Aspirin and Mortality in Patients With Diabetes Sustaining Acute Coronary Syndrome

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OBJECTIVE — We sought to compare mortality reduction associated with secondary prevention in patients with and without diabetes after acute coronary syndrome (ACS).

RESEARCH DESIGN AND METHODS — We conducted a cohort study involving 2,499 patients with ACS recruited from 11 U.K. hospitals. Multivariable analysis comparing all-cause mortality risk reduction associated with pharmacologic agents in patients with and without diabetes.

RESULTS — Aspirin was not associated with significant mortality benefit in diabetes sufferers (95% CI 0.50–1.08); nondiabetic patients derived a 48% mortality reduction ($P < 0.001$). The interaction between diabetes and aspirin use was statistically significant ($P = 0.037$), indicating that patients with diabetes experience less effective mortality reduction from aspirin use.

CONCLUSIONS — Aspirin, but not other secondary prevention agents, is associated with less effective mortality reduction in patients with diabetes and unstable coronary artery disease.

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The last decade has witnessed a significant improvement in use of evidence-based therapies and mortality after acute coronary syndromes (ACSs) (1). Outcomes for patients with diabetes may not have improved, despite similar improvements in the adoption of these strategies (2); the reasons for this are unclear. A recent meta-analysis suggested that antiplatelet agents confer less benefit to diabetic patients with stable vascular disease (3). We assessed whether this relationship remained in patients with unstable coronary artery disease.

RESEARCH DESIGN AND METHODS

— Retrospective analysis of the EMMACE-2 (Evaluation of Methods and Management of Acute Coronary Events-2) study was performed (4) examining outcomes in 2,499 unselected patients with ACS admitted to 11 U.K. hospitals between April and October 2003; all gave informed consent to participate, with ethics committee approval. ACS was diagnosed using established guidelines (5). The U.K. Office of National Statistics provided mortality data (mean 2 years).

Data in multivariable analyses include age, sex, heart failure, cardiovascular disease, chronic renal impairment, ST elevation, biomarker elevation (>0.06 μg/l Troponin I; Beckman Coulter), or creatinine kinase twice the upper reference range in the context of clinical myocardial infarction and provision of reperfusion, revascularization, aspirin, ACE inhibitors, statins, β-blockers, and clopidogrel. Doses were converted to equivalent doses based on the percentage of the maximal dose of other agents within these classes. Chronic renal impairment refers to estimated glomerular filtration rate <30 ml/min per 1.73 m^2. Cardiovascular disease is a composite of coronary, cerebral, or peripheral vascular disease. Reperfusion refers to primary angioplasty or thrombolysis and revascularization to in-hospital or planned percutaneous coronary intervention or coronary artery bypass grafting. Secondary prevention agent utilization was assessed at discharge from hospital. Individuals with diabetes were identified using past history documented in the medical records or provision of diabetes-related dietary or pharmacologic intervention during hospitalization.

Statistical analyses were performed using SPSS (version 13.0; SPSS, Chicago, IL). Groups were compared using *t* tests for continuous data and Pearson's χ^2 for categorical data. Statistical significance was defined as <0.05. Multivariable analysis using Cox proportional hazards analysis estimated hazard ratios (HRs) of clinical variables listed above in relation to all-cause mortality for cohorts with and without diabetes. Covariates were selected a priori and included in analysis without stepwise removal. Further multivariable analysis involving the entire study cohort included interaction terms between diabetes and drug classes to assess differences in mortality risk reduction related to diabetes status. Missing data resulted in omission of 63 patients.

RESULTS

— Seventeen percent of patients were diabetic; mean age was 71.5 years and, 58.5% were male, both similar to patients without diabetes. At 2 years, 162 (38.7%) and 543 (26.9%) deaths oc-

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Abbreviations: ACS, acute coronary syndrome.

