Diabetes mellitus and incident cardiovascular disease: does one risk fit all?

Nazim Ghouri, Miles Fisher

The importance of diabetes mellitus being seen as a major risk factor for cardiovascular disease (CVD) was developed by Haffner et al. in 1998. They suggested that a person with diabetes but without previous CVD had an equivalent risk for an event compared to the risk of a recurrent event in a non-diabetic patient with a previous myocardial infarction. This was the position taken by the influential Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III), and followed by many later important statements. Prior to the data from Haffner et al., data from the Framingham study in the late 1970s suggested that type 2 diabetes mellitus (T2DM) increased the risk of a first CVD event by two- to three-fold. While more modern data from the Emerging Risk Factors Collaboration (ERFC) suggest that CVD risk may still be around two-fold compared to non-diabetic subjects, the ERFC authors acknowledged that duration and age of onset of diabetes were not factored into their analysis, which combined with other recent data has questioned the strength of association. These relatively large longitudinal and linkage studies with incident cardiovascular endpoints have focused on specific factors within the general diabetic population. These include the effect of glycaemic control, duration of diabetes, age of onset of diabetes, gender, type of diabetes and ethnicity.

Making use of contemporary data and reflecting on these factors, we question whether the increased cardiovascular risk is as significant or as uniform as initially portrayed.

Glycaemic control, disease duration and age of onset in type 2 diabetes

Follow-up data from the UKPDS published at the turn of the millennium indicated that risk of incident myocardial infarction (MI) reduced linearly by 14% with 1% (11mmol/mol) reductions in mean updated HbA1c, with subjects being followed up for a median of 10.4 years. This risk was based on a male aged 50–54 who had T2DM for 10 years, so could duration of diabetes or patient age be important confounders influencing the increased risk? For example, recent analysis of the British Regional Heart Study showed that men who develop diabetes after the age of 60, and have a short duration of diabetes (average of 1.9 years), have a coronary heart disease (CHD) risk around half that of men of similar age who develop diabetes before 60 (average duration 16.7 years), with only the latter group having a similar risk to those with previous MI and no T2DM. Thus, duration of diabetes influences CHD risk and, typically, disease duration of close to a decade or more is needed to reach a CHD risk equivalent state. Interestingly, mean duration of diabetes was longer than eight years in the Haffner cohort. By contrast, analysis from Scotland showed CVD mortality risk and risk for hospitalisation for MI to be about three-fold lower in persons with newly diagnosed diabetes (mean age 66 years) compared with patients with recent MI.

Indeed, even if glycaemic control deteriorates in later years, ‘the legacy effect’ from previous tight control has been shown to be associated with positive outcomes in the long term. Thus, the importance of tight glycaemic control in younger people with T2DM who will ultimately have the disease for a longer duration is of extreme value if adverse cardiovascular outcomes are to be avoided.

Effect of gender

The increased risk associated with female gender is becoming more topical. Newly published data from Kahany et al. are of particular interest as the analysis included women who had earlier T2DM (age <60). They examined subjects aged <60 years without coronary artery disease (CAD) at enrolment from three longitudinal studies – the high-risk GeneSTAR Study, Multi-Ethnic Study of Atherosclerosis (MESA) and Nhanes III Mortality Follow-up Study, following-up patients for up to 15 years. The outcome was any CAD event during follow-up (fatal CAD in Nhanes). They found that, in the absence of diabetes, CAD rates were lower among women in GeneSTAR, MESA, and Nhanes (4.27, 1.66, 0.40/1000 person-years, respectively) versus men (11.22, 5.64, 0.88/1000 person-years). In the presence of diabetes, CAD event rates were similar among women (17.65, 7.34, 2.37/1000 person-years) and men (12.86, 9.71, 1.83/1000 person-years). Adjusting for demographics, diabetes was associated with a significant four- to five-fold higher CAD rate among women in each cohort, without differences in men. Further, meta-analyses of the three cohorts, after adjustment for cardiometabolic risk factors, showed the hazard ratio (HR) of CAD in men versus women among non-diabetes was 2.43 (HR 95.76–3.35) and among people with diabetes was 0.89 (HR 0.43–1.83), p=0.013 interaction by diabetes status. Thus, though young and middle-aged women were less likely to develop CAD in the absence of diabetes compared to men, the presence of diabetes made women of equal risk to that of diabetic men.

What are the reasons why women have a disproportionately increased risk of CVD compared to men in the presence of T2DM? The authors posed several possibilities including: gender-unique risk for CVD; the more adverse effects of inflammatory factors of insulin action in women; and women with diabetes may be less adherent to oral antidiabetic drugs and standard cardiovascular prevention treatments. However, the authors acknowledged that they were unable to factor in the effects of glycaemic control and duration, both of which, as mentioned earlier, influence CVD risk. Recently, Sattar suggested that as women have to attain a greater BMI to develop T2DM relative to men, especially at younger ages, this results in greater relative worsening of the CVD risk.
factors that are linked to adiposity and insulin resistance, and these worsen more in women as they transition to T2DM, thus in essence losing their previous protective phenotype and equalising the gender risk. Until further research identifies causal factors, clinicians are likely to do more benefit than harm, by considering women with diabetes as a higher-risk subgroup who should have tight diabetic and CVD risk factor management.

