Cardiovascular risk assessment and screening in diabetes

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Diabetes used to be considered as a coronary heart disease equivalence and universally classified high cardiovascular risk population. However increasing epidemiological evidence now indicates the heterogeneity of risk among the diabetic patients and imposes an importance of stratifying those with relative low-risk from high-risk ones. Despite the existing risk assessment tools, current cardiovascular disease prevention guidelines fail to provide more detailed stratification strategies for patient with diabetes and expose them to either overtreatment or undertreatment. On the other hand, various screening modality, including novel biomarkers and subclinical atherosclerosis scanning, including coronary calcium scanning, carotid intima-media thickness, myocardial perfusion imaging and coronary computed tomography angiography, have provided very promising usage is risk stratification. With better developed test techniques and more extensive evidence, these

modalities may serve in standardized screening algorithm to improve the cardiovascular risk assessment of patients with diabetes and better instruct their individualized preventive therapy. *Cardiovasc Endocrinol* 6:17–22
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Cardiovascular Endocrinology 2017, 6:17–22

Keywords: cardiovascular disease, diabetes, guidelines, risk assessment

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Received 22 October 2016 Accepted 11 January 2017

Introduction

Patients with diabetes mellitus (DM) have a 2–4 fold increased risk for cardiovascular disease (CVD) and CVD remains the leading cause of death among DM patients [1,2]. Although it is now widely accepted that DM is not a CVD equivalent but a heterogeneous group with wide spectrum of CVD risk, reliable and accurate assessment of CVD risk remains a problem [3]. In this review, we discuss the rationale and importance of screening for subclinical CVD in patients with DM and compare the role of risk scoring for the diabetes population as it relates to current guidelines. In addition, we review the role of other screening modalities, including novel biomarkers and subclinical atherosclerosis imaging, to improve CVD risk assessment. Finally, we discuss future improvements in CVD risk prediction including the need for creating new risk scores for diabetic patients.

Why screen cardiovascular disease for diabetes mellitus patients?

Haffner *et al.* [4] first introduced the concept of DM as a coronary heart disease (CHD) risk equivalent in their pioneer study, in which they found that the risk of CHD death for diabetic patients without previous myocardial infarction (MI) was comparable with that of their non-diabetic counterparts who had a history of MI. However, results from subsequent studies have been contradictory, with some more recent studies not supporting DM as a CHD risk equivalent. A recent meta-analysis including 13 cohort studies showed that patients with diabetes have

a 43% lower risk for future hard CAD events compared to those with a previous MI, indicating that at least some subgroups in the DM population have much less risk than we thought before [5]. Data from the United States National Health and Nutrition Examination Survey also showed that 32% of men and 48% of women with DM were actually at low to intermediate risk according to the Framingham Risk Score [6]. In addition, heterogeneity exists with respect to the CVD risk in diabetes on the basis of other coexisting CVD risk factors [7]. Refining risk estimates in DM patients may help to implement prevention strategies in an efficient and cost-saving manner as well as reducing the potential side effects of preventive therapies if not needed. Two meta-analyses of statin trials have shown that statin use may increase the risk of hyperglycemia [8,9]. For those DM patients with low-to-intermediate risk, preventive statin therapy may provide limited protective benefit while potentially influencing hypoglycemia. In such patients, risk assessment should be performed before considering statin initiation or intensification can be recommended.

Cardiovascular disease risk prediction in diabetes mellitus patients

Over the past decades, various CVD risk scoring systems have been developed to aid CVD risk assessment. One meta-analysis identified 45 prediction models that could possibly be used in DM patients, of which 12 were specifically developed for patients with type 2 diabetes mellitus (T2DM). 31% of the risk scores have been

externally validated in a diabetes population, with an acceptable-to-moderate performance [area under the curve (AUC) range: 0.59–0.86] [10]. Also, a few studies have assessed the impact of applying a CVD prediction model in clinical practice on the treatment and prevention of CVD events [11–13], including one specifically designed for DM patients [14].

Among the current guidelines in diabetes management and CVD management, some continue to consider DM as a CHD risk equivalent (10 year CVD risk $\geq 20\%$) or very high risk when combined with pre-existing CVD or end organ damage such as CKD. The 2016 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice and International atherosclerosis society position Paper for Global Recommendations for the Management of Dyslipidemia are examples of such guidelines. Other more recent guidelines (European Association for the Study of Diabetes, Canadian Diabetes Association, International Diabetes Federation, etc.) recommend either using non-specific or DM-specific CVD risk prediction tools for diabetes management [15]. Nonspecific and DM-specific CVD risk prediction tools are two major approaches of CVD risk assessment in DM patients besides the CVD equivalent approach.