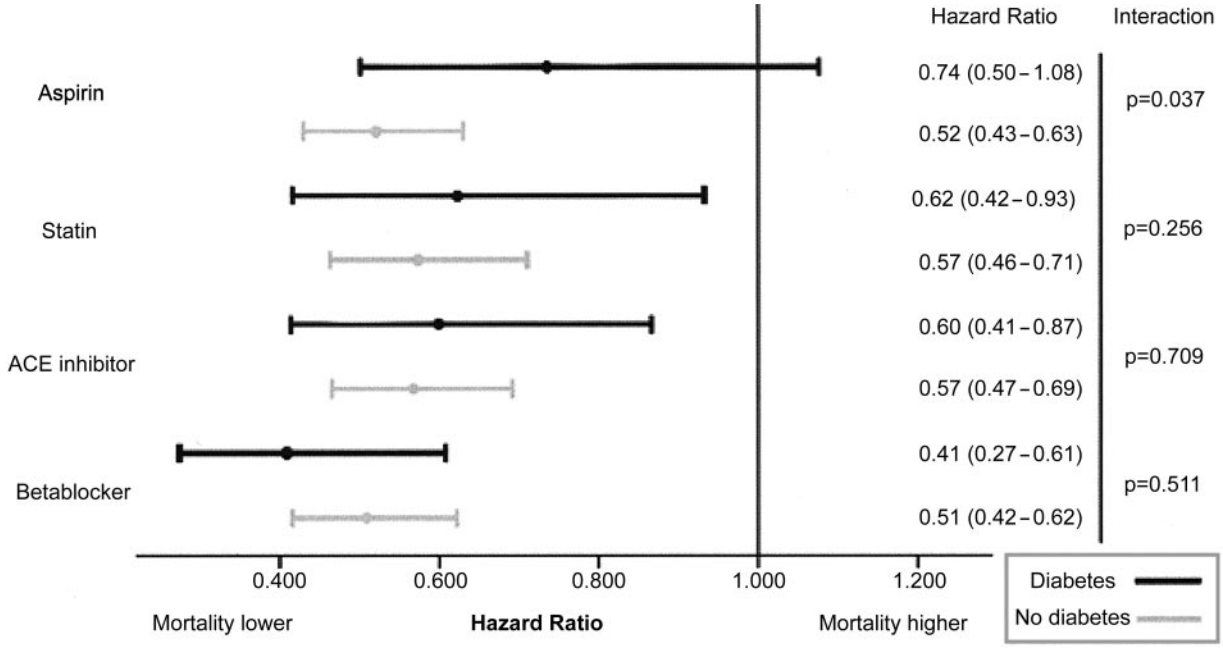

Figure 1—*HRs (95% CI) associated with secondary prevention agents in groups with and without diabetes.*

curred in patients with and without diabetes, respectively. Patients with diabetes experienced rates of heart failure and chronic renal impairment around twice those of nondiabetic patients (10.2 and 7.9%, respectively). Non–ST segment elevation ACS was more common in diabetic patients (80.8 vs. 71.7%). Aspirin, statin, and clopidogrel use was similar, whereas patients with diabetes were more likely to receive ACE inhibitors and received β-blockers less often. The mean ± SD doses of agents (milligrams) received by patients with and without diabetes, respectively, were 108.9 ± 8.9 and 117.8 ± 4.0 for aspirin ($P = 0.07$), 31.6 ± 2.4 and 29.6 ± 0.8 for the simvastatin equivalent ($P = 0.126$), 5.4 ± 0.4 and 4.9 ± 0.2 for the ramipril equivalent ($P = 0.017$), and 4.5 ± 0.3 and 4.4 ± 0.2 for the bisoprolol equivalent ($P = 0.81$). Clopidogrel was always prescribed at 75 mg daily.

HRs associated with the use of pharmacologic agents, after accounting for the clinical variables described in RESEARCH DESIGN AND METHODS, are outlined in Fig. 1. Clopidogrel was associated with nonsignificant mortality reduction in patients with and without diabetes (HR 0.86 [95% CI 0.6–1.23] and 0.92 [0.74–1.14], respectively). The interaction between diabetes status and pharmacologic agent use was statistically significant only for aspirin, suggesting that patients with diabetes derive less survival benefit from this agent but comparable benefits from statins, ACE inhibitors, β-blockers, and clopidogrel.

CONCLUSIONS — Despite similar dosing regimens, our study suggests aspirin offers less effective mortality reduction post-ACS to patients with diabetes, which contrasts with clopidogrel, statins, β-blockers, and ACE inhibitors. Our observations support the need for more effective antiplatelet strategies to improve outcomes in patients with diabetes and unstable coronary disease. Observational research is criticized for not accounting for bias and unknown confounding factors, though clinical trial data are often poorly representative of real-life practice. However, our work compliments the Anti-Thrombotic Trialists' meta-analysis of antiplatelet therapy in stable cardiovascular disease (3) by providing similar findings in unstable coronary artery disease. The distinction between stable and unstable vascular diseases is significant though; as such, our observations are important. Further corroborating evidence comes from studies showing enhanced platelet activity in patients with diabetes treated with aspirin (6–8). The other secondary preventative agents in our study were associated with similar magnitudes of risk reduction in patients with and without diabetes. Supporting data again exists suggesting comparable benefits for statins, ACE inhibitors, and clopidogrel in primary and secondary prevention (9–12).

The mechanisms underlying our observations are unclear. One could speculate that aspirin dosing, antiplatelet agent combinations, compliance, or diabetes-specific factors (e.g., hyperglycaemia) may be relevant (13). Further investigation is required to elucidate the impact of diabetes on platelet biology and assess novel therapeutic strategies. In particular, though, further clinical trials of aspirin in patients with diabetes are needed to improve the poor outcomes they continue to experience after ACS.

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