EDITORIAL

Interplay of diabetes and coronary heart disease on cardiovascular mortality

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Patients with both diabetes mellitus and prior myocardial infarction are at particularly high risk for cardivascular mortality

Diabetes mellitus (DM), mainly type 2 diabetes (90–95% of diabetic patients), affects approximately 100 million people worldwide, including 17 million in the USA and 1.15 million in the UK. A 30% increase in incidence is predicted by 2025, due to both the increased rate of obesity and the aging populations living in industrial countries.[1 2] DM increases by 2–4 fold the risk of coronary artery disease (the leading cause of morbidity and mortality in developed countries), stroke, peripheral vascular disease, and heart failure.[3] DM is a predictor of poor prognosis after acute myocardial infarction, congestive heart failure, and all modes of coronary revascularisation. The acceleration of atherosclerosis and atherothrombosis in diabetic patients has been related to endothelial dysfunction, dyslipidaemia, insulin resistance, and chronic hyperglycaemia. The presence of free fatty acids, glycosylation end products, favours vasoconstriction, inflammation, and thrombosis. Improvements in primary and secondary prevention has led to a decline in mortality rates from cardiovascular (CV) disease in the general population, but to a lesser extent in diabetic patients.[4]

Whether acceleration of the atherothrombosis process alters the prognosis in diabetic patients and confers the same excess risk associated with prior myocardial infarction (MI) still remains a matter for debate. The report in this issue of *Heart* by Wannamethee and colleagues demonstrates that: (1) diabetic middle aged male patients with coronary heart disease (CHD) are at higher risk of cardiovascular events and death; (2) total mortality is not significantly different in diabetic male patients without prior MI and with prior MI but without DM; (3) CHD mortality is higher in men with prior MI compared with diabetic patients without MI; and (4) prolonged duration of DM (> 12 years) increased CHD mortality in male diabetic patients similar to the rate of CHD mortality in male patients with prior MI.[5]

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EPIDEMIOLOGICAL STUDIES

These findings are consistent with several epidemiological studies comparing the risk of total and CV mortality in diabetic patients without overt CHD and non-diabetic patients with prior MI.[6–13] These studies, summarised in table 1, have shown convincingly that patients with both DM and prior MI are at particularly high risk for CV mortality. The risk of total mortality associated with DM is similar to that associated with prior MI or CHD, each conferring a twofold increased risk in death. Whether DM is risk equivalent to prior MI for CV mortality remains controversial. Some of the differences in these reports may be related to selection criteria in study populations, definition of DM, age, ethnicity and size of the groups, modality of DM and CHD report (self reported versus medical record) and end points (MI in some of the reports versus CHD in others). None evaluated the impact of silent myocardial ischaemia on CV events or death, known to be higher and more severe in the diabetic population.

What is the real influence of DM duration on the occurrence of cardiovascular events, reported as being closely linked in the study by Wannamethee and colleagues?[5] Since the duration of DM is a powerful independent risk factor for CHD mortality, this conclusion needs further confirmation.[5 8 11] Finally, the influence of sex also seems important since several studies have demonstrated that DM was a stronger risk factor for CHD in women than in men, with age adjusted CHD mortality rates three times higher in diabetic women than in non-diabetic women, and two times higher in diabetic men than in non-diabetic men.[8 12]

Based on the report from Haffner and colleagues showing that diabetic patients without prior MI had a risk of a CHD event similar to that in non-diabetic patients with prior MI, the adult treatment panel of the National Cholesterol Education Program considered type 2 DM as a coronary artery disease risk equivalent.[6 14] Although Haffner's study was not primarily designed to demonstrate differences in CV mortality in diabetics and non-diabetics with MI, intensive primary prevention in diabetic patients was recommended; this included aggressive blood pressure and lipid level lowering treatment, although the cost–effective consequences were not clearly established.[6] Secondary prevention with statins and angiotensin converting enzyme (ACE) inhibitors demonstrated a greater reduction in mortality in diabetic patients, although such patients are less likely to be treated with these drugs.

Abbreviations: ACE, angiotensin converting enzyme; CHD, coronary heart disease; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction

Table 1 Epidemiologic studies comparing diabetics without prior myocardial infarction (MI) or coronary heart disease (CHD) with non-diabetics with MI or CHD