Nonspecific global risk calculator

Nonspecific global risk calculators are mostly modeled using general population data and DM is usually treated as a dichotomous status as ‘yes’ or ‘no’. More importantly, these tools are based on the rationale that diabetes status does not alter the effect of other cardiovascular risk factors. In the recently developed ASCVD risk calculator, the Pooled Cohort Equation by AHA/ACC [16], DM is considered an independent risk factor with no interaction with other risk factors. In fact, the only effect modifier in this model is age. In other words, other risk factors [such as systolic blood pressure (BP) or high-density lipoprotein-cholesterol] will contribute equally toward the future CVD risk irrespective of DM condition. This has been the basis for other popular risk calculators such as the Framingham cardiovascular risk equations [17]. One disadvantage of this approach is that some unique risk factors for DM patients, including HbA1c, microalbuminuria, etc. were not included in the risk prediction model as their effect is diluted in the general population.

Risk calculators for diabetes mellitus patients

The fundamental difference of this approach from the above one is the existence of an interaction between DM and other risk factors. Such DM-specific models assume that with the presence of DM, some risk factors will affect CVD risk in different ways. Van Dieren *et al.* [10] summarized 12 DM-specific CVD risk prediction tools in their meta-analysis, in which all of these tools have considered including DM-specific risk factors and some of

the factors remain in the prediction model because of their significant predictive values.

Some studies focused on whether or not DM-specific risk calculators are superior to nonspecific ones for future CVD events. Echouffo-Tcheugui and Kengne [3] systematically reviewed 22 pair-wise comparison of these two types of risk tools, among which 14 comparison showed higher C-statistics for the UKPDS, ADVANCE, or DCS diabetes-specific models than the general population CVD risk models. One study has reported that the UKPDS calculator was worse than Joint British Societies Risk Chart for predicting CVD (AUC 0.74 vs. 0.80) and worse than CardioRisk Manager for predicting CHD (AUC 0.65 vs. 0.77) among UK patients with DM [18]. Meanwhile, the justification of different models for patients with diabetes has also been questioned. Most available studies indicate that traditional risk factors affect the CVD risk in similar ways in patients with and without diabetes, showing no evidence of effect modification.

Evidence for atherosclerosis screening

Novel biomarkers

High-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hs-CRP) is a circulatory biomarker indicating the existence of inflammation. Multiple studies have shown that hs-CRP is an established risk factor for CVD [19,20] and is associated with progression of DM [21]. Yeboah *et al.* [22] showed that hs-CRP had an additive predictive capability to the traditional Framingham risk score and similar evidence has recommended further measures of hs-CRP as supplemental CVD risk assessment (ACC/AHA class IIb-B Recommendation), especially among those in the intermediate-risk group (10–20% 10-year CVD risk) [16]. The Reynold risk score is among the few risk calculators that incorporate hs-CRP; however, this risk score is only for the non-DM population. Currently, there is no DM-specific risk score that has included hs-CRP as a risk factor. Additional stratification of hs-CRP into low (<1 mg/l), intermediate (1–3 mg/l), and high (>3 mg/l) groups in those with DM has shown incremental predictive values for future CVD events [23].

Lipoprotein (a)

Lipoprotein (a) [Lp(a)] is a low-density lipoprotein (LDL) particle with apolipoprotein (a) that contributes toward the development of atherosclerosis. In the general population as well as in DM patients, Lp(a) is an independent risk factor for CHD and CVD. A recent cross-sectional study compared cardiometabolic risk factors and macrovascular and microvascular complications in older DM patients and found that patients with high Lp(a) (>30 mg/dl) had a significantly higher prevalence of CHD, CVD, and diabetic nephropathy, suggesting a potential prolonged effect of Lp(a) on CVD in the elderly with a relatively long DM duration [24]. Cohort studies

have also been carried out to answer the same question: in type 1 diabetes mellitus (T1DM) patients, Lp(a) more than 30 mg/dl is identified as a strong and independent predictor of CVD [hazard ratio (HR) 2.23; 95% confidence interval (CI): 1.28–3.87] [25]; three studies targeting T2DM patients also found a positive correlation of Lp(a) with future CVD [26–28]. More importantly, elevated Lp(a) predicts early atherosclerosis independent of other cardiac risk factors. One case–control study that examined the relation of silent CHD and Lp(a) in T2DM patients showed that Lp(a) levels were significantly different in those with versus without CAD, with an adjusted odds ratio of 2.62 (95% CI: 1.01–6.79) comparing high versus low Lp(a) [29]. In contrast, two studies observed an inverse association of Lp(a) levels with the risk of T2DM [30,31], but the association was not determined to be causal from instrumental variable analysis [31]. In addition, Lp(a) was not related to the duration of T2DM, indicating that Lp(a) may promote CVD by mechanisms other than hyperglycemia and insulin resistance.

