Cardiovascular risk profile and clinical characteristics of diabetic patients: a cross-sectional study in China

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Abstract

Background: Cardiovascular (CV) disease is the leading cause of morbidity and mortality in adults with type 2 diabetes (T2D). The aim of this study was to determine the CV risk in Chinese patients with T2D based on the 2019 European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) guidelines on diabetes, pre-diabetes, and CV diseases.

Methods: A total of 25,411 patients with T2D, who participated in the study of China Cardiometabolic Registries 3B study, were included in our analysis. We assessed the proportions of patients in each CV risk category according to 2019 ESC/EASD guidelines.

Results: Based on the 2019 ESC/EASD guidelines, 65.6%, 7.5%, and 0.6% of patients were included in our analysis. We assessed the proportions of patients in each CV risk category according to 2019 ESC/EASD guidelines. While 58.7% of elderly patients were classified to “very high risk” group, 89.6% of patients with obesity were divided into “very high risk” group. Almost all patients with a duration of diabetes >10 years had “very high risk” or “high risk.” However, 26.4% of Chinese T2D patients, who had shorter duration, and one or two risk factors, could not be included in any category (the “unclear risk” category).

Conclusions: In China, most patients with T2D have “very high” or “high” CV risk based on 2019 ESC/EASD guidelines. However, the risk of patients in “unclear risk” group needs to be further classified.

Keywords: Cardiovascular risk; Type 2 diabetes; 2019 ESC/EASD guidelines

Introduction

It is well known that atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in adults with type 2 diabetes (T2D)[1] and patients with T2D have two to four times of the risk of death and cardiovascular (CV) events in comparison with the general population.[2] As China has the highest number of patients with diabetes in the world, the presence of cardiovascular disease (CVD) in patients with T2D will bring heavy economic burden to our country.[3] Therefore, evaluating the CV risk in Chinese patients with T2D is of great importance for making clinical strategy decisions.

Previous studies proved that the assessment of CV risk was quite useful to guide therapies for diabetes, hypertension, dyslipidemia, and obesity, and was the key strategy in prevention of CVD in both the general population and patients with T2D.[4,5] In the general population, a number of risk prediction models have been developed for estimating the risk of initial CVD events.[6-11] The variables of age, gender, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), diabetes mellitus (DM), and current smoking were used by most models.[6-11] However, these models had limitations when applied in patients with T2D in clinical practice. For example, the US Pooled Cohort Equations...
Patients were ineligible if they were pregnant, participating least 6 months before screening, were eligible for inclusion as recommended by the Chinese diabetes guidelines, at T2D according to the World Health Organization criteria. Patients aged 18 years or older who were diagnosed with T2D in China. Moreover, we aimed to examine the risk distribution of different subgroups based on age, sex, duration of T2D, and body mass index (BMI) categories.

Methods

Ethical approval

The study was conducted according to the Good Clinical Practice and the International Conference on Harmonization guidelines. Study protocol was approved by the Ethics Committee of Peking University People’s Hospital (No. [2010]024) and other hospitals where an individual committee review was required. All patients gave written informed consent.

Study population

The China Cardiometabolic Registries 3B study was an observational, cross-sectional, multicenter, multispecialty study of ambulatory patients with established T2D. Participants were enrolled at endocrinology, cardiology, nephrology, and internal medicine clinics in community hospitals (Tier 1), secondary/city level hospitals (Tier 2), and teaching or comprehensive central hospitals (Tier 3) across all major geographical regions in China. Patients aged 18 years or older who were diagnosed with T2D according to the World Health Organization criteria, as recommended by the Chinese diabetes guidelines, at least 6 months before screening, were eligible for inclusion. Patients were ineligible if they were pregnant, participating in any other clinical studies, or unable to report their medical history.

2019 ESC/EASD recommendations for CV risk categories

For each participant, we assessed the established CVD, target organ damage, and major risk factors. Then, we created three CV risk categories following 2019 ESC/EASD guidelines: very high risk, high risk, and moderate risk. Additionally, we created an extra category of unclear risk if patients could not be divided into the above three categories. According to 2019 ESC/EASD guidelines, patients with DM and established CVD, or other target organ damage, or three or more major risk factors were defined as very high risk. Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor were defined as high risk. Young patients (T2D aged <50 years) with DM duration <10 years, without other risk factors, were defined as moderate risk. Patients with DM are never considered low risk.

