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Incidence and predictors for cardiovascular disease in Chinese patients with type 2 diabetes mellitus – a population-based retrospective cohort study

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ABSTRACT

Aims: This study aimed to estimate the 5-year incidence rate of cardiovascular disease (CVD) and determine predictive factors of new CVD in Chinese patients with type 2 diabetes mellitus (T2DM).
Methods: A retrospective cohort study was conducted on 115,470 T2DM patients aged ≥18 years without any history of CVD. Cox Proportional Hazard regression stratified by gender was performed to explore predictive factors of CVD.
Results: For 5.3 years median follow-up, the overall incidence rate of CVD per 1,000 person–years was 17.2 (95% CI: 16.9–17.6), without significant gender difference. Predictors of higher risk of CVD were older age, current smoking, longer duration of T2DM, more severe stage of chronic kidney disease, anti-hypertensive and oral anti-diabetic drugs needed, and higher body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), total cholesterol/high-density lipoprotein-cholesterol ratio (TC/HDL-C ratio) and urine albumin/creatinine ratio (ACR). Lipid-lowering agents needed in men, and ex-smoking and higher hemoglobin A1c (HbA1c) in female were the additional predictive factors of increased CVD risk.
Conclusions: Smoking, BMI, HbA1c, SBP, DBP, TC/HDL-C ratio and ACR were found to be modifiable risk factors of new CVD in Chinese T2DM patients, which should be targeted as tertiary preventive interventions. The lack of association between HbA1c and CVD in men found in this study deserves further investigation.

1. Introduction

Diabetes mellitus (DM) is a global public health issue. In 2014, DM affected 387 million people worldwide, which had been expected to substantially increase to 592 million in 2035 (International Diabetes Federation, 2014). DM can lead to morbidity complications; among which, cardiovascular disease (CVD) is a major one that caused around 70% of deaths in diabetic patients (Gilmer et al., 2005). In the United States (US), the total annual expenditure on CVD management was around US$444 billion, corresponding to 17% of the national health budget (Centers for Disease Control and Prevention, 2010). In the United Kingdom (UK), the medical cost of diabetic patients with CVD was at least twice of those without CVD (Alva, Gray, Mihaylova, Leal, & Holman, 2015). With the aging issue in the world populations, such disastrous consequences and financial impact of CVD in diabetic patients are expected to become more severe. A good understanding of CVD incidence and predictors of CVD development in diabetic patients is needed for proper healthcare and policy planning.

The incidence of CVD among diabetic patients had been scarcely reported, which ranged from 13% to 20% if expressed as a 5-year incidence, and from 22 to 46 if expressed per 1000 person–years (PY) (Adeniyi et al., 2002; Cederholm et al., 2008; Davis, Knuiman, & Davis, 2010; Elley, Robinson, Kenealy, Bramley, & Drury, 2010; Franco, Steyerberg, Hu, Mackenbach, & Nusselder, 2007). In contrast, predictors associated with CVD in the general population have been identified for a long time. The large-scale Framingham Heart and QRisk studies identified that the predictors of CVD were age, sex, smoking status, systolic blood pressure, total cholesterol and high density lipoprotein cholesterol and diabetes (D'Agostino et al., 2008; Hippisley-Cox et al., 2008).

However, current literature focused on identifying predictive factors associated with CVD in the general population, rather than solely in the diabetic population. Diabetic patients were about 2 to 4 times more likely to have CVD than non-diabetic patients (Franco et al., 2007). Moreover, the type and magnitude of the effect of CVD risk factors for diabetic patients may be different from those for non-diabetic patients (Chamnan, Simmons, Sharp, Griffin, &

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Wareham, 2009). Indeed, several studies have pointed out that there are DM specific risk factors such as glycemic control or duration of diabetes applicable to diabetic patients only (Simmons et al., 2009). Hence, large etiological study of CVD in the diabetic population is needed.

In addition, there had been no population-based data on the incidence and the etiology of CVD in Chinese diabetic patients. Chinese accounted 25% of all diabetic patients worldwide and the prevalence of DM in China was 9.3%, which is just below the corresponding 11.4% in the US (International Diabetes Federation, 2014). Unfortunately, current knowledge of CVD in diabetic patients from the west may not be entirely applicable to Chinese, due to differences in race, lifestyles and health seeking behaviors (Forouhi & Sattar, 2006). For instance, Chinese had only half of the risk of CVD when compared with Caucasians in the general UK population (Hippisley-Cox et al., 2008). Even the prevalence of CVD in Chinese was lower than that in South Asians (Anand et al., 2000). The massive Chinese population and its potential difference from other ethnic groups call for more attention to the ethnic group.

In view of scanty population-based etiological study of CVD in a population specific to DM or Chinese, this study aimed to estimate the 5-year incidence rate of CVD and determine predictive factors to the development of CVD in Chinese diabetic patients. It was hypothesized that (1) an incidence rate of CVD in Chinese diabetic population would be higher than population without diabetes but lower than other diabetic population; (2) an incidence rate of CVD between genders would be different; (3) the predictors for CVD risk between Chinese and other diabetic population would be different.

