

Coronary Artery Calcium Score Predicts Long-Term Cardiovascular Outcomes in Asymptomatic Patients with Type 2 Diabetes

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Aims: Type 2 diabetes mellitus (T2DM) is no longer regarded as a coronary risk equivalent, and heterogeneity of cardiovascular risk exists, suggesting that further risk stratification should be mandatory. This study aimed to determine the prevalence and clinical predictors of coronary artery calcium (CAC) score, and evaluate the CAC score as a predictor of cardiovascular outcome in a large asymptomatic T2DM cohort.

Methods: A total of 2,162 T2DM patients were recruited from a Diabetes Shared Care Network and the CAC score was measured. Cardiovascular outcomes were obtained for 1,928 patients after a follow-up of 8.4 years. Multiple regression analysis and Cox proportional hazard regression were applied to identify clinical predictors of CAC and calculate the incidence and hazard ratios (HRs) for all-cause mortality and cardiovascular events by CAC category.

Results: Of the recruited patients, 96.8% had one or more risk factors. The distribution of CAC scores was as follows: CAC=0 in 24.2% of the patients, $0 < \text{CAC} \leq 100$ in 41.5%, $100 < \text{CAC} \leq 400$ in 20.3%, $\text{CAC} > 400$ in 14.7%. The multivariable predictor of increased CAC included age (years) (odds ratio, 1.07; 95% confidence interval, 1.06–1.08), male sex (1.82; 1.54–2.17), duration (years) of T2DM (1.07; 1.05–1.09), and multiple risk factors (1.94; 1.28–2.95). Increasing severity of CAC was associated with higher all-cause or cardiac mortality and higher incident cardiovascular events. The HRs for cardiac death or major cardiac events in $\text{CAC} > 400$ vs $\text{CAC} = 0$ were 8.67 and 10.52, respectively ($p < 0.001$).

Conclusion: CAC scoring provides better prognostication of cardiovascular outcome than traditional risk factors in asymptomatic T2DM patients, and may allow identifying a high-risk subset for enhancing primary prevention.

Key words: Coronary artery calcium score, Primary prevention, Cardiovascular outcome, Type 2 diabetes mellitus

Introduction

Cardiovascular disease is the leading cause of death in 65%–75% of diabetic patients¹. Generally, diabetic patients have more extensive atherosclerosis with a higher prevalence of multi-vessel coronary artery disease (CAD), frequent silent myocardial ischemia, and infarction with a poorer prognosis. Diabetes is associated with at least a two-fold increased risk of coronary heart disease (CHD) and a two- to four-fold increased risk of CHD- and stroke-associated mortality compared those in patients

without diabetes¹⁻³. From a pooled analysis of more than one million Asian participants, patients with diabetes had a 1.89-fold risk of all-cause death and a two-fold risk of cardiovascular-related death compared with patients without diabetes⁴.

Two decades ago, diabetes was regarded as a “CHD risk equivalent,” implying a 10-year cardiovascular risk of >20% for every diabetic patient according to Haffner’s report⁵ and other large observational studies^{6, 7}. However, several studies of different population cohorts provided varying conclusions on the concept of coronary risk

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equivalency in patients with diabetes^{8, 9}). In a systematic review and meta-analysis of 13 studies enrolling 45,108 patients with a mean follow-up of 13.4 years, Bulugahapitiya *et al.*¹⁰ showed that patients with diabetes without prior myocardial infarction have a 43% lower risk of developing total CHD events compared with patients without diabetes with previous myocardial infarction, not supporting the hypothesis of diabetes being a “CHD risk equivalent”. New guidelines have acknowledged the heterogeneity of cardiovascular risk in diabetic patients and suggested further risk stratification before universal treatment¹¹⁻¹³).

