Risk of Myocardial Infarction and Vascular Death After Transient Ischemic Attack and Ischemic Stroke
A Systematic Review and Meta-Analysis

Emmanuel Touze, MD; Olivier Varenne, MD, PhD; Gilles Chatellier, MD, PhD; Séverine Peyrard, MSc; Peter M. Rothwell, MD, PhD, FRCP; Jean-Louis Mas, MD

Background—Whether stroke patients should be investigated for asymptomatic coronary artery disease remains matter of debate. Absolute risks of myocardial infarction (MI) and vascular death after a stroke have not been accurately assessed. We performed a systematic review and a meta-analysis to determine the risk of MI and nonstroke vascular death after transient ischemic attack (TIA) and ischemic stroke. Cohort studies of TIA or ischemic stroke patients were included if they were published between 1980 and March 2005, reported risk of MI and nonstroke vascular death, enrolled >100 patients, and had at least 1 year of follow-up. We included 39 studies in a total of 65,996 patients with mean follow-up of 3.5 years. Two reviewers independently carried out data extraction using a standardized form. Absolute annual risks were estimated through weighted meta-regressions with a random effect. To test the predictions of expected event rates derived from our analysis, we used individual patient data.

Summary of Review—The annual risks were 2.1% (CI 95%: 1.9 to 2.4) for nonstroke vascular death, 2.2% (1.7 to 2.7) for total MI, 0.9% (0.7 to 1.2) for nonfatal MI and 1.1% (0.8 to 1.5) for fatal MI. The time course of risk was linear. Estimated risks fitted well with observed risks at the individual level. There was no heterogeneity in the absolute risks according to baseline study characteristics.

Conclusions—Patients with TIA or stroke have a relatively high risk of MI and nonstroke vascular death. Additional research is needed to identify the determinants of coronary artery disease in stroke patients. (Stroke. 2005;36:2748-2755.)

Key Words: atherosclerosis ■ prognosis ■ risk factors ■ cerebrovascular accident ■ meta-analysis ■ myocardial infarction ■ coronary disease

Stroke and myocardial infarction (MI) share some common risk factors and pathophysiological mechanisms. Compared with the general population, stroke patients have an increased risk of death that notably results from MI. However, systematic evaluation of coronary artery disease (CAD) is not currently recommended in asymptomatic patients with a recent ischemic stroke. A recent American Heart Association and American Stroke Association statement recommends an individual risk assessment based mainly on score risk to identify patients with the highest likelihood of morbidity and mortality from unrecognized CAD after a stroke. However, there is no reliable estimation of the absolute risk of MI and vascular death after stroke, and high-risk populations still have to be defined. We therefore performed a systematic review and a meta-analysis of the absolute risk of MI and vascular death after stroke or transient ischemic attack (TIA). We aimed to determine overall risks, the time-course of risk, heterogeneity across studies, and any relationships between observed risk and study or population characteristics.

Methods

Search Strategy

The databases searched to obtain the articles included Pub Med of the National Library of Medicine (through March 2005) and the Cochrane database of systematic reviews (issue 4, 2004). The search strategy used both keywords and MeSH terms and took the form of (Cerebrovascular Accident or synonyms) and (Cohort Studies OR Randomized Controlled Trial) and (Coronary Arteriosclerosis or Myocardial Infarction or Vascular Death). In the Cochrane database, we studied all references from the systematic reviews related to secondary prevention of stroke. We also searched all included references in the systematic reviews related to secondary prevention of stroke. We also searched the bibliographies of all included studies and any relevant review articles for additional suitable studies. Unpublished data were not sought. Studies that recruited patients with ischemic stroke or TIA were included. Stroke/TIA had to be defined according to the World Health Organization criteria.
Organization criteria or similar. Any prospective cohort study or randomized controlled trial (RCT) was included if: (1) it was published in 1980 or later (such that computed tomography scan was used in a large proportion of patients for the diagnosis of stroke); (2) it reported on long-term follow-up of ≥100 patients; (3) the cohort was followed up ≥1 year with <5% loss to follow-up; (4) it was written in English; and (5) outcome data were reported for MI or vascular death. Articles were excluded if they included hemorrhagic strokes only, had highly selected populations (eg, single sex, young subjects, or specific race), or had patients with a specific unusual cause of stroke. Population-based studies in which a small proportion of patients had hemorrhagic strokes were not excluded. Indeed, although those studies did not provide cardiac events risks for ischemic stroke patients separately, they probably provided the most unbiased risk estimates. We carefully excluded articles that concerned patients already used in another article from the same institution, except when the methods sections made it absolutely clear that the patients did not overlap. In case of multiple publications, we chose the one most appropriate to this review, preferably the most recent.

