studies (1.44%, 95% CI 0.19-2.69, 2 studies, 823 patients, P_{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_{het}<0.001). The risk did not vary markedly over time (P_{int}=0.24) and significantly decreased with the duration of follow-up (range 1.0-6.2 years, P_{int}=0.031, Figure 4). There was no difference in the risk between study designs (P_{int}=0.51) and incident versus combined or unspecified IS/TIA (P_{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_{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

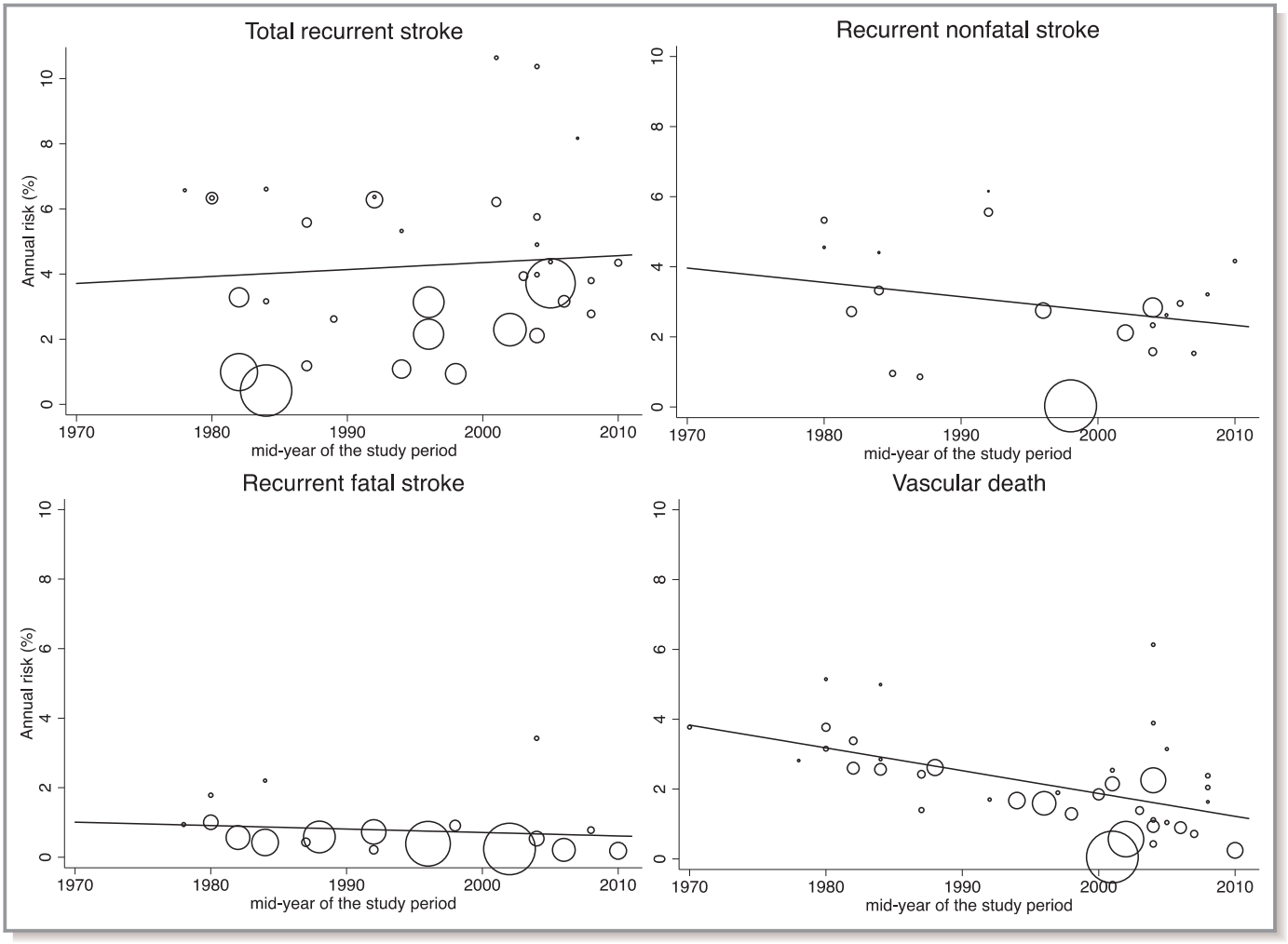

Figure 3. Evolution of the annual risks of recurrent stroke and vascular death in IS/TIA patients over time. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

time (P_{int}<0.001, Figure 1) and was estimated to be 0.54% (95% CI 0.28-0.80, 4 studies, 2145 patients, P_{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_{int}=0.95, Figure 2). There was no significant difference in the risk of cardiac death among study designs (P_{int}=0.60), types of ischemic event (P_{int}=0.51), and incident versus combined or unspecified IS/TIA (P_{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_{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_{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_{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_{int}<0.001, Figure 3) and was estimated to be 1.71% (95% CI 1.11-2.32, 20 studies, 45 060 patients, P_{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_{int}=0.64, Figure 4). There was no significant difference in the risk of vascular death among study designs (P_{int}=0.62), types of ischemic event (P_{int}=0.65), and incident versus combined or unspecified IS/TIA (P_{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_{het}=0.23) than in those without (1.41%, 95% CI 0.95-1.88, 3 studies, 15 160 patients, P_{het}=0.001, P_{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

