EDITORIAL

Improving cardiovascular disease screening for patients with diabetes

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The prevalence of diabetes is increasing worldwide. It is estimated that by 2030, there will be 439 million adults affected by diabetes [101]. According to International Diabetes Federation estimates, diabetes is responsible for approximately 6% of total global mortality, with cardiovascular disease accounting for 50% of diabetes-associated deaths [101]. When compared with patients without diabetes, cardiovascular disease in diabetic patients is more severe, complex and occurs at a younger age [1]. Patients with diabetes are twice as likely to die from a myocardial infarction as those without diabetes [2]. Furthermore, the mortality risk for the patient with diabetes is two to four times higher after a myocardial infarction compared with patients without diabetes.

Since patients with diabetes are at higher risk for cardiovascular events with an overall risk of >20% in 10 years, screening for cardiovascular disease may help to identify patients at highest risk [3]. The USA Preventive Services Task Force defined the general requirements for a screening test as the ability to target a condition earlier with sufficient accuracy and that treating patients with early disease should improve outcomes [102]. Inappropriate screening runs the risk of performing additional costly tests, including imaging studies and angiography, which can result in percutaneous interventions that may not improve outcomes when the alternative is more intensive risk factor management.

Most national guidelines now consider cardiovascular disease risk assessment in their recommendations for people with diabetes. In 1998, the American Diabetes Association (ADA) recommended specialized coronary artery disease screening for patients thought to be at high risk, although the definition of high risk is particularly problematic. Considering asymptomatic patients, the focus was on the number of risk factors, baseline ECG changes and clinical evidence of vascular disease at other sites [4]. However, some studies have demonstrated that the ADA guidelines can lead to poor identification of patients at risk of silent myocardial infarction [5].

Another important factor to consider in the asymptomatic patient with diabetes is, who will benefit most from screening

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since screening every patient with diabetes will not be cost effective? Indeed the prevalence of significant coronary artery disease can be quite low in asymptomatic patients with Type 2 diabetes. Traditional risk factors such as age, sex, hypertension, smoking, dyslipidemia and family history for premature coronary artery disease do not always predict which patients will have abnormal screening tests [5,6]. Other risk factors to consider include presence of peripheral arterial disease, microalbuminuria and chronic kidney disease, abnormal ECG with changes suggestive of silent myocardial infarction (Q waves, T wave inversion or left bundle branch block), presence of autonomic neuropathy or retinopathy, hyperglycemia, unexplained dyspnea and abdominal obesity [3]. The waist-to-height ratio and waist circumference are stronger predictors of cardiovascular disease than BMI. Cardiovascular disease risk and its management is often underestimated and undertreated in patients with Type 1 diabetes. The greater the number of risk factors, the higher will be the pretest probability and more chances that a test will be positive. Therefore, various models have been developed to identify patients with diabetes at highest risk for cardiovascular events using data from Framingham and the UK Prospective Diabetes Study albeit with modest efficiency (see later).

Cardiovascular autonomic neuropathy (CAN) commonly complicates diabetes and its ability to predict increased mortality is receiving increasing attention [7]. For example, in the recently reported Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, during the 3.5 years of follow-up subjects with CAN were 1.55–2.14 times as likely to die as participants without CAN [7]. Sympathetic dysfunction may enhance cardiovascular risk by contributing to the development of hypertension, cardiomyopathy, silent ischemia and by facilitating malignant arrhythmias. In the Detection of Ischemia in Asymptomatic Diabetics study of patients with Type 2 diabetes, impairment of the Valsalva ratio was the best determinant of silent myocardial ischemia [8], and the lowest quartile of the 30:15 test was associated with an adjusted hazard ratio of 4.3 for nonfatal myocardial infarction or cardiac death. CAN is also associated with the development of the adverse cerebrovascular outcomes.

In subjects with Type 1 diabetes with advanced CAN, abnormal cardiac sympathetic innervation and tone is associated with impaired cardiac energy levels, reduced myocardial perfusion reserve and altered left ventricular function [9]. Improved understanding of the natural history of these perturbations and their inter-relationships is urgently required. In the progression of CAN, a subclinical phase which is associated with some early alterations in cardiac function is thought to precede the development of a clinical phase which is associated with enhanced cardiac risk especially when associated with postural hypotension. A simple bedside test for subclinical CAN that can be implemented in routine practice is very attractive since it may allow the identification of subjects at highest cardiovascular risk in order to focus therapy on these subjects.