Study Selection and Data Extraction
Two reviewers (E.T. and O.V.) independently assessed abstracts to determine eligibility and independently performed data extraction from the full articles using a predefined, standardized form. Any disagreement was resolved by discussion. We did not contact authors to clarify details or provide additional information. In one study,1 mean follow-up duration was not available, but all patients were followed up for ≥2 years. Therefore, we extracted events that occurred during this 2-year period.

Study Characteristics and Outcome Measures
We recorded information on the study population (community- or hospital-based cohort or RCT), proportion of TIA, sample size, prevalence of baseline traditional risk factors (hypertension and diabetes mellitus), prevalence of other atherothrombotic disease (peripheral arterial disease [PAD] and MI) at baseline, delay between stroke/TIA and inclusion in the cohort, follow-up duration, and number of deaths.

Fatal and nonfatal MI and nonstroke vascular death were considered as outcomes. Stroke was not included in vascular death. Definitions of MI and nonstroke vascular death were recorded if available. When death certificates were used only to record outcomes, the definition of those outcomes was considered not available.

Additional Data
To test the predictions of expected event rates derived from our analysis of published studies, we also used individual patient data from those studies included in the Cerebrovascular Cohort Studies Collaboration4 that were eligible for inclusion.

Data Analysis
Analyses were performed using STATA 8.0 and SAS 8.01 software packages. Because we did not have any individual data and because time to an event was generally unavailable, we were not able to use survival analysis methods. Therefore, we plotted the proportion of patients who had an outcome against the average follow-up time. We expected that the rate of nonstroke vascular events would be constant and that the scatter of points could therefore be reasonably modeled on a straight line through the origin. Metaregressions showed that for each outcome, the line of the best fit did not differ from a linear relation through the origin (ie, the P value of the intercept did not significantly differ from 0). Thus, overall annual risks and their 95% CI were estimated using weighted metaregressions with a random effect and no intercept.9 10 Residual between-trial variance was calculated using restricted maximum likelihood estimate.7 Metaregressions were also used to explore sources of heterogeneity for total MI and nonstroke vascular death outcomes. We first compared the residual between-trial variances estimated in models with follow-up duration as covariate to those estimated in models, with follow-up duration and each of the following baseline characteristics: age, percentage of patients with diabetes mellitus, previous MI, PAD, hypertension, and gender. As recommended, this comparison was not based on a statistical test.6 Second, we estimated absolute risks after having separated studies according to the prevalence of baseline risk factor prevalence using median of the whole studies as threshold (66 years of age; 63% males; 50% hypertension; 17% diabetes mellitus; 11% previous MI; and 9% PAD) and according to the cohort starting date (through 1990 versus 1990). This limit was chosen because use of statins has increased from this period.

To assess the predictive accuracy of the results, the risk of MI and nonstroke vascular death was estimated using metaregressions after exclusion of studies for which individual data were available.8, 8–11 We then calculated the expected risk and their 99% CIs at the median follow-up in each individual study and graphically compared the expected and observed risks.

Results
The 2 reviewers agreed on the inclusion/exclusion status of 87% of the abstracts reviewed, and the search resulted in 65 articles considered in detail for inclusion. Thirty-two studies were then excluded because of missing outcomes (n=26), inclusion criteria not fulfilled (n=5), and patients already included in another study (n=1). Search of bibliographies of selected studies provided 6 additional articles that fulfilled our inclusion criteria. Thus, 39 independent studies met all inclusion criteria and were included in the analysis. There were 25 RCTs,8–10, 33 3 population-based cohorts,3,9,34–36 and 6 single-center hospital-based cohorts,40–45 including a total of 65 996 patients with a mean (range) follow-up of 3.5 (1–10) years (online Table available at http://stroke.ahajournals.org).

Incidence of MI and Nonstroke Vascular Death
The Table shows the frequency of the different outcomes and annual risks. Figure 1 shows the absolute risk of each outcome plotted against mean follow-up and the fitted regression lines. There was an overall statistically significant heterogeneity between studies in the absolute annual risk of nonstroke vascular death (χ2 for heterogeneity; P<0.0001), total MI (P<0.0001), nonfatal MI (P=0.001), and fatal MI (P<0.0001). The ranges of individual annual risks were 0.4% to 3.8% for nonstroke vascular death, 0.5% to 4.7% for total MI, 0.4% to 3.2% for nonfatal MI, and 0.2% to 3.7% for fatal MI. The annual risks obtained through meta-regressions were 2.1% (95% CI, 1.9 to 2.4) for nonstroke vascular death (29 studies), 2.2% (95% CI, 1.7 to 2.7) for total MI (22 studies), 0.9% (95% CI, 0.7 to 1.2) for nonfatal MI (16 studies), and 1.1% (95% CI, 0.8 to 1.5) for fatal MI (19 studies). The absolute risk of nonstroke vascular death estimated through metaregressions was lower in studies that enrolled patients after 1990 than in those that enrolled patients before. Otherwise, metaregressions did not reveal any significant heterogeneity in the risk of total MI or nonstroke vascular death according to the baseline study characteristics (Figure 2) or for fatal MI and nonfatal MI (data not shown).