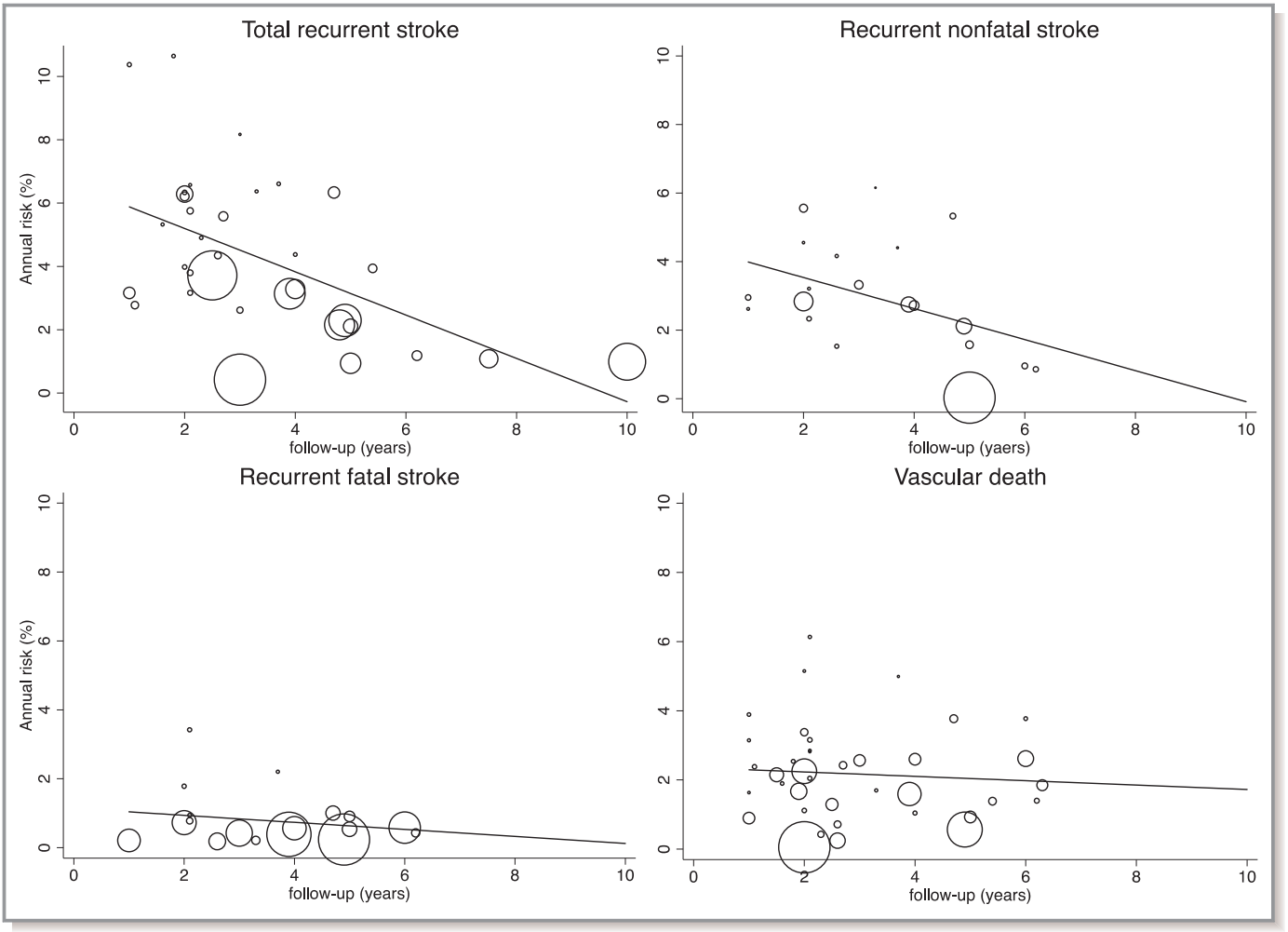

Figure 4. Evolution of the annual risks of recurrent stroke and vascular death in IS/TIA patients with the duration of study's follow-up. The size of the plot is inversely proportional to the within-study variance. IS indicates ischemic stroke; TIA, transient ischemic attack.