Coronary artery calcium (CAC) score measured by multi-detector computerized tomography is a reliable measure of subclinical atherosclerosis^{14, 15}). The presence, extent, and progression of CAC have been shown to enable better prognostication of adverse cardiovascular events than traditional risk factors and global risk scoring among asymptomatic intermediate-risk individuals^{16, 17}). There is significant heterogeneity between traditional risk and observed events, with discrepant event rates driven by the directly observed burden of atherosclerosis^{18, 19}). CAC scoring may help reclassifying individuals at intermediate-risk to low- or high-risk groups to aid clinical decision-making in primary prevention^{16, 17}).

Patients with type 2 diabetes (T2DM) harbor larger amounts of CAC than nondiabetic patients of similar age. Some studies have demonstrated that increased CAC in individuals with T2DM is associated with increased prevalence of myocardial ischemia^{20, 21}), more coronary events^{22, 23}), and higher all-cause mortality²⁴). Zero CAC was present in one-third of T2DM patients and predicted low short-term risk of death (around 1% at 5 years)^{23, 24}). The aim of this study was to determine the prevalence and clinical predictors of CAC score in uncomplicated T2DM patients, and evaluate CAC score as a predictor of long-term cardiovascular outcome in a large asymptomatic Taiwanese T2DM cohort.

Methods

Study Participants

We recruited 2412 consecutive asymptomatic T2DM patients from Lan-Yan Diabetes Shared Care Network from August 2006 to August 2007 (61.2% referred by the Public Health Bureau of Yilan County, 31.3% from the Lo-Tung Poh-Ai Hospital, and 7.5% from local practitioners). Inclusion criteria were having T2DM for more than 1 year and age between 40 and 80 years old. The exclusion criteria were documented coronary artery disease, typical angina, abnormal resting electrocardiogram (e.g., Q waves and

LBBB), cerebrovascular or peripheral arterial disease, or serious life-threatening illness. Seventy-six patients were excluded. One hundred and sixty-eight patients were not interested in taking part in the study and refused baseline blood test. Finally, 2162 subjects (aged 40 to 80 years, mean 64.5 ± 9.3 , 48% male) fulfilled the eligibility criteria, provided informed consent in written form for collection of baseline and follow-up data, and underwent CAC score measurement.

Risk Factor Assessment

Information of participant demographic characteristics, medical histories, including traditional cardiovascular risk factors (hypercholesterolemia, hypertension, smoking, family history of premature CHD, macro/microalbuminuria), duration of T2DM, treatment history, height, weight, body mass index, waist-to-hip ratio, and blood pressure were recorded. Hypercholesterolemia was defined as total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >100 mg/dL, high-density lipoprotein cholesterol <35 mg/dL, or being on statin treatment. Hypertension was defined as blood pressure $>140/90$ mmHg or being on anti-hypertensive treatment. Family history of premature CHD was determined by asking patients whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and coronary revascularization. Patients were considered to have a history of premature CHD if such events occurred before 55 years of age in male relatives or before 65 years of age in female relatives. Fasting blood and urine samples were obtained for checking glucose, HbA1c, lipid profiles, urea, creatinine, and urine microalbumin.

CAC Scores Measurement

CAC imaging was performed using a 16-sliced or 64-sliced multi-detector computerized tomography scanner (Siemens Somatom 16, Philips Brilliance 64) equipped with high-resolution detectors. Contiguous 3-mm slices were obtained during a single breath-hold starting at the carina and proceeding to the level of the diaphragm. Scan time was 100-ms per slice, with image acquisition electrocardiographically synchronized to 60% of the R-R interval. A calcified lesion was defined as ≥ 3 contiguous pixels, with a peak attenuation of at least 130 Hounsfield units. Each lesion was then scored using the method developed by Agatston *et al.* A single experienced radiologist blinded to the clinical data calculated all CAC scores. CAC scores were classified into four categories based on cut-offs that have been widely used in the literature as follows: 0, $0 < \text{CAC} \leq 100$

(mild CAC), $100 < \text{CAC} \leq 400$ (moderate CAC), and $\text{CAC} > 400$ (severe CAC).