2. Materials and methods

2.1. Study design

This was a territory-wide retrospective cohort study on patients aged 18 years or above who were diagnosed of type 2 DM (T2DM) without history of CVD, and under the primary care in Hong Kong between 1 August 2008 and 31 December 2008. The data were made available from a large scale study for the evaluation of a local diabetic program, which were collected from outpatient clinics managed by the Hong Kong Hospital Authority (HA) (Fung et al., 2012). The HA was the governmental body of all public hospitals and outpatient clinics in Hong Kong, managing the majority of DM patients in Hong Kong. The clinical diagnosis of T2DM was identified by the International Classification of Primary Care-2 (ICPC-2) code of 'T90'. The database had follow-up records until 31 December 2013. Hence, most patients were followed up for at least 5 years.

Ethics approval of this study has been granted by all local institutional review boards.

2.2. Cardiovascular Disease Identification

For each patient, an incidence of CVD was identified by the diagnosis coding system of ICPC-2 and International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM). Specifically, CVD was taken as Coronary Heart Diseases, including ischaemic heart disease, myocardial infarction, coronary death and sudden death (ICPC-2 K74 to K76 and ICD-9-CM 410.x, 411.x to 414.x, 798.x), heart failure (ICPC-2 K77 or ICD-9-CM 428.x) and stroke (ICPC-2 K89 to K91 or ICD-9-CM 430.x to 438.x).

2.3. Measurements

We collected data on patient's socio-demographics, clinical parameters, disease characteristics, and treatment modalities through the clinical management system database of Hong Kong Hospital Authority. Socio-demographics included age, gender, smoking status and drinking habit. Clinical parameters included body mass index (BMI), waist-to-hip ratio (WHR), haemoglobin A1c (HbA1c), systolic and diastolic blood pressure (SBP & DBP), low-density lipoprotein-cholesterol (LDL-C), total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) ratio, triglyceride, and urine albumin to creatinine ratio (ACR). Disease characteristics included self-reported duration of diabetes mellitus and family history of diabetes mellitus. The stage of chronic kidney disease was classified according to the estimated glomerular filtration rate (eGFR) suggested by clinical guidelines from the National Kidney Foundation (Levey et al., 2003). Treatment modalities included the usage of anti-hypertensive drug, oral anti-diabetic drug (OAD), insulin and lipid-lowering agent. All laboratory assays were performed in laboratories accredited by the College of American Pathologists, the Hong Kong Accreditation Service or the National Association of Testing Authorities of Australia.

2.4. Data Analysis

The earliest record of outpatient clinic attendance between 1 August 2008 and 31 December 2008 was taken as the baseline for predicting the risk of CVD development. Missing data were handled by multiple imputation (Royston, 2004). The method was designed to allow the inclusion of patients with incomplete data into analysis to increase the power of the analysis and produce models that are statistically more reliable and applicable within clinical practice (Royston, 2004). Hence, it was also used in the development of CVD prediction model in QRisk study (Hippisley-Cox et al., 2008). In this study, every missing value based on the assumption of missing completely at random was imputed by the chained equation method for 5 times, which attained a relative efficiency of at least 95% (Rubin, 2004). For each of the 5 imputed datasets, we repeated the analysis, and the five sets of results were combined using the Rubin's rule (Rubin, 2004).

Baseline differences in socio-demographics, clinical parameters, disease characteristics, and treatment modalities between male and female patients were assessed using independent t-test for continuous variables and chi-square test for categorical variables. The incidence rate of CVD was estimated by an exact 95% confidence interval (CI) based on a Poisson distribution. Kaplan–Meier survival curves for CVD development for the two gender groups were obtained, and their difference was assessed by the log-rank test.

Predictors of CVD were identified by using multivariable Cox proportional hazards regression. Since some studies speculated that HbA1c, SBP and DBP were curvilinearly correlated with the risk of CVD incidence (Currie et al., 2010; Kontopantelis et al., 2015), the quadratic terms of these predictors were considered in the model. All factors were included in the model and the quadratic terms were excluded if not statistically significance. The proportional hazards assumption was assessed by examining plots of the scaled Schoenfeld residuals against time for the predictors. Presence of multicollinearity was checked by examining the tolerance. To assess the sensitivity of our results, the analysis was repeated in the cohort of complete cases. As the literature has stipulated a potential difference in predictors of CVD incidence between genders (He et al., 2001), the analysis was stratified by gender.

All significance tests were two-tailed and a p-value less than 0.05 was considered statistically significant. The statistical analysis was performed in STATA version 13.0.

3. Results

A total of 125,099 Chinese adults diagnosed of T2DM were receiving care in primary care clinics of HA between 1 August 2008 and 31 December 2008. Of which, 9,492 patients had CVD at baseline and 137 patients had no follow-up record. Excluding them resulted in 115,470 diabetic patients for the analysis. Data completion rate for