patients, P_{he}<0.001) and those with completeness of follow-up ≥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

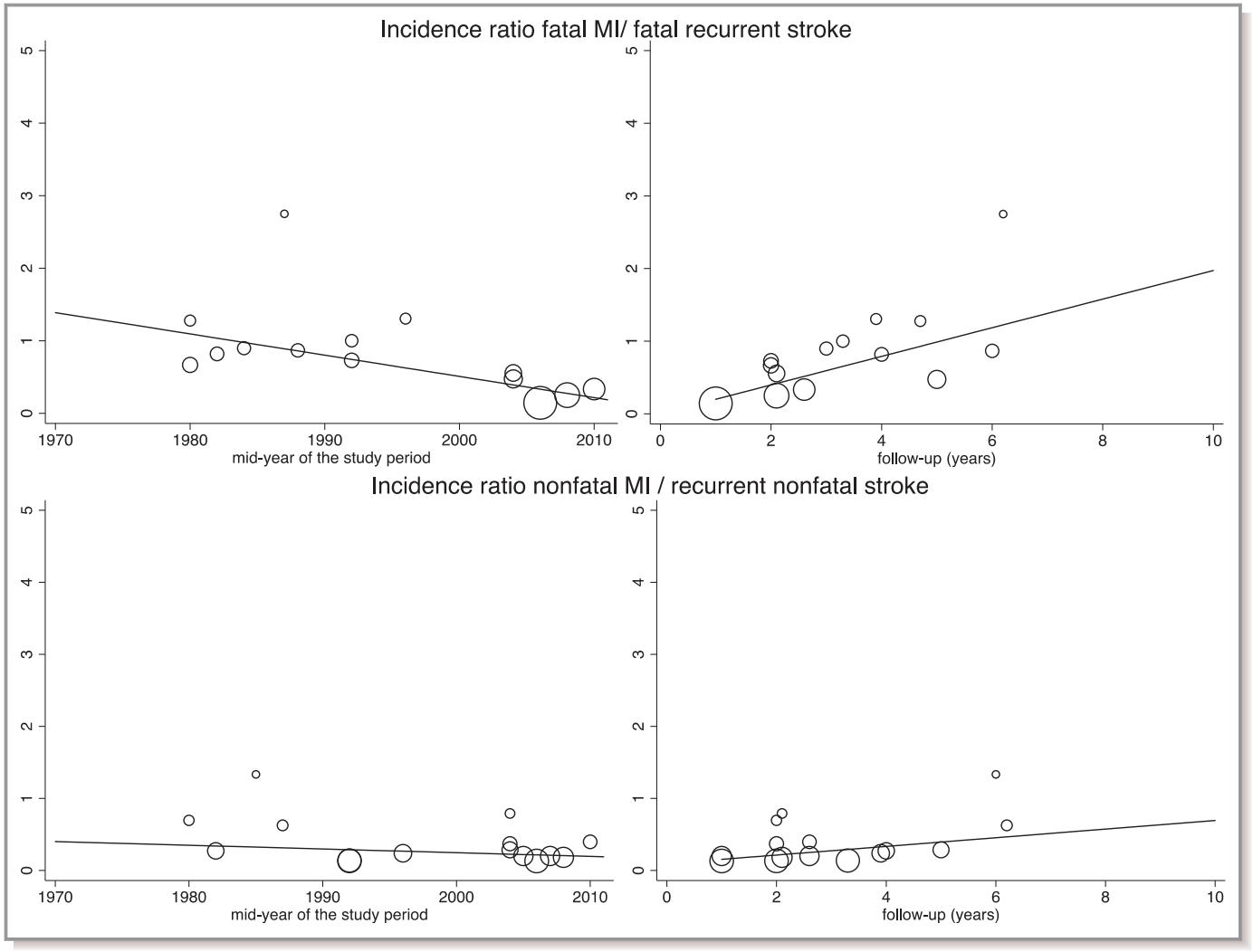

Figure 5. Evolution of the incidence ratio of fatal and nonfatal myocardial infarction (MI)/recurrent stroke over time and with the duration of study's follow-up. The size of the plot is inversely proportional to the within-study variance.