**Does type 1 DM confer a risk similar to type 2 DM?**

Historic data consisting of 23,000 type 1 diabetes (T1DM) patients in the UK showed that both men and women had increased CHD risk compared to the general population, with reported CHD standardised mortality ratios (SMRs) of 4.5 and 8.8 in men and women, respectively, relative to the general population for a period of follow-up from 1972–2000. SMRs were as high as 8.9 and 41.7 in men and women, respectively, who were aged 1–40. Moreover, further analysis on this cohort showed that people with T1DM had a risk similar to T2DM for cerebral vascular disease. Nearly 20 years on, data from the Scottish Care Information-Diabetes Collaboration (SCI-DC) database, which captures over 99% of people with diabetes living in Scotland, have been published on incident CVD events and CVD mortality in patients with T1DM. The age-adjusted incidence rate ratio (IRR) for CVD mortality associated with T1DM was increased compared to the general population and was similar for both men and women (men 3.4, 95% CI 2.7–4.2; women 3.5, 95% CI 2.4–4.9). While these risks are elevated, they are considerably lower than data published on populations followed 20–40 years ago. For example, in the Wisconsin Epidemiologic Study of Diabetic Retinopathy for the period 1980–1988, Moss et al. reported SMRs for ischaemic heart disease of 9.1 in males and 13.5 in females in 1200 young-onset diabetes patients. Data from the SCI-DC database also demonstrated the IRR for a first CVD event associated with T1DM versus the non-diabetic population was higher in both genders, but more so in women (3.0, 95% CI 2.4–3.8, p<0.001) than men (2.3, 95% CI 2.0–2.7, p<0.001). Finally, as for T2DM, the duration of disease was positively associated with the increasing IRRs for CVD for T1DM people even after adjustment for age. The IRRs were 2.17 (95% CI 1.69–2.77), 2.37 (95% CI 1.98–2.83), and 2.41 (2.01–2.88) in those with duration 10.8, 10.8–22, and >22.0 years, respectively, in men, and 2.63 (95% CI 1.95–3.54), 2.91 (95% CI 2.05–4.13), and 3.22 (95% CI 2.52–4.13) in women adjusted for age. Thus, people with T1DM seem to have an increased risk of adverse cardiovascular outcomes compared to people with T2DM and, just like in T2DM, women appear to have an increased risk compared to men in the type 1 population.

**Effect of ethnicity**

The role of ethnicity influencing CVD risk should also be considered. For example, South Asians who have increased prevalence of T2DM have been shown to have poorer CVD outcomes compared to their European peers. In the South Asian group, T2DM increased the CHD mortality risk nearly three-fold compared with South Asians without diabetes at baseline; yet in the Europeans, the excess mortality associated with diabetes was only 1.5-fold. The ethnic difference in CHD mortality persisted in subjects with diabetes, with a doubling of CHD mortality in South Asians. Whether this is a reflection of the poorer glycaemic control South Asians have compared to Europeans with T2DM, or for some other reason, remains to be determined.

**Practical implications for patient management**

It can be concluded from this brief review of the historic and contemporary data that the magnitude of increased risk of CVD in patients with diabetes may not be uniform in this population as a whole, with certain phenotypes having an exaggerated risk compared to others. Interestingly, the recent American cholesterol guidelines recommend the use of statin therapy for people with diabetes aged 40–75 years. They recommend calculating risk using a risk calculator that includes conventional risk factors plus ethnicity. For patients with lower risk moderate-intensity statin therapy is recommended, and for patients with high estimated risk high-intensity statins are recommended – so different levels of risk are identified in people with diabetes depending on conventional factors and ethnicity.

Overall, the magnitude of risk appears to be reducing both in type 1 and type 2 diabetes, with duration of diabetes being the main factor that increases risk of CVD compared to non-diabetics. Thus, the importance and benefit of optimising glycaemic control and associated CVD risk factors by following key guidelines remain just as significant. Ray et al. have calculated that while improving HbA1c reduces microvascular outcomes, greater benefit in CVD risk reduction can be achieved by managing other modifiable risk factors such as blood pressure and cholesterol, highlighting that a holistic approach is required when managing patients with diabetes. However, the latest data from SCI-DC published in the 2012 Scottish Diabetes Survey (www.scotpho.org.uk/opt/Reports/SDS%202012.pdf) have shown that there is significant room for improvement, with only 55.6%, 77.5% and 79.5% of all people with diabetes meeting national targets in glycaemic control, blood pressure and cholesterol respectively.

Clinicians need to improve the overall management of patients with diabetes if reduction in incident cardiovascular disease is to become a consistent reality – particularly if they are aiming to succeed in the higher risk subgroups, such as those with an earlier onset of diabetes, those who have it for a longer duration, in women, those with type 1 diabetes, or those from a higher-risk ethnic background.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available in Practical Diabetes online at www.practicaldiabetes.com.
References