Established CVD was defined as the presence of coronary heart disease or stroke or peripheral artery disease. Target organ damage included proteinuria, renal impairment (defined as estimated glomerular filtration rate <30 mL·min⁻¹·1.73 m⁻²), left ventricular hypertrophy, or retinopathy. Major risk factors included age (men ≥55 years; women ≥63 years), hypertension (blood pressure [BP] ≥140/90 mmHg or on antihypertensive medication), dyslipidemia (TC ≥4.5 mmol/L, low density lipoprotein cholesterol [LDL-C] ≥2.6 mmol/L, triglyceride [TG] levels ≥1.7 mmol/L, decreased HDL-C <1.0 mmol/L, or patients being treated with anti-hyperlipidemic medication), smoking, and obesity (BMI ≥28.0 kg/m² using the Working Group for Obesity in China criteria).

Statistical analysis

Data were presented as mean ± standard deviation for continuous variables and as proportions for categorical variables. We assessed the proportions of the patients in each CV risk category. We also determined CV risk stratified on the basis of gender (categorized as males and females), age (categorized as 18–64 years, and ≥65 years), BMI (categorized as <18.5, 18.5–23.9, 24.0–27.9, and ≥28.0 kg/m²), and duration of diabetes (categorized as <1, 1–4, 5–9, 10–19, and ≥20 years). All continuous variables were tested for normality. Student’s t test or nonparametric tests (Mann-Whitney test and Kruskal-Wallis test) were used to compare the differences between risk categories for continuous variables. χ² test or Fisher exact test was performed to assess differences in categorical variables between risk categories. Test of linearity was used to analyze the trend over various groups. Statistical analysis was performed using SPSS software (version 20.0, SPSS Corp, Chicago, IL, USA). P value <0.050 for the two-tailed test was considered as statistically significant.

Results

Study population

Totally, we analyzed 25,411 individual data from 3B study. They had a mean age of 62.6 ± 11.9 years and a mean duration of diabetes of 8.0 ± 6.7 years. Males
accounted for 47.0% of the patients. Among these individuals, 6017 (23.7%) had a history of cardiovascular disease, 4188 (16.5%) had diabetes retinopathy, and 3668 (14.4%) had diabetes kidney disease. Of these patients, 4165 (16.4%) were obese and 10,668 (42.0%) were overweight.

**Clinical characteristics in each CV risk category according to 2019 ESC/EASD guidelines**

Based on the 2019 ESC/EASD guidelines, 65.6%, 7.5%, and 0.6% of Chinese T2D patients were categorized as the “very high risk” group, “high risk” group, and “moderate risk” group, respectively [Table 1].

In the very high risk group, patients had a mean age of 63.8 ± 10.9 years, and a mean duration of diabetes of 9.0 ± 7.1 years. Among them, 62.7% were overweight or obese. A total of 7.1% of them had a duration of diabetes of <1 year; while 40.1% of them had a duration of diabetes ≥10 years. Among them, 78.9% had more than three risk factors. In the high risk group, patients had a mean age of 61.4 ± 10.4 years, and a mean duration of diabetes of 14.4 ± 4.4 years; 45.9% of patients were overweight or obese. One third of patients had one risk factor, and two thirds of patients had two risk factors. In the moderate risk group, patients had a mean age of 42.5 ± 5.4 years, and a mean duration of diabetes of 3.1 ± 2.6 years.

With the increase of CV risk (from moderate risk group to high and very high risk groups), patients were more likely to be older, have higher BMI, SBP, diastolic blood pressure, TC, TG, and LDL-C levels, and longer duration (all \( P \) for trend <0.001), and lower HDL-C levels (\( P \) for trend 0.012). However, no obvious trend of HbA1c was observed (\( P \) for trend 0.903) [Table 1].

**CV risk categories stratified by sex, diagnosis of age, BMI, duration according to 2019 ESC/EASD guidelines**

The proportions of CV risk categories varied substantially by sex, diagnosis of age, BMI, and duration of diabetes.