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 (≥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

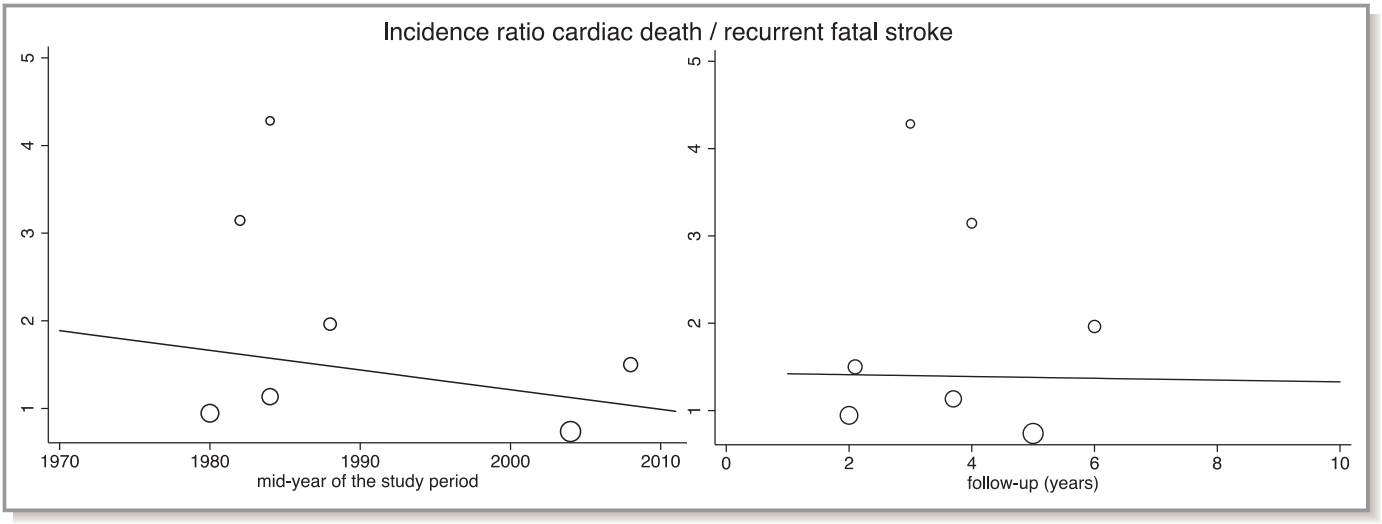

Figure 6. Evolution of the incidence ratio of cardiac death/fatal recurrent stroke against study's duration of follow-up and over time. The size of the plot is inversely proportional to the within-study variance.

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 2006[15]) 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

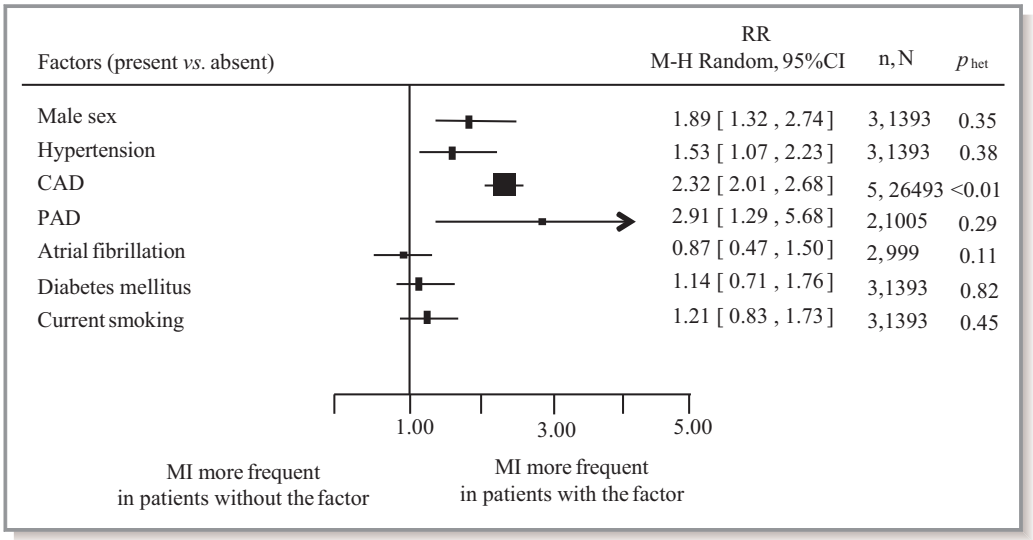

Figure 7. Forest plots of the meta-analyses of potential risk factors for myocardial infarction (MI) in IS/TIA patients. The size of the square is proportional to the sample size of the study. CAD indicates coronary artery disease; CI, confidence interval; IS, ischemic stroke; M-H, Mantel-Haenszel; MI, 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, Covidiem, 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 subgoups 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 baises (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 *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 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 ablinded 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 + dypiridamole *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 + dypiridamole	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 natiowide database) in patients who survived in hospital or whitin 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 admisssions 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 neuroloy 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 admisssions 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
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, strioke, PE
Wijnhoud[58]	ND	ND	MI, SD	MI, srroke, 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 unequivoqual 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: 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 unequivoqual neurological stability or improvement, lasting ≥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)		

Gent (CAPRIE)[24]	6431	1.9	95 (0.8)	25 (0.2)	70 (0.6)								204 (1.7)
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)**
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)							
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)										
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

