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DIABETES AND CARDIOVASCULAR DISEASE (S MALIK, SECTION EDITOR)

Update on Type 2 Diabetes as a Cardiovascular Disease Risk Equivalent

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Abstract Type 2 diabetes increases the risk of cardiovascular disease (CVD) from two- to four-fold. In our large Finnish population-based study published in 1998 subjects with medication for type 2 diabetes had as high a risk of fatal and nonfatal myocardial infarction (MI) during the 7-year follow-up as non-diabetic subjects with a prior MI, suggesting that type 2 diabetes is a CVD equivalent. In another large study, including all 3.3 million residents of Denmark, subjects requiring glucose-lowering therapy exhibited a CVD risk similar to that of non-diabetic subjects with a prior MI. Subsequent studies have not systematically replicated aforementioned results. Some studies have supported the concept that type 2 diabetes is a CVD equivalent only in some subgroups, and many studies have reported negative findings. This is likely to be due to many differences across the studies published, for example ethnicity, gender, age and other demographic factors of the populations involved, study design, validation of diabetes status and CVD events, statistical analyses (adjustments for confounding factors), duration of diabetes, and treatment of hyperglycemia among diabetic participants. Varying results reflect the fact that not all diabetic patients are at a similar risk for CVD. Therefore, CVD risk assessment and the tailoring of preventive measures should be done individually, taking into consideration each patient's long-term risk of developing cardiovascular events.

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Introduction

Diabetes increases the risk of cardiovascular disease (CVD) from two- to four-fold [1, 2]. Patients with type 2 diabetes with a history a previous myocardial infarction (MI) are at a particularly high risk of CVD. In our study, originally published in 1998, we wanted to investigate whether patients with diabetes who have not had myocardial infarction (MI) should be treated as aggressively for CVD risk factors as patients who have had MI [3]. To this aim, we compared in a Finnish population-based study the seven-year incidence of fatal and nonfatal MI among 1373 non-diabetic subjects with the incidence among 1059 type 2 diabetic subjects. Diabetic subjects were selected for our study from the Finnish nationwide drug imbursement register including patients with diabetes who were receiving glucose-lowering medication (oral drug treatment or insulin). The 7-year incidence rates of MI in non-diabetic subjects with prior MI at baseline was 18.8 % and in diabetic subjects without prior MI at baseline 20.2 %. The hazard ratio (HR) for death from coronary heart disease (CHD) for diabetic subjects without prior MI as compared with non-diabetic subjects with prior MI was not significantly different from 1.0 after adjustment for age sex, total cholesterol, hypertension, and smoking. Our data suggest that diabetic patients without previous MI have as high a risk of CHD death as non-diabetic patients with previous MI [3]. These findings suggest that diabetes is a CVD equivalent. Practically similar results were obtained after a longer 18 -year follow-up of the same cohort [4]. Our findings led to a conclusion that intensive primary prevention of CVD in patients with type 2 diabetes was recommended.

Subsequent studies have reported varying results and questioned the concept of type 2 diabetes as a CVD equivalent [5]. In the following we review the recent literature and discuss the concept of type 2 diabetes as a CVD equivalent based on studies published after 1998. All available longitudinal studies investigating the equivalency of the presence of type 2 diabetes and prior MI or other CVD event as a risk for future CVD events were reviewed. In addition, two meta-analyses available are discussed.

Review of Recent Studies

Studies Supporting the Concept of Diabetes as a CVD Equivalent

A few other studies have shown that diabetes carries a CVD equivalent risk for future CVD events. A large landmark study, including all 3.3 million Danish residents who were at least 30 years of age and required glucose-lowering therapy based on the National Prescription Registry, was published in 2008 [6•]. The selection criteria of patients with diabetes were identical to those in our study [3].

Individuals with diabetes exhibited a register-confirmed CVD risk comparable to that of non-diabetic individuals with a prior MI, regardless of sex and diabetes type. The age-adjusted HRs for CVD death were 2.42 in men with diabetes but no prior MI at baseline, and 2.44 in non-diabetic men with a prior MI (P=0.60 between the groups). HRs for women were 2.45 and 2.62, respectively (P= 0.001). For the composite end point, including MI, stroke, and CVD death, the HRs were 2.32 (95 % confidence interval, CI, 2.27 to 2.38) and 2.48 (95 % CI, 2.43 to 2.54) in men with diabetes at baseline vs. in non-diabetic men with prior MI. HRs for women were 2.48 (95 % CI, 2.43 to 2.54) and 2.71 (95 % CI, 2.65 to 2.78), respectively. Thus, the study supported the concept that patients with diabetes and treated with glucose-lowering therapy are at the same risk of CVD events as are non-diabetic individuals who have suffered from prior MI.

