Editorial

Diabetes abolishes the gender gap in coronary heart disease

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Prior to menopause, the incidence of coronary heart disease (CHD) is considerably lower among women than men. One reason to account for this disparity is that males are more likely to be associated with an adverse risk profile. Interestingly, the relative risks conferred by several of the various coronary risk factors, including cholesterol level, diastolic blood pressure, smoking and social class, were approximately similar for both sexes. However, the adverse relationship of other coronary risk factors, such as diabetes, low high-density lipoprotein cholesterol and high triglycerides, was greater in women. Indeed, patients with diabetes, especially women, were twice as likely to suffer from coronary events.1 Subsequent data from the Finnish Study suggested that patients with diabetes, regardless of sex, were considered as coronary equivalents.2

In this issue of the European Heart Journal, Becker et al.3 evaluated the 10-year risk of cardiovascular events in a cohort of 2461 Caucasians with and without diabetes. Although diabetes was associated with a greater risk for adverse cardiovascular events, the effect was modified by gender. Comparing individuals without diabetes but with prior cardiovascular disease to those with diabetes but without prior cardiovascular disease, the risk for unfavourable cardiovascular events was lower for men (adjusted hazard, 0.5; 95% confidence interval [CI], 0.3–0.9) but similar for women (adjusted hazard, 1.0; 95% CI, 0.6–1.7). The authors concluded that only women but not men with diabetes should be considered as coronary equivalents.2

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Compared with earlier studies,2,4,5 this study3 employed a different definition of patients with prior cardiovascular disease. Previous reports2,4,5 used prior MI as the basis for comparison while several medical conditions, including prior MI, coronary revascularization procedures, angina pectoris, transient ischaemic attack or stroke, intermittent claudication or the use of nitrates, were used in this study. Furthermore, the endpoint employed in this study was a composite of various disease states and revascularization procedures. This broad range of inclusion conditions may have impacted on their findings and conclusions.

Another factor that has a consistent effect on coronary risk is the duration of diabetes.4,5 This risk increases strikingly during the first few years and stabilized after 5 years. However, Becker et al.3 commented that their conclusion did not change when their data were re-analysed using only those with prior MI (about a third of their patients) or excluding newly-diagnosed diabetics. Unfortunately, the relative risks and confidence intervals were not provided. Conversely, in a larger study of 51,316 men in the Health Professionals Follow-up Study,4 the adjusted relative risk for 10-year all-cause mortality for patients with diabetes but without prior MI compared with those without diabetes but with
prior MI was \( \sim 0.9 \). But the discrepancies between these two groups of men were larger for cardiovascular and fatal coronary deaths.

Indeed previous large cohort studies have suggested differences in relative coronary risk for diabetes and CHD between the two sexes. The Physicians’ Health Study\(^6\) followed-up 91 285 male physicians for 5 years. Compared with those without diabetes or CHD (defined as prior MI or angina), the *adjusted* relative risks for all-cause mortality were 2.1 (95% CI, 1.9–2.4) and 2.2 (95% CI, 2.0–2.4) for physicians with diabetes but without prior CHD and those without diabetes but with prior CHD, respectively. These relative risks suggested that there was little difference in the risk conferred by diabetes or prior CHD in men. Correspondingly, the Nurses’ Health Study\(^5\) followed-up 101 046 female nurses for up to 20 years. Compared with those without diabetes or prior MI, the *adjusted* relative risks for all-cause mortality were 3.1 (95% CI, 2.8–3.4) and 2.6 (95% CI, 2.6–3.1) for female nurses with diabetes but without prior MI and those without diabetes but with prior MI, respectively. It appeared that diabetes might have conferred a greater mortality risk than prior MI in women. However, the *adjusted* relative risk for cardiovascular mortality was comparable between female nurses without diabetes but with prior MI and those with diabetes but without prior MI.

Part of these variations may be explained by the extent of coronary atherosclerosis as determined in a population-based autopsy study.\(^7\) Not unexpectedly, the prevalence of significant coronary atherosclerosis was higher among decedents with diabetes than non-diabetics. Notably, there was little difference in the prevalence of significant coronary atherosclerosis between men and women with diabetes. Among women, the prevalence of significant coronary atherosclerosis was similar between those with diabetes but without antemortem history of CHD and those without diabetes but with antemortem history of CHD. This finding may partly account for the excess in all-cause but not cardiovascular mortality which was observed in a cohort study.\(^4\)

Conversely, the prevalence of significant coronary atherosclerosis was higher among younger men (age 30 to 64 years) with antemortem CHD but without diabetes compared with younger men without antemortem CHD but with diabetes. Likely, the impact of diabetes and prior MI is dissimilar between men and women.

Several physiological differences may also exist between the two sexes. Vascular susceptibility to coronary risk factors differs between the two sexes and may be greater for men. Part of this variation was attributed to estrogen in women. However, the pivotal Heart Estrogen/Progestin Replacement Study did not show that routine replacement with oestrogen/progestin in postmenopausal women reduced CHD events.\(^8\) On the other hand, hormonal therapy has been shown to improve glycaemic profile, and may lower the risk of MI in postmenopausal diabetic women.\(^9\) Likely, diabetes obliterates the protective effects of female hormones and increases the coronary risk to that of a male.

Importantly, diabetes even in patients without CHD confers a greater atherosclerotic risk in men and women. Although the impact may be greater for women, aggressive management of concomitant risk factors should be recommended for both sexes. Indeed, patients with type 2 diabetes derived greater benefit from targeted, intensified multifactorial intervention than usual care. In the Steno-2 Study,\(^10\) 160 patients were randomly assigned to conventional or intensive treatment. After a mean follow-up of 7.8 years, the risks for cardiovascular disease (hazard, 0.47; 95% CI, 0.24–0.73), nephropathy (hazard, 0.39; 95% CI, 0.17–0.87), retinopathy (hazard, 0.42; 95% CI, 0.21–0.86) and autonomic neuropathy (hazard, 0.37; 95% CI, 0.18–0.79) were substantially lower among those receiving intensive treatment. Nonetheless, the results of other clinical trials, such as the proposed Prevention of Cardiovascular Disease in Diabetes Mellitus Study Group and subgroup analysis of diabetics in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), are desperately needed to define the efficacy of current preventive strategies for this high-risk group of patients.

References