The percentage of residual variance explained by the baseline characteristic covariates was low varying from 0.5% to 7.0% depending on the covariate. In studies specifically devoted to patients with TIA or stroke attributable to atherosclerosis,10,11, 13,15,19,32 the risk of MI (4 studies) was 1.9% per year (95% CI, not estimable) and that of nonstroke vascular death (5 studies)
2.3\% per year (95\% CI, 1.9 to 2.7) ie, not different from the risks derived from the other studies. Nonstroke vascular death risk did not differ between RCTs and population-based studies (Figure 2). Pooled risk of total MI could not be estimated in population-based cohorts because only one study was available for this outcome.\(^9\) Similarly, vascular death and total MI outcomes were each available in only 2 hospital-based studies, not allowing metaregressions.\(^{16,42-44}\)

### Predicted and Observed Risks

After exclusion of studies for which individual data were available, annual risks estimated by metaregressions were 2.1\% (95\% CI, 1.8 to 2.4) for nonstroke vascular death, 2.3\% (95\% CI, 1.6 to 2.9) for total MI, 1.0\% (95\% CI, 0.7 to 1.2) for nonfatal MI, and 1.1\% (95\% CI, 0.7 to 1.5) for fatal MI. Figure 3 shows predicted versus observed risks of these events at median follow-up in studies with individual data.
The estimated values were reasonably close to the absolute risk of nonfatal MI and nonstroke vascular death but slightly overestimated that of fatal and total MI.

**Discussion**

The main result of this meta-analysis is that after a stroke or a TIA, the risks of MI and nonstroke vascular death are each \( \approx 2\% \) per year. Such risks are usually considered high absolute risks in different guidelines for assessment of cardiovascular risk.\(^4\) Estimates obtained through metaregressions using a large number of studies including community- and hospital-based populations fitted well with those observed at the individual level, except for fatal and total MI, for which our prediction tended to overestimate the risk. In fact, the definition of fatal MI varied according to studies, notably because sudden deaths were inconstantly considered fatal MI. Conversely, the definition of nonfatal MI was consistent between studies, being based on clinical data, ECG changes, and cardiac enzyme elevation.

Whether stroke patients should be investigated for asymptomatic CAD remains a matter of debate.\(^2\) The relevance of coronary investigations strongly depends on the prevalence of asymptomatic CAD, the spontaneous risk of coronary events, and the feasibility of preventive therapeutics. Small studies have suggested that 25% to 60% of stroke patients without any clinical CAD may have silent myocardial ischemia on noninvasive tests,\(^2\) and one study found that about one third of patients (including stroke patients) evaluated before carotid surgery had \( \geq 1 \) coronary artery stenosis \( \geq 70\% .\)\(^4\) Although we showed that the risk of coronary events after a stroke is relatively high, many patients will not have such events. It is therefore essential to determine highest-risk patients, who will benefit most from CAD screening. We found a significant heterogeneity across studies; however, baseline characteristics of the populations, including age, gender, and prevalence of diabetes mellitus, hypertension, previous MI, or PAD, were not correlated with the absolute risk of MI or nonstroke vascular death. This finding could be explained by the low power of metaregressions to detect heterogeneity sources.\(^5\) We may also speculate that after stroke, the risk of severe coronary events is not related solely to the presence of risk factors. These results are in agreement with the Framingham cohort, in which the number of factors associated with an increased risk of CAD was lower in patients with previous CAD or stroke than in those free of cardiovascular disease.\(^4\) Therefore, it remains unknown whether classical risk scores accurately predict risk of MI and nonstroke vascular death after a stroke.\(^4\) Other character-

![Figure 1. Absolute risk of each outcome plotted against mean follow-up and the fitted regression lines obtained through weighted metaregressions. Each circle represents a study. Its size is inversely proportional to the within-trial variance.](http://stroke.ahajournals.org)
istics such as cause of stroke and severity of atherosclerotic disease may play a more important role in the prediction of subsequent coronary events. Although MI is invariably caused by atherosclerosis, stroke may result from various causes. Depending on its definition, atherosclerosis explains 20% to 40% of strokes. There are several arguments suggesting that patients with stroke related to atherosclerosis are at higher risk of MI or nonstroke vascular death than are patients with nonatherosclerotic subtypes. First, anatomical studies have shown a correlation between the extent and the severity of atherosclerosis in carotid or vertebral arteries and in coronary arteries. Second, asymptomatic carotid artery stenosis is an independent risk factor for CAD. Third, cross-sectional studies have suggested that the prevalence and the severity of asymptomatic CAD increase in case of stroke attributable to large artery disease and with the severity of carotid artery stenosis. Finally, it has been shown that patients with stroke attributable to large artery atherosclerotic disease have a higher risk of death than those with strokes attributable to small vessel disease or of unknown origin, although cardiac causes were not always individualized in those studies. In this meta-analysis, because individual data were not available, patients with stroke attributable to atherosclerosis could not be analyzed separately. In studies specifically devoted to strokes related to intracranial or carotid artery atherosclerosis, the risk of MI or nonstroke vascular death did not differ from that found in other studies. Nevertheless, those studies were scarce and included patients with heterogeneous severity of atherosclerosis ranging from plaques to severe stenosis.