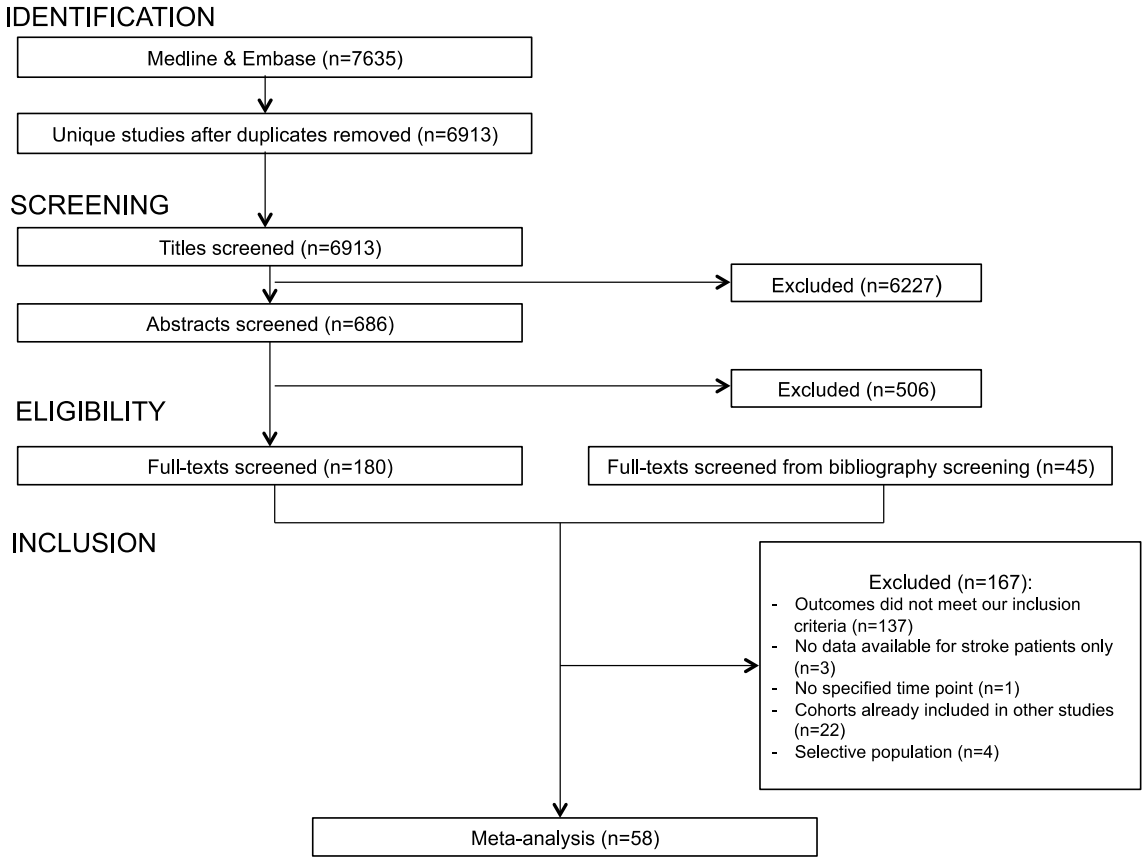
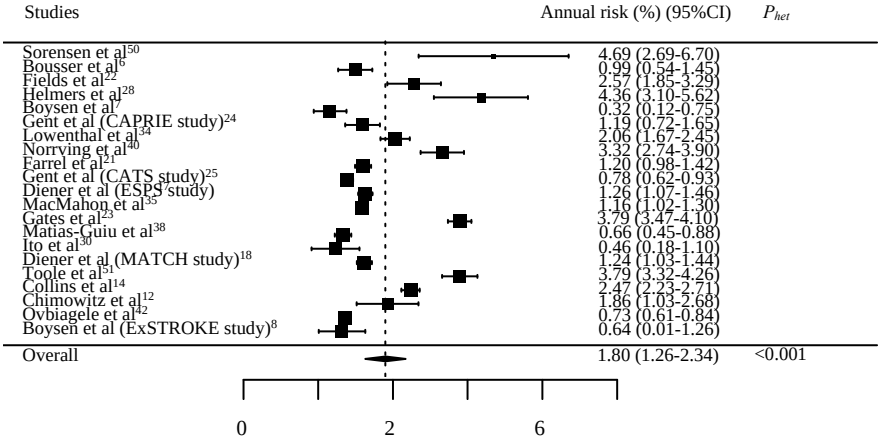
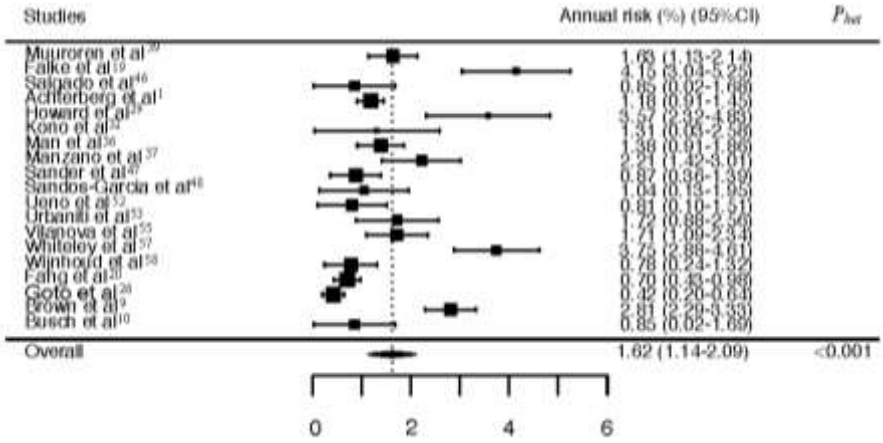