Among men and women, 71.3% and 60.5%, respectively, had very high CV risk (\( P < 0.001 \)). More patients in the elderly group were included in the very high risk group compared to that in the non-elderly group (\( P < 0.001 \)). For patients with overweight and obesity, 62.9% and 89.6%, respectively, were divided in very high risk subgroup. As the duration of diabetes increased, the patients with very high risk increased significantly (\( P \) for trend <0.001) from 52.3% in 0 to <1 years subgroup to 86.1% in ≥20 years subgroup.

High risk was observed in 5.5% of men and 9.2% of women. Respectively, 9.7%, 9.7%, 7.5%, and 1.6% patients who were in BMI categories of underweight, normal weight, overweight, and obesity were included in the high risk group (\( P \) for trend <0.001). Additionally, 24.2% of patients with a duration of 10 to 19 years, and 13.5% of patients with a duration ≥20 years, had high CV risk. Almost all patients with a duration of diabetes ≥10 years had very high or high risk of CV.

In addition, 0.6% of the patients were categorized as the “moderate risk” group; also, 1.8%, 1.1%, and 0.4% of patients with underweight, normal weight, and overweight, and obesity were included in moderate risk group (\( P \) for trend <0.001). Moderate risk was observed in 1.8% patients with duration <1 year, 1.0% patients with duration of 1 to 4 years, and 0.5% patients with duration of 5 to 9 years.

**Clinical characteristics and risk factors of unclear risk group**

Interestingly, 26.4% of Chinese T2D patients could not be included in the above categories according to 2019 ESC/EASD guidelines, and we divided these patients as “unclear risk” group. Patients in this group had a mean age of 55.3 ± 10.9 years, and a mean duration of diabetes of 3.9 ± 2.8 years. More than 95% of them had one or two risk factors. Compared with those T2D patients with moderate risk, patients in unclear risk group were older and had longer duration of diabetes (all \( P < 0.001 \)). Compared with those T2D patients with high risk, patients

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**Table 1: Clinical characteristics in each CV risk category according to 2019 ESC/EASD guidelines in 3B study.**

<table>
<thead>
<tr>
<th>Items</th>
<th>Total</th>
<th>Very high risk</th>
<th>High risk</th>
<th>Moderate risk</th>
<th>( P ) for trend</th>
<th>Unclear risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25,411</td>
<td>16,663 (65.6%)</td>
<td>1895 (7.5)</td>
<td>152 (0.6)</td>
<td>&lt;0.001</td>
<td>6701 (26.4%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53.0</td>
<td>49.0</td>
<td>65.6</td>
<td>67.1</td>
<td>&lt;0.001</td>
<td></td>
<td>59.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.60 ± 11.9</td>
<td>65.84 ± 10.93</td>
<td>61.44 ± 10.38</td>
<td>42.47 ± 5.37</td>
<td>&lt;0.001</td>
<td>55.32 ± 10.94</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.83 ± 3.57</td>
<td>25.29 ± 3.78</td>
<td>23.64 ± 2.73</td>
<td>22.50 ± 2.66</td>
<td>&lt;0.001</td>
<td>24.08 ± 3.03</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>8.04 ± 6.67</td>
<td>9.01 ± 7.05</td>
<td>14.41 ± 4.37</td>
<td>3.08 ± 2.55</td>
<td>&lt;0.001</td>
<td>3.88 ± 2.82</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>7.62 ± 2.02</td>
<td>7.62 ± 1.96</td>
<td>7.98 ± 2.15</td>
<td>7.60 ± 2.40</td>
<td>&lt;0.001</td>
<td>7.52 ± 2.12</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>133.0 ± 15.7</td>
<td>136.3 ± 16.0</td>
<td>128.4 ± 13.6</td>
<td>118.8 ± 9.18</td>
<td>&lt;0.001</td>
<td>126.3 ± 12.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.8 ± 9.0</td>
<td>79.5 ± 9.4</td>
<td>77.0 ± 7.8</td>
<td>74.8 ± 6.1</td>
<td>&lt;0.001</td>
<td>77.6 ± 8.0</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.98 ± 1.44</td>
<td>4.97 ± 1.30</td>
<td>5.00 ± 1.33</td>
<td>3.74 ± 0.54</td>
<td>&lt;0.001</td>
<td>5.01 ± 1.34</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.98 ± 1.67</td>
<td>2.00 ± 1.62</td>
<td>1.85 ± 1.61</td>
<td>0.95 ± 0.33</td>
<td>&lt;0.001</td>
<td>1.99 ± 1.80</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.31 ± 0.53</td>
<td>1.29 ± 0.56</td>
<td>1.36 ± 0.45</td>
<td>1.40 ± 0.34</td>
<td>0.012</td>
<td>1.34 ± 0.45</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.83 ± 0.91</td>
<td>2.84 ± 0.92</td>
<td>2.81 ± 0.89</td>
<td>1.98 ± 0.43</td>
<td>&lt;0.001</td>
<td>2.83 ± 0.90</td>
</tr>
</tbody>
</table>

