All-Cause Mortality up to and After Coronary Heart Disease and Stroke Events in European Middle-Aged Men

The PRIME Study

Bilal Majed, MD; Michèle Montaye, MD; Aline Wagner, MD; Dominique Arveiler, MD; Pierre Ducimetière, PhD; Muriel Tafflet, MSc; Jean Ferrieres, MD; Jean-Bernard Ruidavets, MD; Frank Kee, MD; Alun Evans, MD; Philippe Amouyel, MD; Christof Prugger, MD*; Jean-Philippe Empana, MD*

Background and Purpose—The aim was to investigate prospectively the all-cause mortality risk up to and after coronary heart disease (CHD) and stroke events in European middle-aged men.

Methods—The study population comprised 10,424 men 50 to 59 years of age recruited between 1991 and 1994 in France (N=7855) and Northern Ireland (N=2747) within the Prospective Epidemiological Study of Myocardial Infarction. Incident CHD and stroke events and deaths from all causes were prospectively registered during the 10-year follow-up. In Cox’s proportional hazards regression analysis, CHD and stroke events during follow-up were used as time-dependent covariates.

Results—A total of 769 CHD and 132 stroke events were adjudicated, and 569 deaths up to and 66 after CHD or stroke occurred during follow-up. After adjustment for study country and cardiovascular risk factors, the hazard ratios of all-cause mortality were 1.58 (95% confidence interval 1.18–2.12) after CHD and 3.13 (95% confidence interval 1.98–4.92) after stroke.

Conclusions—These findings support continuous efforts to promote both primary and secondary prevention of cardiovascular disease. (Stroke. 2015;46:1371-1373. DOI: 10.1161/STROKEAHA.115.008903.)

Key Words: cardiovascular disease ■ epidemiology ■ prevention ■ survival analysis

All-cause mortality risk has seldom been compared between the period up to and the period after coronary heart disease (CHD) and stroke. Such unified epidemiological approach allows quantifying the effect of CHD and stroke events on all-cause mortality relative to a baseline risk period. We addressed this issue within the Prospective Epidemiological Study of Myocardial Infarction (PRIME).

Study Population and Case Ascertainment

The study population comprised 10,424 men 50 to 59 years of age who were recruited in 1991–1994 from 4 WHO MONICA centers in France (N=7855) and Northern Ireland (N=2747) and followed up for all-cause mortality over 10 years.1 Incident CHD (stable and unstable angina, myocardial infarction, and coronary death) and ischemic stroke events were adjudicated as reported previously.1,2

Study Periods

All-cause mortality in the period up to CHD and stroke, including deaths that occurred within 28 days of such events, was investigated in the entire study population. All cause mortality in the period after CHD or stroke was investigated in those who survived >28 days after such events.

Statistical Analysis

Hazard ratios and 95% confidence intervals of all-cause mortality were estimated by Cox’s proportional hazards models using intercurrent CHD and stroke events as time-dependent covariates (Simple Model).3 Hazard ratios were further adjusted for country and...
CHD and stroke events within the same study population over investigations by dissociating periods up from periods after long-term prognosis after CHD and stroke. We extend these mortality after CHD and, to a lesser extent, after stroke or the Previous authors investigated either the short-term all-cause symptoms. The increased risk of all-cause mortality after CHD and remained virtually unchanged after adjustment for socioeco-
fidence interval 1.98–4.92) after stroke (Table 1), hazard ratios of all-cause mortality were 1.58 (95% con-
ance. They also raise the issue of organizing acute care, particularly the dissemination of stroke units and multidisciplinary teams with cerebral revascularization facilities.

cardiovascular risk factors (Model 1), socioeconomic characteristics (Model 2), physical activity (Model 3), and depressive symptoms (Model 4; model specifications are detailed in the online-only Data Supplement). Further, analyses were stratified by country, personal history of cardiovascular disease, and estimated 10-year cardiovascular disease risk using the recalibrated 2008 Framingham equation.4 R software was used for the statistical analysis (R Foundation for Statistical Computing).

Results
Mean age was 54.90 (SD 2.89) years. During follow-up, 741 men experienced CHD, 104 stroke, and 28 both events; 9551 remained free of CHD and stroke.

All-Cause Mortality Rates
In the period up to CHD and stroke, 569 deaths occurred, including 494 among men who remained free of CHD and stroke. In the period after CHD and stroke, 66 deaths occurred among 798 men who survived at least 28 days after their event. The crude annual all-cause mortality rates by study periods are reported in Table 1, overall and by subgroups.

Hazard Ratios of All-Cause Mortality
After adjustment for cardiovascular risk factors and country (Model 1), hazard ratios of all-cause mortality were 1.58 (95% confidence interval 1.18–2.12) after CHD and 3.13 (95% confidence interval 1.98–4.92) after stroke (Table 2). Associations remained virtually unchanged after adjustment for socioeconomic characteristics, physical activity, and depressive symptoms. The increased risk of all-cause mortality after CHD and stroke was consistent across strata examined (Figure).