Figure S2. Forest plot of the meta-analysis of the risk of MI after TIA/IS in randomized controlled trials (RCTs).



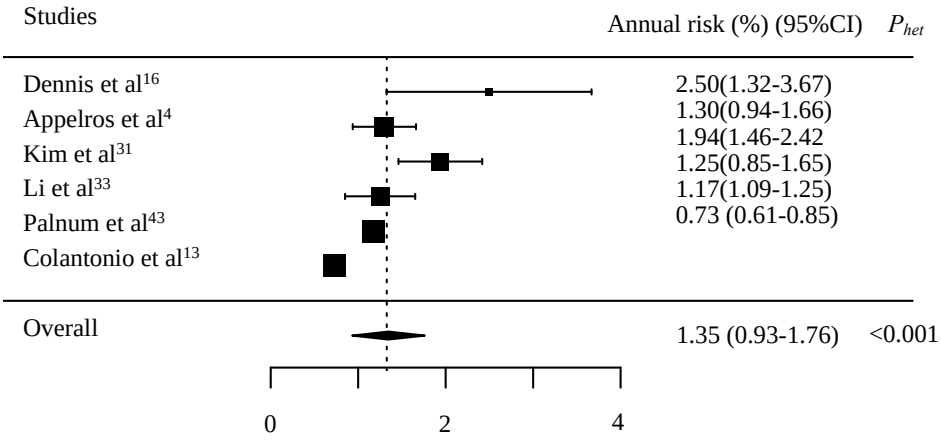
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



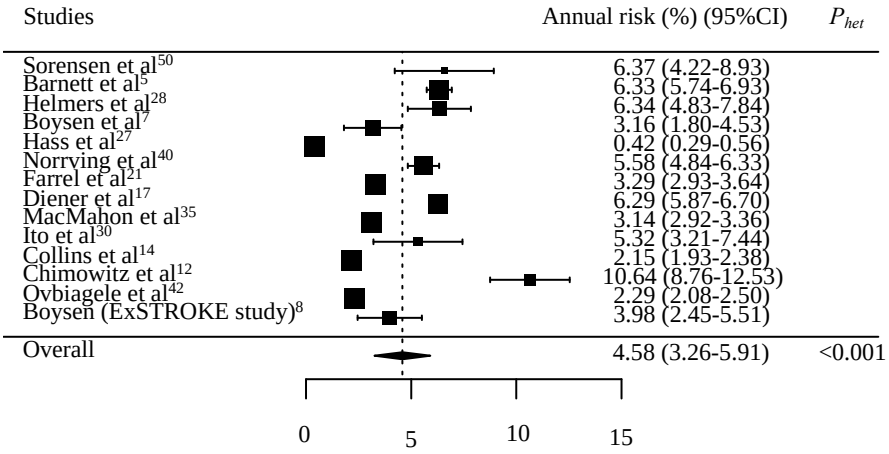
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



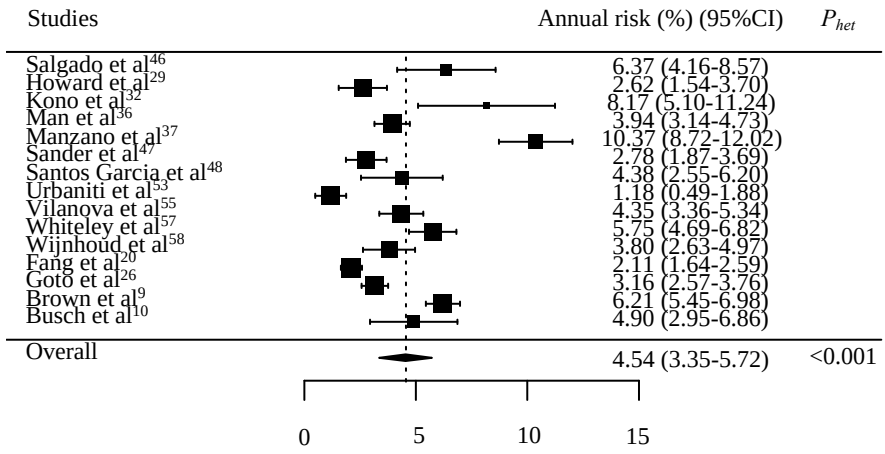
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