Clinical Endpoints Ascertainment

Clinical endpoints include all-cause mortality, cardiac mortality, acute myocardial infarction (AMI), any coronary revascularization (percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG]), and ischemic stroke. Major CHD events were defined as combinations of cardiac mortality, AMI, and any coronary revascularization. All cardiovascular events were surveyed by a study nurse via telephone interview with the patient or a family member between 2014 and 2015 within a 14-month interval. Adequate information was obtained for 1928 patients.

Statistical Analysis

Data analysis was performed using the statistical SAS software 9.2 version. Means were compared by analysis of variance. One-way ANOVA and chi-square test were applied to test for difference in demographic and risk factors and to describe the percentage of risk factors among four CAC categories. Multiple regression analysis was used to determine the relationships between cardiovascular risk factors and the severity of CAC. The incidence rate of clinical endpoints (all-cause mortality, cardiac mortality, non-cardiac mortality, major CHD, AMI, PCI, CABG, coronary revascularization, and ischemic stroke) among the four CAC categories was calculated and the chi-square test was used to determine the differences among four CAC categories. We constructed Kaplan–Meier cumulative-event curves for all-cause mortality, cardiac mortality, coronary revascularization, and major CHD events. Cox proportional-hazards regression was employed to estimate hazard ratios as compared between CAC categories for all endpoints, and all models were adjusted for age, diabetes duration, and number of risk factors. A two-sided $p < .05$ was considered to indicate statistical significance.

Results

Baseline Characteristics

Of 2,162 enrolled participants, 1,928 had complete demographic, risk factor, blood test, and endpoint data with a mean 8.4 years interval after CAC measurement, constituting the final analyzed population. The risk factors among the 1928 study participants were hypertension in 69.1% (96.2% being treated), hypercholesterolemia in 75.9% (26.9% on statin), smoking in 30.8%, family history of

premature CHD in 7.3%, and macro/microalbuminuria in 41.6%. The distribution of coronary risk factors was 3.2% without any risk factor, 17.2% with one, 38.8% with two, and 40.8% with three or more risk factors. The mean T2DM duration was 7.0 ± 6.0 years, HbA1C was $8.0\% \pm 1.6\%$, and the mean body mass index was $26.8 \pm 4.8 \text{ kg/m}^2$. The distribution of CAC scores was as follows: $\text{CAC}=0$ in 24.2% of the participants, $0 < \text{CAC} \leq 100$ (mild CAC) in 41.5%, $100 < \text{CAC} \leq 400$ (moderate CAC) in 20.3%, and $\text{CAC} > 400$ (severe CAC) in 14.7%. The medical treatments of the participants included aspirin use in 36.6%, statin in 26.8%, angiotensin-converting enzyme inhibitor in 14.7%, angiotensin receptor blocker in 19.5%, beta-blocker in 21.1%, oral hypoglycemic agents in 84.5%, insulin in 1.9%, and both anti-diabetic medication in 3.8%.

CAC Score and Risk Factor Burden

The baseline characteristics and risk factors condition among the four CAC category groups are shown in **Table 1**. Patients with higher CAC score tended to be older, of the male sex, had longer duration of T2DM, higher systolic blood pressure, poorer renal function, and lower high-density lipoprotein cholesterol. By multivariable analysis, only age (years) (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.06–1.08), male sex (OR, 1.82; 95% CI, 1.54–2.17), and diabetic duration (years) (OR, 1.07; 95% CI, 1.05–1.09) were significant predictors of increased CAC ($p < 0.001$). Any single traditional factor did not correlate with the severity of CAC. There was no difference in the severity of CAC in diabetic patients with two or less risk factors (**Fig. 1**). Only clustering of three or more risk factors predict increased CAC (OR, 1.94 vs 0 risk factor; 95% CI, 1.28–2.95; $p = 0.002$). Among patients without any risk factor, 33.9% had a CAC score = 0 and 11.3% had a CAC score > 400 , whereas among patients with 3 or more risk factors, 20.5% had a CAC score = 0 and 16.4% had a CAC score > 400 .