Low-density lipoprotein particle number and high-density lipoprotein particle number

In patients with T2DM, low-density lipoprotein particle number (LDL-P) levels tend to be discordant with low-density lipoprotein-cholesterol (LDL-C) levels. Cromwell *et al.* [32] found that in those with low or extreme low LDL-C values, the distribution of LDL-P remained heterogeneous and a large proportion of LDL goal achievers still had high LDL-P levels. More importantly, they found that when there is discordance, LDL-P was more predictive for CVD than LDL-C levels, which may explain the residual risk when the LDL-C level is well controlled in DM patients [33]. Similar to LDL-P, the Multiethnic Study of Atherosclerosis (MESA) showed that high-density lipoprotein particle, but not the high-density lipoprotein-cholesterol, was associated independently with CHD and carotid intima–media thickness [34]. LDL-P may be considered an alternate target for multiple lipid-lowering therapies, but randomized clinical trials are needed to explore the effect of treatment on LDL-P and consequent CVD events in the diabetic population.

Lipoprotein-associated phospholipase A2

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an inflammatory biomarker involved in atherogenesis, particularly in plaque rupture. Measures of Lp-PLA2 include Lp-PLA2 activity and Lp-PLA2 mass. Previous meta-analysis showed that both Lp-PLA2 activity and Lp-PLA2 mass predicted CHD and stroke [9,35]. However, in several single studies, Lp-PLA2 activity seems to be a more useful tool in predicting CVD. One cohort study examining Lp-PLA2 and incident CHD in T2DM patients found that Lp-PLA2 activity was associated independently with total CHD and hard CHD (HR = 1.39 for total CHD comparing third vs. first tertile

of Lp-PLA2 levels and HR = 1.75 for hard CHD) [36]. Unlike the independent effect in T2DM, the association between Lp-PLA2 activity and CAD tends to vary by CRP and haptoglobin genotype in T1DM patients [29]. The relation of Lp-PLA2 and incident diabetes was inconsistent across different studies: Nelson *et al.* [30] found that Lp-PLA2 correlated positively with both prevalent and incident T2DM, whereas Onat *et al.* [31] reported that Lp-PLA2 mass was lower in those with DM compared with those without DM. Further basic biomedical studies need to be carried out to explain the possible link between Lp-PLA2 and the occurrence of DM. Although several currently used drugs including statins, β -blocker, and aspirin may reduce Lp-PLA2 levels, none of them specifically target Lp-PLA2. Darapladib, an inhibitor of Lp-PLA2, failed its phase III clinical trial, showing no benefit to prevent CVD endpoints (cardiovascular death, MI, or stroke) in patients with stable CHD or those with acute coronary syndrome, although secondary endpoints including major coronary events and total coronary events were modestly significantly reduced by about 10% [37,38]. Given this evidence, it may be unlikely to benefit high-risk populations including those with DM.

Subclinical atherosclerosis imaging

Coronary artery calcium

Calcium deposits in the coronary arteries serve as an indicator of subclinical atherosclerosis. The most widely used coronary artery calcium (CAC) measure is the Agatston Score, which incorporates the density and volume of plaque calcium [39]. DM patients have higher rates of CAD/CVD in each predefined CAC score stratum (CAC = 0, CAC = 1–100, CAC = 101–400, CAC > 400); however, DM patients with a CAC score of 0 have lower CVD event rates than those without DM but with a high CAC score [40]. The EISNER Study, which included patients both with and without DM, examined 2137 volunteers who were assigned randomly to either the CAC scanning group or the nonscanning group on the basis of the changes in CVD risk; in the scanning group, an increase in the baseline CAC score was associated with an improvement in risk factors including BP, LDL-C, and waist circumference ($P < 0.05$); the Framingham risk score remained stable in the computed tomography scanning group, but increased in the nonscanning group [41].