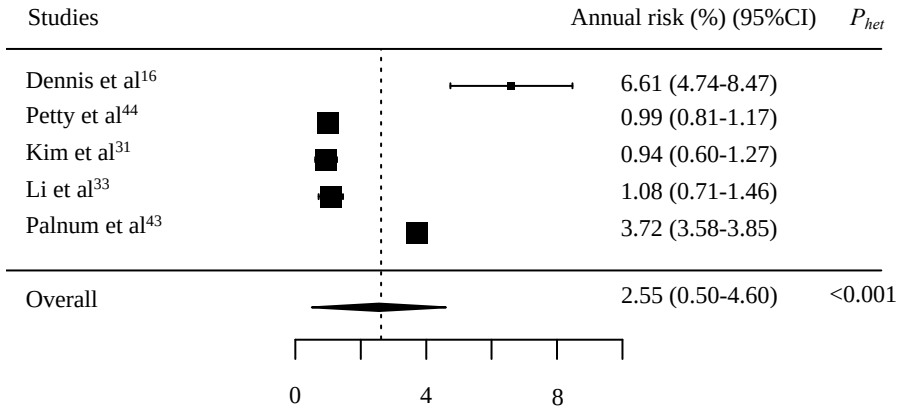
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



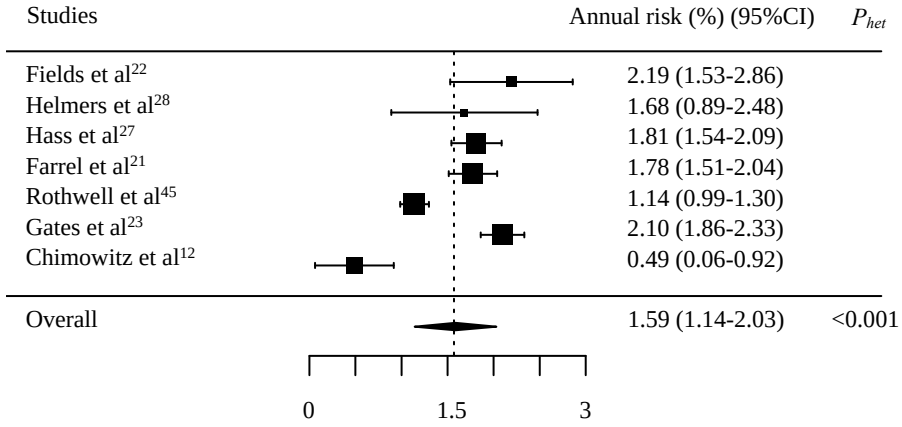
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



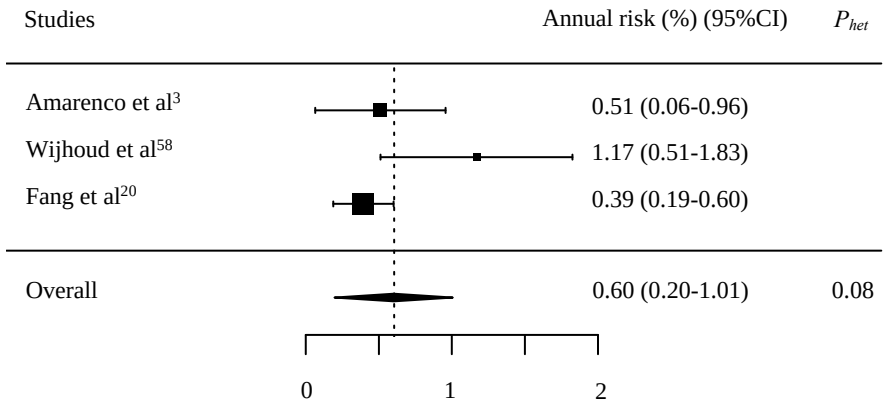
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