CAC Score and Cardiovascular Events

During a mean 8.4 years follow-up, a total 211 all-cause and 43 cardiac death events and 207 major CHD events occurred. The incidence rate of all clinical endpoints is shown according to CAC score categories at **Table 2**. A stepwise increase in the observed event rate of all-cause mortality, major CHD (cardiac mortality, AMI, coronary revascularization), and ischemic stroke was seen with increasing severity of CAC score categories. The all-cause mortality and major CHD event rate were 6.4 and 3.9 per 1000 person-year, respectively, in diabetic patients with

Table 1. Baseline Characteristics among Four Coronary Artery Calcium (CAC) Categories (*N*= 1,928)

Variable mean (SD)	CAC=0 (<i>N</i> =466)		0 < CAC ≤ 100 (<i>N</i> =800)		100 < CAC ≤ 400 (<i>N</i> =392)		CAC > 400 (<i>N</i> =270)		<i>P</i> value
	mean/ <i>N</i>	(SD)/%	mean/ <i>N</i>	(SD)/%	mean/ <i>N</i>	(SD)/%	mean/ <i>N</i>	(SD)/%	ANOVA/ Chi-square ¹
CAC value, AU	0.0	(0.0)	28.1	(28.2)	218.5	(85.0)	1097.4	(762.6)	< .001
Age, years	59.8	(9.4)	64.2	(8.9)	66.8	(8.0)	68.5	(8.7)	< .001
Male	177.0	38.0%	385.0	48.1%	203.0	51.8%	168.0	62.2%	< .001 ¹
Body high, cm	158.0	(7.7)	158.7	(8.8)	158.7	(8.3)	160.0	(8.4)	.029
BMI, kg/m ²	26.8	(3.9)	27.2	(5.9)	26.5	(3.8)	26.2	(3.7)	.008
Waist circumference, cm	87.4	(9.9)	89.3	(9.2)	88.7	(9.2)	88.3	(8.4)	.125
Duration of DM, years	5.1	(4.7)	6.4	(5.4)	8.5	(7.1)	9.2	(6.8)	< .001
Blood pressure									
SBP, mmHg	133.7	(15.9)	136.9	(16.6)	137.5	(16.1)	139.0	(15.8)	< .001
DBP, mmHg	80.4	(11.1)	80.5	(10.7)	80.1	(10.6)	79.6	(11.1)	.671
Blood sugar									
AC Blood sugar, mg/dL	158.7	(52.6)	160.7	(55.8)	157.0	(52.0)	163.9	(57.0)	.421
PC Blood sugar, mg/dL	208.5	(74.3)	209.4	(81.0)	211.9	(82.4)	232.9	(92.3)	.061
HbA1c, %	7.9	(1.6)	8.0	(1.6)	8.0	(1.6)	8.1	(1.6)	.502
BUN, mg/dL	17.4	(10.0)	17.3	(7.4)	20.4	(12.8)	20.5	(12.2)	< .001
Creatinine, mg/dL	1.0	(0.9)	1.0	(0.6)	1.1	(0.7)	1.2	(0.8)	.002
Cholesterol, mg/dL	203.5	(39.6)	203.2	(43.1)	202.2	(43.3)	199.0	(42.7)	.516
LDL, mg/dL	124.8	(31.6)	126.5	(33.1)	126.8	(34.9)	124.5	(37.2)	.804
HDL, mg/dL	45.3	(14.9)	43.8	(13.4)	43.7	(13.2)	40.9	(10.5)	.004
Triglyceride, mg/dL	160.0	(112.6)	172.1	(129.5)	163.5	(116.8)	175.6	(106.3)	.255
Medication use									
Aspirin	146	31%	283	35%	156	39%	121	44%	.001
ACEI	58	12%	122	15%	63	16%	41	15%	.438
ARB	80	17%	170	21%	72	18%	59	21%	.229
Statin	124	26%	208	26%	120	30%	66	24%	.269
OHA	395	84.8%	699	87.4%	322	82.1%	223	82.6%	.204
Insulin	10	2.1%	12	1.5%	10	2.6%	14	5.2%	.009
OHA + Insulin	11	2.4%	33	4.1%	23	5.9%	18	6.7%	.020
Risk factor group									
RF=0	21.0	4.5%	25.0	3.1%	9.0	2.3%	7.0	2.6%	< .001 ¹
RF=1	113.0	24.2%	127.0	15.9%	48.0	12.2%	44.0	16.3%	
RF=2	171.0	36.7%	336.0	42.0%	151.0	38.5%	90.0	33.3%	
RF>=3	161.0	34.5%	312.0	39.0%	184.0	46.9%	129.0	47.8%	
Risk factor									
Smoking	129.0	27.7%	234.0	29.3%	123.0	31.4%	108.0	40.0%	.003 ¹
Family history of CAD	42.0	9.0%	51.0	6.4%	26.0	6.6%	21.0	7.8%	< .001 ¹
Hypercholesterolemia	351.0	75.3%	608.0	76.0%	312.0	79.6%	192.0	71.1%	< .001 ¹
Macro/microalbuminuria	172.0	36.9%	322.0	40.3%	185.0	47.2%	124.0	45.9%	.008 ¹
Hypertension	277.0	59.4%	587.0	73.4%	294.0	75.0%	210.0	77.8%	< .001 ¹