A 25-year prospective population-based follow-up study from Scotland, including 7052 men and 8354 women, aged 45–64 years at baseline, and followed for 25 years included patients with diabetes either on diet or glucose-lowering drug therapy [7]. The risk for CHD mortality verified from medical records was comparable in men with diabetes and without prior MI at baseline and non-diabetic men with prior CHD, with adjusted HR of 1.17 (95 % CI, 0.78-1.74, P=0.56). In women, CHD mortality was even higher among those with diabetes and no prior MI compared to that in non-diabetic women with prior MI, with adjusted HR of 1.97 (95 % CI, 1.27-3.08, P=0.003).

In the 15-year follow-up of the Cardiovascular Health Study from the four U.S. communities including 5784 men and women aged≥65 years at baseline diabetes was defined by fasting plasma glucose≥7.0 mmol/l or the use of glucose-lowering medication [8]. Patients with diabetes had CHD mortality equal to that in non-diabetic subjects with prevalent CHD at baseline (HR 1.04, 95 % CI, 0.83-1.30). The results for CVD and total mortality were essentially similar. The authors concluded that diabetes is a CHD equivalent for CVD mortality among older adults, and that 'risk equivalency' argument is even stronger in women than in men [8].

Most of the published studies on the subject have registered CHD or total CVD events during the follow-up. However, in a study by Ho et al. [9], the risk of fatal stroke in subjects with diabetes at baseline was compared to that of non-diabetic subjects with prior stroke or MI in a 8.3-year follow-up study of 27,269 women from nine epidemiological cohorts. Diabetic subjects without CVD had a fatal stroke risk similar to that of non-diabetic subjects with a history of prior stroke and similar risk factor profile. Thus, the study indicates that diabetes may be classified as a stroke risk equivalent.

Studies Supporting the Concept of Diabetes as a CVD Equivalent in Subgroups but not in the Entire Study Population

Several recent studies have shown that type 2 diabetes is a CVD equivalent only in some subgroups of the participants. In a study by Wannamathee et al. [10•] CHD mortality and all-cause mortality was evaluated in a 9-year population-based follow-up study of 4045 men, aged 60–79 years. Both early and late onset of diabetes were associated with increased risk of major CHD events during a 9-year follow-up, but only patients with early-onset diabetes diagnosed before the age of 60 years were at a CHD risk which was equivalent to that of non-diabetic subjects with a prior MI. This study suggests that a longer duration of diabetes (a longer exposure to chronic hyperglycemia) is needed to increase the risk related to the diabetic state toward a CHD risk equivalent.

In the native American population of 4465 men and 4549 women, aged 45–74 years, diabetes increased the risk of 10-year incidence of CHD, but only diabetic subjects with multiple additional CVD risk factors had CHD incidence equal to that of non-diabetic individuals with CHD at baseline [11].

Hadaegh et al. [12] investigated whether the known diabetes mellitus or newly diagnosed diabetes mellitus could be regarded as a CHD risk equivalent among a relatively young Middle East population (2267 men and 2931 women, aged ≥30 years) with a high prevalence of diabetes during a 7.6 -year follow-up. The HR of CHD events did not differ between subjects with previously diagnosed diabetes without prior CHD and non-diabetic subjects with prior CHD in either

genders. However, the HR of women with newly-diagnosed diabetes without prior CHD was marginally lower than the HR of non-diabetic women with prior CHD ($P=0.085$). Thus, male and female subjects with previously diagnosed diabetes and male subjects with newly diagnosed diabetes exhibited a CHD risk comparable to non-diabetic subjects with a prior CHD.

There are some studies suggesting that women, but not men, with diabetes but without CVD at baseline have similar CVD risk as women without diabetes but with prior CVD event. In the 10-year follow-up of the population-based Hoorn Study [13] the risk of CVD events was compared among 208 Caucasian individuals with diabetes to that of 2253 Caucasian individuals without diabetes. The risk of CVD events was significantly lower in men with diabetes but without prior CVD than in men without diabetes but with prior CVD (adjusted HR, 0.5; 95 % CI, 0.3 to 0.9). In contrast, this risk was equal in women with diabetes but without prior CVD and women without diabetes but with prior CVD (adjusted HR, 1.0; 95 % CI, 0.6 to 1.7; $P=0.05$ for the interaction between gender and diabetes). These findings suggest that women with type 2 diabetes are at particularly high risk of incident CVD even without prior CVD.

Similar gender difference was reported in the study by Hu et al. [14]. The baseline cohort study included 2416 Finnish patients with prior diabetes or MI at baseline, and the follow-up cohort study included 4315 patients with incident diabetes or MI diagnosed during the follow-up. In women, prior MI at baseline conferred a lower risk on CHD mortality than prior diabetes, but incident MI during the follow-up conferred a greater risk than incident diabetes [14].