Data are displayed as mean ± SD, \( n \) (%). BMI: Body mass index; CV: Cardiovascular; DBP: Diastolic blood pressure; EASD: European Association for the Study of Diabetes; ESC: European Society of Cardiology; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; SD: Standard deviation; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride.
Risk factor assessment

In this study, we found that 65.6%, 7.5%, and 0.6% of Chinese patients were included in “very high risk,” “high risk,” and “moderate risk” category, respectively, based on the recent 2019 ESC/EASD guidelines. The proportions of patients in each category varied based on diagnosis of age, sex, BMI, and duration.

Based on the new reclassification of CV risk, more than two-thirds of patients with T2D in our study were included in the “very high risk” and “high risk” group, which was similar to previous studies. In Chinese T2D patients aged 40 to 70 years without CVD history, 28% of them had ASCVD score ≥10% using equations developed by Yang et al20 to calculate the ASCVD risk score.21 In Iranian patients with DM aged 30 to 74 years, the 2013 PCE-ASCVD (7.5% high risk threshold) identified that 59% of them had high risk.22 In T2D patients aged 18 to 70 years in Sweden, it has been ascertained that 54% and 29% of them had risks ≥10% and ≥15%, respectively, by using Swedish National Diabetes Register risk equation.23 However, no study has applied recent 2019 ESC/EASD guidelines to large sample of patients with T2D so far.

The high proportion of T2D patients with very high CV risk indicated heavy CVD burden in our country. Therefore, multiple CV risk factors should be addressed simultaneously,14,16 including the use of aspirin, and the control of blood pressure, cholesterol, and glycemia, to prevent and manage CVD in patients with T2D. Importantly, more intensive and novel therapies may be considered in very high/high risk category16,24 following healthy lifestyle. Combination therapy or proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors is recommended if other therapies fail to reduce the LDL-C to target goals.13 Therefore, in clinical practice for T2D patients, the CV risk should be fully evaluated before initiating therapy and throughout the whole therapy adjustment to intensify relative therapy for reducing the risk of CVD.

The proportions in each risk stratiﬁcation varied by age and duration of diabetes, which reminded us that CVD management among younger and newly diagnosed patients with T2D should be performed cautiously. Apparently, the risk of CVD in patients with T2D increased with age and duration. Patients with younger age were more likely to have an increased lifetime risk for CVD after decades. This was similar to our ﬁnding that almost all patients had very high or high risk in patients with a duration > 10 years. Therefore, there may be greater potential gains from more aggressive treatment in younger

Table 2: CV risk category stratiﬁed by sex, age, BMI, duration, and risk factors (n = 25411).

<table>
<thead>
<tr>
<th>Items</th>
<th>Total</th>
<th>Very high risk (N = 16,663)</th>
<th>High risk (N = 1895)</th>
<th>Moderate risk (N = 152)</th>
<th>Unclear risk (N = 6701)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>2257 (7.1)</td>
<td>41 (27.0)</td>
<td>1035 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td>19 years</td>
<td>31 (20.4)</td>
<td>2126 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Risk factor assessment</td>
<td></td>
<td>5</td>
<td>152 (35.1)</td>
<td>213 (49.2)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>&lt;18.5 kg/m²</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.5–23.9 kg/m²</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.0–27.9 kg/m²</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥28.0 kg/m²</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>Female, n (%)</td>
<td>11,344 (44.0)</td>
<td>3973 (43.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male, n (%)</td>
<td>11,277 (40.7)</td>
<td>3,478 (40.7)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are displayed as n or n (%). Data in brackets indicate the proportion of the population in each risk stratiﬁcation and subgroups stratiﬁed by sex, age, BMI, duration, respectively. BMI: Body mass index; CV: Cardiovascular; SD: Standard deviation.
patients with diabetes. However, it is unclear about the cost-effective if initiating treatment early in younger patients who could not be divided into very high risk or high risk groups, and with elevated CVD risk factors in the long run.