AU, Agatston unit; CAC, coronary artery calcium; BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; OHA, oral hypoglycemic agent; RF, risk factor; CAD, cardiovascular disease. Risk factors group were counted by smoking, family history of CAD, hypercholesterolemia, macro/microalbuminuria and hypertension.

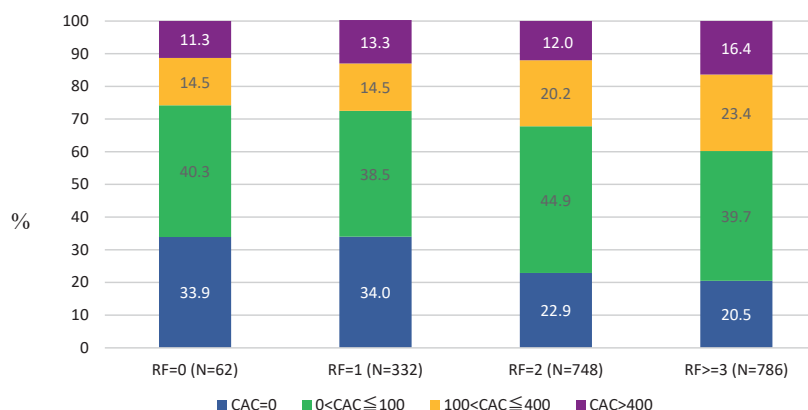


Fig. 1. Distribution of coronary artery calcium (CAC) scores by number of coronary risk factors

Table 2. Incidence of Events According to Four Coronary Artery Calcium (CAC) Categories

Variable	CAC=0 (N=466)			0<CAC≤100 (N=800)			100<CAC≤400 (N=392)			CAC>400 (N=270)			P value
	N	%	incidence per 1,000 Person-years	N	%	incidence per 1,000 Person-years	N	%	incidence per 1,000 Person-years	N	%	incidence per 1,000 Person-years	
All cause mortality ^a	26	5.6%	6.4	74	9.3%	10.8	51	13.0%	15.6	60	22.2%	28.6	< .001
Cardiac mortality	3	0.6%	0.8	12	1.5%	1.8	9	2.3%	2.7	19	7.0%	8.6	< .001
Non-cardiac mortality	23	4.9%	6.0	62	7.8%	9.5	42	10.7%	13.4	41	15.2%	19.7	< .001
Major CHD ^b	16	3.4%	3.9	67	8.4%	9.8	49	12.5%	15.3	75	27.8%	38.3	< .001
AMI	3	0.6%	0.8	16	2.0%	2.4	11	2.8%	3.4	9	3.3%	4.0	.045
Coronary revascularization	13	2.8%	3.2	56	7.0%	8.1	43	11.0%	13.2	62	23.0%	30.5	< .001
Ischemic stroke	16	3.4%	4.1	43	5.4%	6.5	23	5.9%	7.1	29	10.7%	13.5	< .001

^aClinical endpoints include all-cause mortality, cardiac mortality, acute myocardial infarction (AMI), any coronary revascularization [percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)] and ischemic stroke.