Also a meta-analysis by Gonzalez-Clemente et al. [15], including 13 studies based on a systematic search (the PubMed database) up to February 2006, suggested that women with diabetes and no CHD at baseline have similar CHD and CVD mortality as women without diabetes but with prior CHD.

In fact, also some studies included in the aforementioned meta-analysis by Bulugahapitiya et al. [5], showed a similar risk of incident CHD in a subgroup of diabetic subjects without CHD at baseline, compared to that of non-diabetic individuals with previous MI. In the study by Wannamathee, included in the meta-analysis by Bulugahapitiya et al., men with diabetes only had a higher risk for CVD than those with prior history of angina, but lower risk than men with diabetes with prior MI [16].

Studies not Supporting the Concept of Diabetes as a CVD Equivalent

In 2008, Bulugahapitiya et al. published a systematic review and meta-analysis of 13 studies, involving 45,108 patients based on MEDLINE, EMBASE, Cochrane and MeSH databases [5]. The meta-analysis consisted of cohort or observational studies, with follow-up times between 5–25 years, and performed mainly in the US or UK. The number of study subjects varied from 478 to 8223, and the follow-up duration from 5 to 25 years. The age of subjects in 13 studies varied between 25 to 84 years. Two studies included only men, one study only women and all others both sexes. Results in all of these studies were adjusted at least for age and sex. The hard endpoints included total CHD events (fatal or non-fatal MI), stratified for patients with diabetes but no previous MI, and patients without diabetes but with previous MI. In many of the studies, the diagnosis of diabetes was self-reported. Only in three studies glucose measurement was included, and therefore the diagnosis of diabetes remained often uncertain. Furthermore, only diabetes status was reported and it is unclear in several studies if diabetic participants represent type 2 diabetes or individuals having either type 1 diabetes or type 2 diabetes. Data on MI at baseline and follow-up was collected in the majority of studies by self-reports and in some cases validated with registers. In all studies, except for two included in the review, the risk for CHD was significantly lower (43 %) in diabetic subjects without prior MI than in non-diabetic subjects with a prior MI, with a summary odds ratio of 0.56 (95 % CI, 0.53-0.60) [15]. Unfortunately, this meta-analysis did not include the largest study on 3.3 million Danish subjects which indicated that type 2 diabetes is a CHD equivalent [6•].

In the study by Cano [17], published in 2010 and not included in meta-analysis by Bulugahapitiya et al. [6•], the risk of CHD and CVD mortality was evaluated in 2260 patients with type 2 diabetes recruited in 53 primary care health centers and 2150 patients with the first MI recruited in ten hospitals. The risk of CVD mortality and CHD incidence was significantly lower in diabetic subjects compared to non-diabetic individuals with prior MI, with HRs ranging from 0.15 to 0.36 for CVD mortality and from 0.34 to 0.56 for CHD incidence.

Possible Explanations for Contradictory Results in Different Studies

Several previous studies have shown that diabetes, indeed, is a CVD equivalent for future events, but on the other hand even more numerous studies have reported that diabetes is not a CVD equivalent. From these studies we can conclude beyond reasonable doubt that type 2 diabetes is a CVD equivalent in patients who are receiving antidiabetic medication based on our original findings and the largest study published in this area of research including 3.3 million Danes [3, 6•]. Also other studies give support for this conclusion in the entire study population [7–9], or in a subgroup of the study population [7–9,10•, 11–14, 16]. However, there

are several other studies which have not concluded that type 2 diabetes is a CVD equivalent. There are many possible explanations for the discrepancy.

First, ethnicity, gender and age seem to modify the CVD risk in diabetic subjects. As shown in the study by Whiteley et al. [7], the risk of American Indians with diabetes is equal to that of non-diabetic individuals with previous MI. In contrast, most of the studies not showing CVD equivalence for diabetes has been performed in the U.S. and U.K. populations [5]. In a few studies, gender has affected the relative risk for CVD, suggesting that diabetic women are at a particularly high risk for CVD [13]. Also the age may affect the risk of CVD, and the relative risk for CVD is relatively higher in young subjects with diabetes than in older subjects with diabetes [10•].

Second, the study design affects the results. Large, unselected population-based studies [3, 6•, 7] are less prone to bias than small studies or studies based on patient populations.

Third, the diagnosis of diabetes and verification of CVD at baseline and CVD end points during the follow-up may explain the differences between the studies. Measuring blood or plasma glucose, or performing an oral glucose tolerance test results in a more precise definition of diabetes, especially compared to self-reported diabetes [5]. Furthermore, in many studies the classification of people with diabetes into two main subcategories, type 1 and type 2 diabetes has not been performed. The register or medical record verified CVD events [3, 6•, 7] compared to self-reported CVD events [5] are more likely to produce the foundation for solid diagnosis of CVD events.