Study author Design	n D− MI+ *v* n D+ MI− % female DM type	Mean age DM duration Follow up	CV events DM− MI+ *v* DM+ MI−	Total mortality CV mortality DM− MI+ *v* DM+ MI−	Comments
Haffner 1998, Register Finnish[6]	69 *v* 890 45% F Type 2 DM	58 years 8 years 1982–1990	Incidence of MI 18.8% *v* 20.2%, p<0.001 Incidence of stroke 7.2% *v* 10.3%, p<0.001	CV mortality 15.9% *v* 15.4%, p<0.001 HR for mortality 1.2 (95% CI 0.6 to 2.4), p=0.5 between D+ *v* D−	Lack of power to detect differences between the two groups
Simons 1998, Prospective Australia[7]	478 *v* 130 48% F Type 1 + 2 DM	70 years NR 8.2 years	Incidence of CHD 52.7% *v* 31.5%, p NR HR 0.67 (95% CI 0.46 to 0.97), p<0.04, D+ CHD− *v* D− CHD+	NR	
Hu 2001, Prospective USA[8]	1302 *v* 3705 100% nurses Type 2 DM	62 years NR 1976–1996	NR	Total mortality RR* 2.58 *v* 2.44 CV mortality RR* 7.46 *v* 4.86 Fatal CHD RR* 10.7 *v* 5.65	Women who were D+ >15 years were similar with prior CHD
Lotufo 2001, Prospective PHS,USA[9]	5906 *v* 2317 100% M Type DM NR	62 years NR 5 years	NR	Total mortality RR* 2.2 *v* 2.3 CHD mortality RR* 5.6 *v* 3.3	DM+ CHD+ identifies a high risk group
Evans 2002 Transversal cohort studies Scotland[10]	Transversal 1347 *v* 1155 42% F Type 2 DM Cohort 7414 *v* 3977 49% F	57 years 6 years 1988–1995 66 years	Hospitalisation for MI Transversal RR 2.27 DM− MI+ *v* DM+ MI− Cohort RR 3.10 DM− MI+ *v* DM+ MI−	Total mortality RR 1.33 D− MI+ *v* D+ MI− Total mortality RR 1.35 D− MI+ *v* D+ MI− CV mortality RR 2.93 D− MI+ *v* D+ MI−	Increased risk with male sex for total death and age for total and CV death in the 2 studies
Cho 2002, HPFS USA[11]	2038 *v* 230 100% M Type 2 DM	61 years 0–26 years 10 years	NR	Total mortality RR* 2.07 *v* 1.76 CV mortality RR* 5.51 *v* 2.75 Fatal CHD RR* 8.39 *v* 3.37	Duration of DM independent risk factors for total and CHD death
Becker 2003, Register Dutch[12]	234 *v* 208 48% F Type 2 DM	62 years 6.4 years 1989–2000	Men HR* 7.1 D− CVD+ HR* 4.0 D+ CVD− Women HR* 3.5 D− CVD+ HR* 4.0 D+ CVD−	Fatal event Men HR* 2.4 D− CVD+ HR* 1.2 D+ CVD− Women HR* 2.6 D− CVD+ HR* 5.1 D+ CVD-	Women DM+ CVD− have a risk of CV event and death similar with women DM− CVD+
Lee 2004, Prospective, ARIC USA[13]	283 v 1460 % F NR Type 2 DM	45–64 years NR 9 years	NR	Fatal CHD + non-fatal MI RR 1.86 D− MI+ *v* D+ MI− Fatal + non-fatal stroke RR 1.05 D− MI+ *v* D+ MI− CV mortality RR 1.82 D− MI+ *v* D+ MI−	Same results when newly diagnosed DM (self reported) at baseline are included
Wannamethee 2004, Prospective UK[5]	547 v 202 100% M Type DM NR	63 years NR 10 years	Incidence CHD events 19% D+ CHD− *v* 19.9% D−Angina+ *v* 30% D− MI+ RR D− MI+ *v* D+ MI− CHD event 1.59, stroke 0.87	Total mortality D− MI+ *v* D+ MI− RR 1.25 (95% CI 0.94 to 1.67) CHD mortality D− MI+ *v* D+ MI− RR 1.47 (95% CI 0.94 to 2.29)	Increased CHD events and death with duration of DM >12 years

CHD, any manifestation of coronary heart disease; CV, cardiovascular; CVD, history of any of the following: acute MI, CABG, PCI, stroke, intermittent claudication, or use of nitrates; DM, diabetes mellitus; D+, diabetic patients; D−, non-diabetic patients; F, female; HR, hazard ratio; M, male; MI, myocardial infarction; NR, not reported; RR, risk ratio; *RR or HR in comparison with D− CHD− or MI− or CVD−.

DRUG INTERVENTIONAL STUDY

Time has come to design a randomised drug interventional study to establish CV morbidity and mortality reduction in the diabetic population. There is growing evidence that aspirin, statins, and ACE inhibitors reduce cardiac death in such patients. Two prevention studies—HOPE (heart outcomes prevention evaluation) using an ACE inhibitor in cardiac patients, and LIFE (losartan intervention for endpoint reduction in hypertension) using an angiotensin II receptor blocker in hypertensive patients with ECG proven left ventricular hypertrophy—have been shown to decrease the incidence of new onset diabetes mellitus in high risk patients with no history of prior diabetes (risk reduction −34% and −25%, respectively).[15 16] The armamentarium of drug treatment in diabetic patients to decrease the risk of CV events might also include new antiplatelet drugs and β blockers.

The increasing burden of diabetes mellitus in developed countries and related cardiovascular consequences in the diabetic population deserves intensive strategies for risk reduction in both primary and secondary prevention. Recommendations from observational and interventional studies specifically focused on diabetic populations may help physicians to apply adequate guidelines and drug treatment, and thus achieve the main goals of cardiovascular disease prevention.

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