Once high-risk asymptomatic diabetic patients are identified by risk assessment, the next question is what tests (if any) are suitable in order to correctly diagnose significant cardiac disease? Current guidelines do not recommend routine screening of asymptomatic patients for structural cardiac disease even though left ventricular hypertrophy is a strong predictor of cardiovascular disease in Type 2 diabetes. However, accurate diagnosis of left ventricular hypertrophy, whether by electrophysiological or by biochemical testing, remains problematic in the community setting. For the detection of coronary artery disease the ADA guidelines initially recommend exercise treadmill testing (ETT) for high-risk patients with a multiple risk factor burden or the presence of atherosclerosis at other sites. Imaging for ischemia is recommended for patients with an abnormal baseline ECG. Indeed the performance of a maximal graded exercise test in 5783 asymptomatic overweight/obese subjects with Type 2 diabetes demonstrated exercise-induced abnormalities (electrophysiological and symptomatic) in 22.5% of subjects [10]). In the Milan Study on Atherosclerosis in Diabetes, ST segment changes were present in 13.2% of subjects [11] undergoing exercise testing.

However, while screening for cardiac disease with ETT is inexpensive and widely available, as indicated previously, its use may be limited by high false-positive results among asymptomatic individuals, especially women, leading to unnecessary testing, overtreatment and labeling [12]. Stress testing with single-photon emission CT or echocardiography are other valid and reliable methods with sensitivities of 91–96% and a specificity of 75–82% [3]. These tests are accurate in the case of both men and women and are also useful in patients with an abnormal ECG.

In the Detection of Ischemia in Asymptomatic Diabetics study, risk assessment was performed using the UK Prospective Diabetes Study risk engine, the Framingham score, criteria of the French-Speaking Association for the Study of Diabetes and Metabolic Diseases and the presence of metabolic syndrome. The majority of participants were defined as being either intermediate or high risk [13]. A total of 22% of participants were found to have inducible ischemia [5], a rate that was similar irrespective of risk categorization. Overall annual cardiac event rate was low (<1–2% dependent on the risk engine used) and was not altered by screening for inducible ischemia [5,13].

Reflecting the progress of cardiovascular imaging technologies along with the increasing debate regarding the importance of detecting coronary artery disease in asymptomatic patients with multiple risk factors [14], professional societies are now updating their recommendations for the use of nuclear cardiac procedures, cardiac CT and coronary artery calcium screening [15,16]. The use of a coronary artery calcium score as a marker for the overall coronary atherosclerotic burden by cardiac CT with either electron beam or multislice technology is gathering momentum as an appropriate screening test (potentially coupled with a stress study such an ETT) in asymptomatic patients with intermediate risk of cardiovascular disease. Patients with a calcium score of ≥400 have a high likelihood of cardiac ischemia, which can be investigated further while patients whose calcium score is <100 have a low probability of abnormal perfusion on a nuclear scan or significant obstruction on catheterization [17].

Newer technologies such as cardiac magnetic resonance scanning and carotid intima-media thickness (CIMT) performed with high-frequency B mode ultrasonography will play an important role in screening for cardiovascular disease in diabetic patients in the near future [16,18]. Cardiac magnetic resonance scanning has the advantage of providing further information about coronary flow and stenosis, assessing wall motion and evaluating myocardial perfusion without subjecting patients to ionizing radiation. By contrast, CIMT is simple and widely available; however, limitations include a lack of accepted technical standards for testing. Moreover, additional data are required to support the utility of CIMT in risk stratification.

Whilst the debate rages about whom to screen with which tool, it is important to remember that medical management of risk factors and addressing poor lifestyle choices remains the cornerstone of strategies to reduce cardiovascular risk in diabetes. Whatever the choice of screening test, it is increasingly apparent that improved risk stratification is required, involving the development and testing of risk-prediction models that incorporate adequate representation of sexes, all racial and ethnic groups and the latest therapeutic approaches to disease management. Current risk stratifications schemes tend to overestimate risk and the routine screening of patients for inducible ischemia based upon these tools cannot be recommended. With the development of improved diabetes-specific risk engines, the impact on cardiovascular outcomes of screening with coronary calcium scores or CIMT in concert with ETT as well as a CAN assessment will need to be evaluated.

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