

Extreme ischaemic heart disease risk in people with type 1 diabetes

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Observational epidemiology shows strong associations between diabetes and risk of ischaemic heart disease (IHD).[1] Data, mainly from population-based cohorts in high-income countries, suggest diabetes doubles the risk of IHD, and this association may be doubled again in countries where healthcare resources to treat diabetes are limited.[2] Diabetes associates with several known cardiovascular disease risk factors, but the persistence of this excess risk despite accounting for the effects of blood pressure, lipids and lifestyle factors including smoking, suggests other important mediators of risk exist.[1]

Most large-scale observations of diabetes, glycaemic control and IHD have come from populations where type 2 diabetes predominates. In this edition of *Heart*, Matuleviciene Anängen and colleagues have studied IHD risk in type 1 diabetes and assessed how glycaemic control and reduced kidney function influence this risk.[3] Studying these exposures in type 1 diabetes is an attractive strategy as the condition is often diagnosed in otherwise healthy young people without existing cardiovascular disease risk factors, and any reduced kidney function is likely a consequence of diabetes. This contrasts with type 2 diabetes, which generally develops later in life after prolonged exposure to other risk factors for IHD and chronic kidney disease (CKD), such as excess adiposity, high blood pressure or dyslipidaemias, is possible.

This large and important study from the Swedish National Diabetes Register included observations from 33,000 people with type 1 diabetes, with an average age of 35 years and diabetes duration of 20 years, and a mean glycosylated haemoglobin level (HbA1c) of 8.2% (66 mmol/mol).[3] Over about 8 years of follow-up, risk of fatal or non-fatal IHD was quadrupled compared to age and sex matched controls, highlighting the importance of type 1 diabetes as a risk factor for IHD in otherwise healthy people. Indeed, this risk was much higher than the 30% relative increase in cardiovascular mortality in people with type 2 diabetes followed by the same registry and analysed using the same methods (perhaps in part reflecting the 3-4-times longer duration of diabetes in the current study). Given Sweden's rating as a top provider of diabetes care in Europe,[4] the relative risk of 4 from these Swedish data may not represent the association between diabetes and risk of IHD for people with type 1 diabetes from other parts of the world, where healthcare resources are more limited and so risk could be even higher..

A key strength of the study was the availability of baseline measures of diabetes duration, glycaemic control and kidney function. Using these data, extreme associations of both poor glycaemic control and CKD with IHD risk were demonstrated. Overall, those with type 1 diabetes and an HbA1c $\geq 9.7\%$ (≥ 83 mmol/mol) were at about 11-times increased risk of IHD compared to controls, whilst those with CKD stages 4 and 5 were at 13-times and 19-times increased risk, respectively. Moreover, these relative hazards increased further when poor glycaemic control and CKD were combined. A limitation of the study was that it was not possible to adjust for some key mediators of risk, including smoking. If smoking was more common in controls, the diabetes-associations may be underestimates of the true association.

The relative hazards for IHD were particularly high among women. For example, women with type 1 diabetes and HbA1c $\geq 9.7\%$ were at 18-times higher risk of IHD compared to controls. The finding of higher relative risks in women than men mirrors data from prospective studies

of type 2 diabetes,[1 5 6] in which relatively higher diabetes-associated IHD risk in women exists despite similar levels of vascular risk factors, cardiovascular protective treatment use and glycaemic control.[5] As well as showing that in type 1 diabetes, these relative risks for IHD were larger in women versus men for a given HbA1c,[3] Matuleviciene Anängen and colleagues have reduced the list of possible causes for these sex differences by excluding CKD: type 1 diabetes-associated risk of IHD was higher in women than men at any given level of albuminuria or kidney function. Importantly, although the reason for sex differences in diabetes-associated relative risks remains unclear, men in Sweden were at higher baseline risk of IHD than women, so the absolute rate of IHD within age groupings was similar in men and women with type 1 diabetes. In young adulthood (ages 18-34 years), men and women with type 1 diabetes both had a 10-year risk of IHD of nearly 1%, increasing to 6% by ages 35-49. These absolute risks were high for both sexes.

Clinical trials and Mendelian randomization experiments support a causal role for hyperglycaemia in IHD,[7 8] and 30-year follow-up of intensive versus standard glycaemic control in the Epidemiology of Diabetes Interventions and Complications study (the long-term follow-up of the Diabetes Control and Complications Trial) specifically supports this hypothesis in type 1 diabetes.[9] The steep positive association between glycaemia and IHD risk reported in individuals with a 20-year history of type 1 diabetes in the Swedish National Diabetes Register[3] reinforces current guidelines encouraging glycosylated haemoglobin targets of 6.5% (48 mmol/mol) in people with long life expectancy.[10] However, the observation that IHD risk was 3-times higher in women with type 1 diabetes compared to controls even when glycosylated haemoglobin levels were <7% (<53 mmol/mol) and in the absence of albuminuria or abnormal kidney function, suggests other mediators of IHD risk may have been present and supports the argument that interventions to lower risk should be offered early.

There is clear evidence that intensive low-density lipoprotein (LDL) lowering in people with diabetes reduces vascular risk. Individual participant data meta-analysis has shown that - irrespective of the presence or absence of hypercholesterolaemia - the relative benefits per 1.0 mmol/L lower LDL-cholesterol on vascular risk were similar among those with or without diabetes, and these benefits appear similar when those with type 1 and 2 diabetes were considered separately.[11] Blood pressure lowering is also beneficial,[12] and given that reduced kidney function was associated with substantially higher IHD risk,[3] it would seem logical to consider early treatment with renin-angiotensin system inhibitors. This strategy has the added benefits not only of renoprotection, but may also reduce the development of other non-atherosclerotic arterial and structural heart disease, which are common in people with CKD. Interventions to lower IHD risk should also include smoking cessation support: the study showed 1-in-7 of those with type 1 diabetes in Sweden was a smoker.

In summary, new data from the Swedish National Diabetes Register have shown that since 1998 - and despite Sweden being rated as a top provider of care for people with diabetes - type 1 diabetes was associated with about a four-fold higher risk of IHD. On average, by age 18-34 years, 10-year IHD risk for a man or woman with type 1 diabetes was about 1%, increasing to 6-7% by ages 35-49. These risks could be substantially higher among those with poor glycaemic control and particularly among those who have developed CKD, but such risk factors were not pre-requisites of IHD risk.

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References: 12 (limit up to 8)

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