Fourth, different prior CVD events and CVD endpoints used in the study may affect the equivalence of diabetes as a CVD risk. For the most part, a prior MI has been used as the baseline CVD event in comparing the CVD risk equivalence with diabetes. If another baseline CVD definition is used, the equivalence between CVD and diabetes may vary. For example, in one study, men with diabetes only at baseline had a higher risk for CVD than those with a prior history of angina but a lower risk than those with a prior MI [16]. Other manifestations of CVD other than CHD have been uncommonly investigated. In one study, the risk of fatal stroke in subjects with diabetes at baseline, however, was similar to that of non-diabetic subjects with a prior stroke, and higher compared to that of subjects with a prior MI [9].

Fifth, other risk factors such as hypertension, dyslipidemia, insulin resistance and smoking affect the risk of CVD in diabetic subjects [1, 2, 18]. In one study, indeed, only diabetic subjects with multiple additional CVD risk factors had CHD incidence equal to that of patients with CHD at baseline [11].

Sixth, the hyperglycemia burden, defined by the duration and severity of hyperglycemia, affects the CVD risk [19]. In the study by Wannamathee [10•], only those with an early-onset diabetes diagnosed before age 60, and consequently, a longer history of hyperglycemia, had a CHD risk equivalent to that of subjects with previous MI and no diabetes.

Finally, the severity of type 2 diabetes, indicated by the use of oral drug treatment or insulin for hyperglycemia may affect the risk for CVD. In three studies [3–5], diabetic subjects on antidiabetic medication had a CVD equivalent risk for future CVD. In the study by Hadaegh, the HR of CHD events did not differ between diabetic subjects with any kind of glucose lowering medication and those with CHD at baseline, whereas the total diabetic group including all diabetic subjects had somewhat lower risk for CHD events [12]. Diabetic subjects with glucose-lowering medication usually have more severe diabetes with longer duration of hyperglycemia than those without medication, which may partly explain the difference in CVD between these groups. However, recent studies have suggested that strict hyperglycemia control with glucose-lowering medication might even increase the risk for CVD events in diabetic subjects [20].

Mechanisms Increasing Risk for CVD in Diabetes

Atherosclerosis is accelerated in diabetes [1, 2]. Several studies have shown that the presence of diabetes not only increases the risk of CVD events but also atherosclerotic lesions in coronary arteries are more severe [1, 2]. For the reasons not yet clear, atherosclerotic process is particularly accelerated in women with diabetes [1]. The atherosclerotic process begins well before frank diabetes is present. The prediabetic state is characterized by multiple adverse changes in CVD risk factors increasing the risk for CVD [21]. After diabetes has evolved, hyperglycemia and further deterioration of other CVD risk factors, such as elevated blood pressure, dyslipidemia, insulin resistance, high levels of circulating free fatty acids and low-grade inflammation accelerate the atherosclerotic process [2, 18]. Supporting the importance of atherosclerosis as the underlying cause for increased CVD risk in diabetic subjects, one study has suggested that the risk of future CHD events in diabetic subjects without significant CHD on coronary angiography at baseline is similar to that of non-diabetic subjects without angiography-verified CHD at baseline [22].

In addition to accelerated atherosclerosis, other cardiac mechanisms may contribute to increased risk for CVD in diabetic subjects. Coronary plaques are more unstable and more prone to ulceration and thrombosis in diabetic than in non-diabetic subjects [23]. Microvascular dysfunction, shown to be present in diabetic subject with normal coronary angiography, may attribute to CHD event risk in diabetic subjects [24]. Diabetic cardiomyopathy, characterized by increased myocardial lipids, myocardial fibrosis and impaired cardiac function, very likely contributes to the

higher fatality rate of CVD events often found in diabetes [25, 26].

Conclusions

Diabetes increases the risk of CVD events substantially, very often up to the level in individuals with a prior CVD. Several factors, however, modify the risk of CVD in patients with diabetes. Age, gender, ethnicity, other CVD risk factors and the hyperglycemia burden, characterized by the duration and severity of diabetes, affect the relative CHD risk in an individual patient. Moreover, the presence of diabetic cardiomyopathy and metabolic disturbances, including glucose-lowering medication-induced hypoglycemia, may further increase the risk of CVD in diabetic subjects. On the whole, the risk for CVD in diabetic subjects is so high that active measures in CVD prevention are warranted.

There is a consensus that all CVD risk factors should be carefully treated in patients with type 2 diabetes, especially in patients with a prior CVD event. Should we apply primary prevention approach to all patients with type 2 diabetes is a more difficult question given the fact that evidence for this conclusion is not supported by the majority of the studies published. Current evidence favors individual risk assessment and the tailoring of preventive measures individually, taking into consideration each patient's absolute risk of developing cardiovascular events.

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