Though the 2019 ESC/EASD reclassification of CV risk has not been tested in Chinese population, we used this risk model in Chinese patients with T2D for several reasons. On the one hand, the new CV risk stratification in 2019 ESC/EASD guidelines was more practical, clear, and do not need complex calculation. The new guidelines recommend stratification of the CV risk in patients with either pre-established DM into moderate-, high-, and very-high risk levels, which was thought to supersede the use of the terms primary and secondary prevention, which provide less accurate definitions of CV disease. On the other hand, few risk prediction models have been developed in diabetes cohorts in Chinese population. Therefore, we used this new CV risk stratification recommended by 2019 ESC/EASD guidelines for CVD risk evaluation in Chinese patients with T2D. However, the new stratification also had several limitations. Firstly, about one quarter of Chinese patients with T2D could not be categorized in any groups following ESC/EASD guidelines. These patients were older, and had longer duration than the patients with moderate risk, and most of them had one or two risk factors. Therefore, most of these patients actually had a risk stratification that ranged from high risk to moderate risk at the time of the evaluation. The main reason for the existence of the “unclear” risk category was that the risk factors such as age and duration of diabetes were constantly changing. For example, an obese and younger man with newly diagnosed diabetes and with no other risk factors could not be classified based on the new guidelines. The unclear grouping of these patients can complicate clinical decision-making, and need to be further classified. Secondly, a continuous distribution between levels of most risk factors and CVD risk were identified. The new risk assessment tends to falsely reassure patients deemed to be at moderate risk who may have multiple marginal abnormalities. Thirdly, the HbA1c concentration was significantly related to prevalent CV disease, and the new stratification ignores the impact of glycemic control on CV risk. Fourthly, some of CV risk factors, such as age and duration, were uncontrollable, while some were controllable, such as blood pressure, blood glucose, blood lipid, and weight. For controllable risk factors, according to the guideline, the definition of “with or without” was often used. Therefore, it was impossible to see the value and effect of controlling risk factors. In addition, the weight of each risk factor was very different, which needed to be emphasized in clinical work. The new CV risk stratification requires prospective validation before it can be recommended for widespread use.

Our findings hold important clinical implications for CVD clinical management in China. However, our study also has several limitations. First, the 3B study was a cross-sectional study and we could not provide predictive performance of the 2019 ESC/EASD new CV risk stratification based on 3B study. Clinicians may consider interpreting absolute ASCVD risk estimates analyzed in our study with caution. Second, our analysis was based on cross-sectional samples that did not account for changes in risk and treatment patterns over time. Third, stratification to the respective ESC/EASD risk strata depends strongly on the definitions used for the risk criteria. The definition of risk factors was not well-defined in 2019 ESC/EASD guidelines, and the risk factors varied in different ethnic backgrounds and regions. In this study, we defined risk factors mainly according to Guidelines of T2D in China. Risk factors should be well-defined in Chinese patients with T2D, to some extent stratified by sex and age. Fourth, we could not find any risk of CV prediction model that was developed based on Chinese diabetes cohorts. The risk of CV prediction model developed by China-PAR project (Prediction for ASCVD Risk in China) was regarded as a standard risk prediction algorithm for ASCVD in Chinese population. However, this risk prediction algorithm was not primarily designed for patients with T2D but for the general population. In addition, this risk of CV prediction model needs complex calculations, which was not a practical one for clinical use. Therefore, we did not use other risks of CV prediction algorithms, such as China-PAR project, in this study.

Conclusions
In this study, the risk of CVD was high in Chinese T2D patients based on 2019 ESC/EASD guidelines. Clinical comprehensive treatment strategies should be taken to reduce relevant risk factors. The risk of patients in “unclear risk” category need to be further classified, especially among younger and newly diagnosed patients with T2D.

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Conflicts of interest
Linong Ji has received fees for lecture presentations and consulting fees from AstraZeneca, Merck, Novartis, Novo Nordisk, Lilly, Roche, Sanofi-Aventis, and Takeda, and grants/research support from AstraZeneca, Merck, Novartis, Novo Nordisk, and Sanofi-Aventis; no other relationships or activities exist that have or could appear to have influenced the submitted work.

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