^bMajor coronary heart disease (CHD) events were defined as combinations of cardiac mortality, AMI and any coronary revascularization.

CAC score=0, but up to 28.6 and 38.3 per 1,000 person-year in patients with CAC >400 ($p<0.001$). Kaplan–Meier analysis of event-free survival curve for all clinical endpoints showed a significant difference among the 4 CAC score categories during the 8 years follow-up, with a lower event-free survival rate in patients with a higher CAC score (Fig. 2A, B, C, D). In four patients’ stratum with various risk factor burdens, the incidence rate of all-cause mortality and major CHD event increase with the CAC score (Fig. 3A, B). Individuals with no risk factor and CAC >400 had much higher mortality and major CHD events compared with individuals with three or more risk factors but no CAC (40.0 and 12.2 per 1,000 person-year versus 6.0 and 6.1 per 1,000 person-year, respectively). In the Cox proportional regression analysis adjusted for age, T2DM duration, and number of risk factors, increasing CAC score was

associated with higher hazard ratio (HR) of major CHD event and cardiac mortality, with 10.5- and 8.7-fold risk for CAC score >400 versus CAC=0 or 4.2- and 3.4-fold risk for CAC score <100–400 versus CAC=0 (Table 3). Macro/microalbuminuria is a significant predictor of the clinical endpoints all-cause mortality (HR=1.54, $p=0.003$), cardiac mortality (HR=2.67, $p=0.002$), major CHD (HR=1.45, $p=0.013$), and ischemic stroke (HR=1.77, $p=0.004$). The incidence of ischemic stroke tended to increase as the severity of CAC increased; however, the association became non-significant after correction for confounding factors (Tables 2 and 3).

Discussion

This is the largest prospective study evaluating the relationship between long-term cardiovascular