Surprisingly, we did not find any positive correlation between diabetes mellitus prevalence at baseline and risk of MI during follow-up. The common association between diabetes mellitus and small vessel disease, which seems to carry a low risk of cardiac events, may partly explain this finding. Similarly, in the MATCH trial, which enrolled an important proportion (68%) of diabetic patients, the risk of total MI was only 1.2% per year. Atherosclerosis and cerebral small vessel disease share common risk factors, but their pathophysiology is different. It is possible that patients who develop small vessel cerebral disease are not particularly prone to develop CAD because of other inherited or acquired characteristics.
Although the time course of the risk of each outcome seems to be linear over a 5-year period, we cannot rule out a higher early risk of cardiac events because patients were generally included several weeks to months after their initial event. Similarly, the very long-term risk remains not well estimated because all the major studies had an average follow-up ranging from 2 to 4 years. Nevertheless, short-term risk assessment is most valuable when aiming to reinforce secondary prevention.

The present systematic review is subject to several limitations. First, we were not able to estimate the risk of MI and nonstroke vascular death in patients without any previous clinical CAD at the time of stroke because those patients were not analyzed separately in studies selected here. Only a meta-analysis on individual data would allow such an analysis. Nevertheless, the proportion of patients with previous symptomatic CAD at baseline was relatively low (median 11%; range 2% to 27%), and we did not find any correlation between that proportion and the subsequent risk of MI or nonstroke vascular death. Second, metaregressions have several well-known methodological limitations, including lack of power to explain heterogeneity and risk of ecological and confounding biases. Even if metaregressions were undertaken correctly from a technical point of view, relationships with averages of patients’ characteristics are potentially misleading. Indeed, the relationship between risks and patients’ characteristics across the studies may not be the same as the relationships within trials. Therefore, our findings should be interpreted with caution. However, only metaregressions were feasible with continuous variables such as an absolute risk. Third, our systematic review mainly included RCTs and quite old population-based studies. Although RCTs tend to recruit healthier patients and may underestimate risk of MI and nonstroke vascular death, they were the best available source of data for the present review. Conversely, treatments were heterogeneous in RCTs. Patients included in the most recent trials were most often treated with antithrombotic therapies and other agents, such as lipid-lowering agents and angiotensin-converting inhibitors, that lower the risk of MI as well as stroke and are theoretically more representative of the current practice than those included in old trials. Indeed, in our review, risk of nonstroke vascular death was lower in studies that had enrolled patients after 1990 than in those performed before. However, this result was not observed for MI, and the number of studies that had enrolled patients after 1990 is low. In addition, in practice, many patients do not receive optimal prevention according to guidelines and results of RCTs.

The high risk of MI and nonstroke vascular death in stroke patients should urge us to improve secondary prevention.

Figure 3. Expected vs observed (and their 99% CI) risks of each event at median follow-up in studies with individual data.
Several strategies can be considered. First, a widespread reinforcement of all medical preventive measures without CAD screening. Second, a systematic screening of asymptomatic coronary lesions requiring specific treatments. Third, a selective screening based on risk stratification. Indeed, screening could potentially improve prognosis because several studies suggest that medical treatment (eg, β-blockers) or revascularization (coronary artery bypass surgery or angioplasty) alter prognosis in patients with silent ischemia beyond risk factor reduction.2,58 More research is needed to identify the determinants of the CAD risk and to assess the best strategy to decrease cardiac morbidity and mortality in stroke patients.2

Acknowledgments
This study was supported in part by the Institut de l’Athérombose, Sanofi-Aventis and Bristol-Myers-Squibb pharmaceuticals, which had no role in the analysis or interpretation of the data or in the decision to publish this manuscript. We thank the Cerebrovascular Cohort Studies Collaboration for access to data.

References
Risk of Myocardial Infarction and Vascular Death After Transient Ischemic Attack and Ischemic Stroke: A Systematic Review and Meta-Analysis
Emmanuel Touzé, Olivier Varenne, Gilles Chatellier, Séverine Peyrard, Peter M. Rothwell and Jean-Louis Mas

Stroke. 2005;36:2748-2755; originally published online October 27, 2005;
doi: 10.1161/01.STR.0000190118.02275.33
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/12/2748

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/