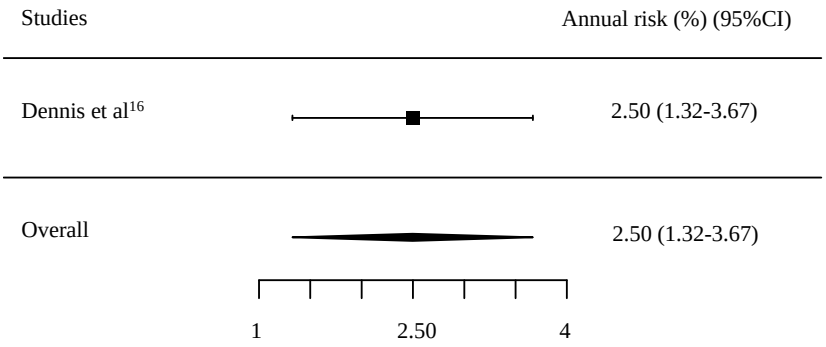
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



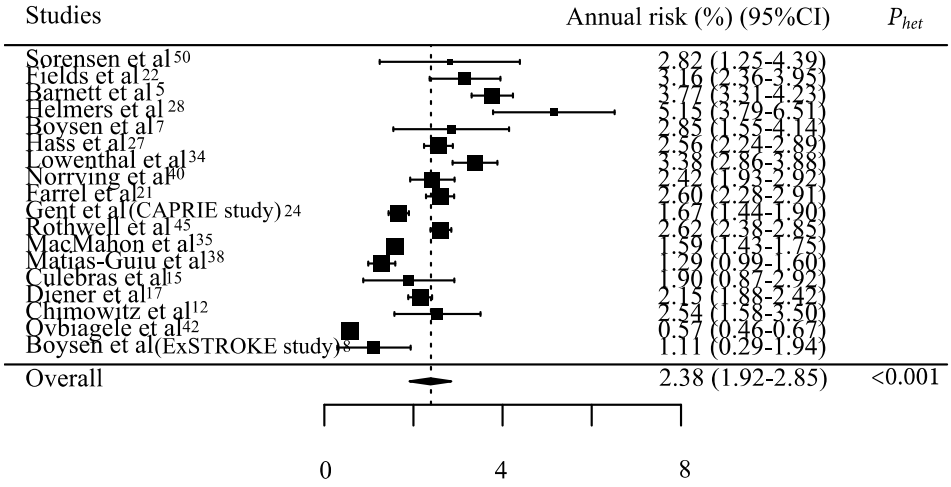
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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



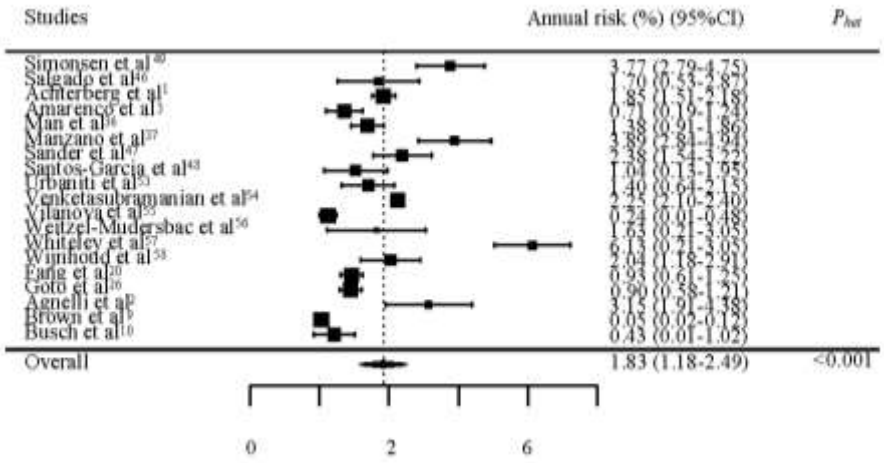
Bars indicate 95% confidence intervals (CI).

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



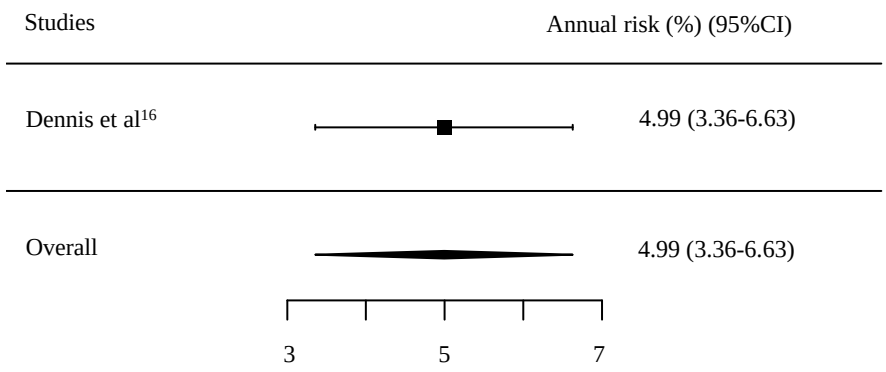
The dashed line represents the overall risk of MI. Bars indicate 95% confidence intervals (CI). P_{het}: Heterogeneity across studies.

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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