Discussion
Previous authors investigated either the short-term all-cause mortality after CHD and, to a lesser extent, after stroke or the long-term prognosis after CHD and stroke. We extend these investigations by dissociating periods up to from periods after CHD and stroke events within the same study population over a long follow-up. This approach allowed us to evaluate the effect of cardiovascular disease events on the subsequent risk of all-cause mortality in the context of a baseline risk period in a given population.

In the present study, the stronger effect of intercurrent stroke as compared with CHD events on all-cause mortality may first be driven by age, although mean age at CHD and stroke events was similar in the PRIME study and survival models were age-adjusted. It may also reflect a gap in acute care, pharmacotherapy, rehabilitation, and recovery between CHD and stroke patients. Urgent revascularization strategies were first applied in the late 1980s among patients with acute coronary syndromes as compared with the early 2000s in ischemic stroke patients.5 Despite the rapid implementation of acute revascularization strategies in the management of stroke, to date a limited proportion of patients presenting in clinical practice are eligible for such treatment.6 Finally, stroke events are a major cause of disability in adults, which may contribute to the higher risk of death after stroke compared with CHD.7

We conclude that a substantial increase in all-cause mortality was observed after the occurrence of CHD and even more after stroke in comparison to a baseline period. These results reinforce the major importance of primary and secondary prevention of cardiovascular disease. They also raise the issue of organizing acute care, particularly the dissemination of stroke units and multidisciplinary teams with cerebral revascularization facilities.

Acknowledgments
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Table 1. Crude Annual All-Cause Mortality Rates per 1000 Person-Years With 95% Confidence Intervals up to and After Coronary Heart Disease (CHD) and Stroke Events Over 10 Years of Follow-Up

<table>
<thead>
<tr>
<th>Event</th>
<th>Up to CHD or Stroke</th>
<th>After CHD</th>
<th>After Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (N=10424)</td>
<td>5.91 (5.43–6.40)</td>
<td>15.58 (11.31–19.86)</td>
<td>34.52 (18.11–50.93)</td>
</tr>
<tr>
<td>No personal history of CVD (N=9551)</td>
<td>5.42 (4.93–5.90)</td>
<td>13.12 (8.83–17.40)</td>
<td>21.73 (7.53–35.93)</td>
</tr>
<tr>
<td>Personal history of CVD (N=573)</td>
<td>11.70 (9.25–14.14)</td>
<td>28.39 (14.02–42.75)</td>
<td>102.16 (31.37–172.95)</td>
</tr>
<tr>
<td>French subpopulation (N=7712)</td>
<td>5.13 (4.61–5.65)</td>
<td>15.36 (9.86–20.85)</td>
<td>27.55 (9.55–45.54)</td>
</tr>
<tr>
<td>Northern Irish subpopulation (N=2712)</td>
<td>8.17 (7.04–9.31)</td>
<td>15.92 (9.11–22.73)</td>
<td>48.27 (14.82–81.72)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease.

Table 2. Hazard Ratios With 95% Confidence Intervals of Intercurrent Coronary Heart Disease (CHD) and Stroke Events for All-Cause Mortality Over 10 Years of Follow-Up

<table>
<thead>
<tr>
<th>Event</th>
<th>Simple Model</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>2.03 (1.52–2.71)</td>
<td>1.58 (1.18–2.12)</td>
<td>1.64 (1.22–2.20)</td>
<td>1.60 (1.19–2.14)</td>
<td>1.57 (1.17–2.11)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.98 (3.18–7.80)</td>
<td>3.13 (1.98–4.92)</td>
<td>2.71 (1.71–4.28)</td>
<td>3.05 (1.93–4.81)</td>
<td>3.19 (2.02–5.04)</td>
</tr>
</tbody>
</table>

Simple model adjusted for coronary heart disease and stroke event; Model 1, simple model+classical risk factors and country; Model 2, model 1+socioeconomic characteristics; Model 3, model 1+physical activity; Model 4, model 1+depressive symptoms.
de Chimie Biologique de la Faculté de Médecine de Strasbourg; the Department of Health (Northern Ireland); and the Northern Ireland Chest Heart and Stroke Association. We also thank the members of the event validation committees.

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Disclosures
None.

References
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SUPPLEMENTAL MATERIAL
The estimated hazard ratios and 95% confidence intervals compare the risk of all-cause mortality between the period following CHD or stroke and the period up to such events. Cox’s proportional hazards regression analyses were systematically adjusted for coronary heart disease and stroke event used as time dependent covariates and additional adjustments were sequentially made as detailed below:

**Simple Model** simultaneously and solely adjusted for coronary heart disease and stroke events (time dependent covariates).

**Model 1** (classical risk factors and country): simple Model + age, smoking status, systolic blood pressure, heart rate, body mass index, alcohol consumption, waist on hip ratio, personal history of cardiovascular disease, total and high density lipoprotein cholesterol, antidiabetic, antihypertensive and lipid lowering medications, and country

**Model 2** (socioeconomic characteristics): model 1 + educational level, living with a partner and employment status.

**Model 3** (physical activity): model 1 + physical activity.

**Model 4** (depressive symptoms): model 1 + 13-items Centre for Epidemiological Studies-Depression score and antidepressants.