Carotid intima–media thickness

Carotid intima–media thickness (CIMT) is a measure used to diagnose the extent of carotid atherosclerotic vascular disease. Thickening of the inner two layers of the vascular wall indicates atherosclerosis. Yoshida *et al.* [42] found that CIMT was a significant predictor of CVD beyond the Framingham Risk Score in asymptomatic DM patients. The incremental predictive value of CIMT was also noted in MESA, a diverse ethnic cohort aged 45–84 years [22]. Using the Atherosclerosis Risk in

Communities Study, a larger US cohort, Nambi *et al.* [43] showed that 23% of patients were reclassified on adding CIMT to traditional risk factors, with a net improvement index of 9.9%. Meta-analysis and pooled cohort studies showed that the addition of common CIMT to traditional risk models was associated with only a modest improvement and may not be clinically useful [44]. CIMT is therefore not recommended in the current AHA/ACC risk assessment guidelines.

Myocardial perfusion imaging

The Detection of Ischemia in Asymptomatic Diabetics clinical trial failed to show the effect of myocardial perfusion imaging screening on improving clinical outcomes [45] even though the participants demonstrated resolution of ischemia upon repeat testing [46]. Other studies show contradictory results. One meta-analysis evaluated the prognostic value of normal stress myocardial perfusion single (MPS) photon emission computed tomography for future CHD among patients with DM. The study included a total of 14 studies that recruited 13 493 DM patients. The negative predictive value for nonfatal MI and cardiac death of normal MPS was 94.92% (95% CI: 93.67–96.05), and can therefore relatively safely exclude those without CAD and validly define the ‘low-risk’ group among the DM ones [47]. Such new evidence may alter the screening modality of CVD among the DM population.

Coronary computed tomography angiography

Coronary computed tomography angiography (CCTA) is an invasive assessment of nonobstructive disease, coronary stenosis and proportion of occlusion, plaque characterization and calcification, etc. [48]. However, the FACTOR-64 clinical trial randomizing 900 patients with T1DM or T2DM to CCTA-directed therapy or to guidelines-directed optimal diabetes care showed that CTA screening not to reduce the risk for all-cause mortality, nonfatal MI, or unstable angina, and therefore failed to support CTA screening in this population. A HR of 0.80 did indicate a trend toward a benefit and the study was probably underpowered because of the relatively low event rate [49]. Similar to myocardial perfusion imaging, a recent meta-analysis examined the results of CCTA (obstructive CAD, nonobstructive CAD, or no CAD) in relation to future events (all-cause mortality or other CVD events) among DM patients. The final sample included eight studies and 6225 participants (56% men and weighted age of 61 years) with a follow-up period ranging from 20 to 66 months, finding that obstructive and nonobstructive CAD were associated with an increased HR of 5.4 and 4.2, respectively [50]. This meta-analysis may provide comparably strong evidence to better support the role of CCTA in risk assessment for those with DM.

Future of cardiovascular disease risk assessment in diabetes

Although a higher proportion of DM patients are receiving CVD preventive treatment, residual CVD risk remain a major concern and many with DM remain suboptimally treated by CVD risk reduction therapies, with inadequate attainment of risk factor targets. Wong *et al.* [51] recently found that only 41.8, 32.1, and 41.9% of DM patients were at target levels for BP, LDL-C, and HbA1c, respectively, but only 7.2% were at three targets altogether in a pooled cohort study of DM patients from MESA, ARIC, and JHS. In addition, heterogeneity in CVD risk among individuals with DM calls for a very accurate risk assessment to pinpoint the treatment target and maximize the treatment effect. We previously summarized the different algorithms using various screening methods [52]. These algorithms were based on a similar pre-evaluation of traditional risk factors, but vary in the order of different modalities and some screening criteria. Few studies have compared the effectiveness of each individual modality or these algorithms as a whole in DM patients. The future of CVD risk assessment should focus on the following aspects: (I) external validation of the current risk scoring systems with head-to-head comparison in DM patients, especially for those recommended in the guidelines; (II) longitudinal surveillance of risk factor changes in DM patients and the impact of such changes on future CVD risk. Such an approach may be more accurate as it includes the effect of preventive therapy and resultant changes in risk factors in a dynamic manner; (III) randomized clinical trials to compare the effect of various screening methods on future CVD events (instead of surrogate intermediate endpoints); and (IV) assessment of the cost-effectiveness of novel screening modalities, which will help better discriminate the low-risk and high-risk subgroups from those at intermediate risk and more accurately predict the actual risk when the population is experiencing continuous changes in risk factors.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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