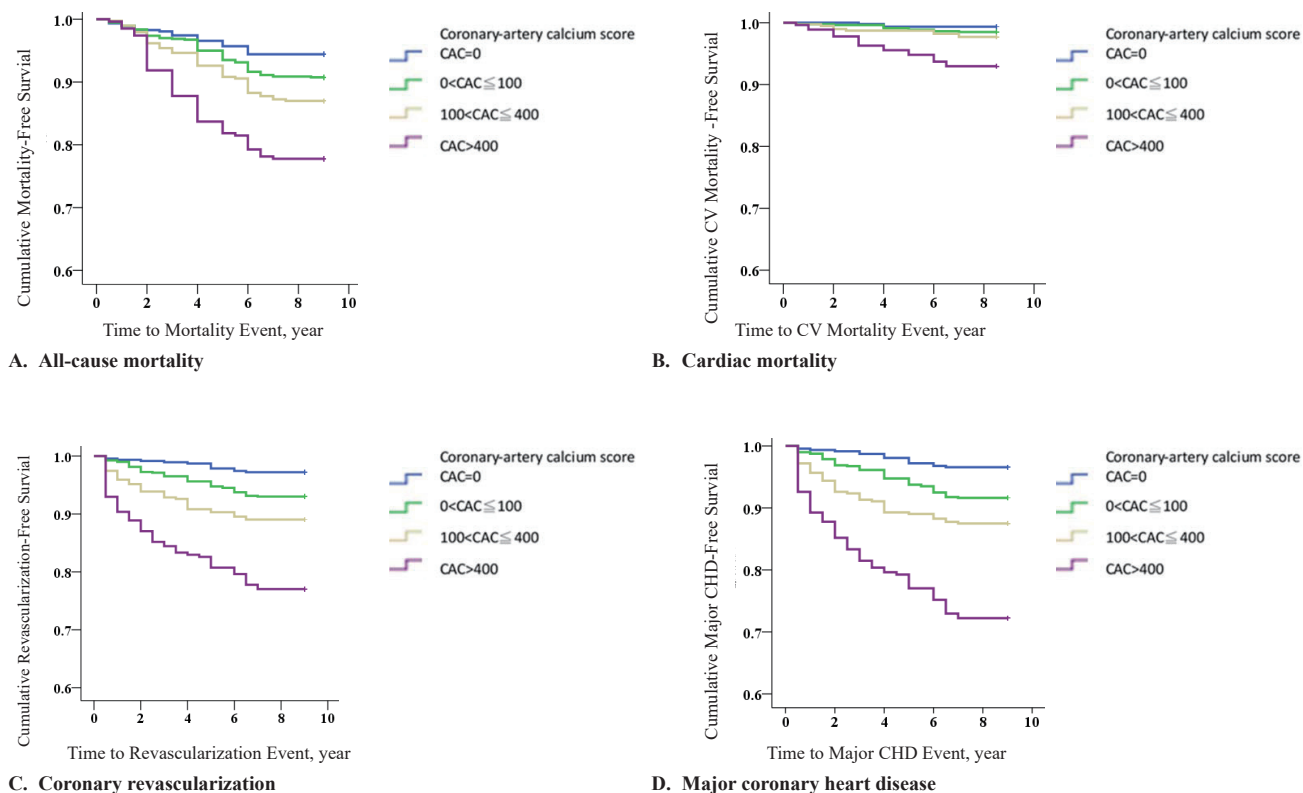


Fig. 2.

Kaplan–Meier Cumulative-Event Curves for all-cause mortality (A), cardiac mortality (B), coronary revascularization (C), and major coronary heart disease (D) in participants with diabetes by four coronary artery calcium (CAC) categories. The differences between the four CAC categories among all survival curves are statistically significant (all $p < 0.05$).

Table 3. The Associations between CAC Categories and Clinical Endpoints in Participants with Diabetes Examining by Cox Proportional Hazards Regression model

CAC score category	All cause mortality			Cardiac mortality			Non-cardiac mortality		
	Hazard Ratio	(95% CI)	<i>p</i> value	Hazard Ratio	(95% CI)	<i>p</i> value	Hazard Ratio	(95% CI)	<i>p</i> value
CAC=0	1 (reference)			1 (reference)			1 (reference)		
0<CAC≤100	1.07	0.63–1.81	.797	2.16	0.46–10.11	.329	0.95	0.54–1.67	.862
100<CAC≤400	1.45	0.84–2.52	.184	3.35	0.69–16.30	.134	1.22	0.68–2.22	.505
CAC>400	2.08	1.18–3.66	.011	8.67	1.87–40.27	.006	1.38	0.73–2.59	.324
	Cox model: $p < .001$			Cox model: $p < .001$			Cox model: $p < .001$		

CAC score category	Major CHD			Coronary revascularization			AMI			Ischemic stroke		
	Hazard Ratio	(95% CI)	<i>p</i> value	Hazard Ratio	(95% CI)	<i>p</i> value	Hazard Ratio	(95% CI)	<i>p</i> value	Hazard Ratio	(95% CI)	<i>p</i> value
CAC=0	1 (reference)			1 (reference)			1 (reference)			1 (reference)		
0<CAC≤100	3.14	1.54–6.41	.002	3.39	1.52–7.58	.003	5.71	0.73–44.44	.096	1.19	0.63–2.25	.590
100<CAC≤400	4.18	1.99–8.80	< .001	4.57	1.98–10.52	< .001	6.31	0.76–52.23	.087	1.18	0.57–2.43	.652
CAC>400	10.52	5.07–21.83	< .001	10.83	4.76–24.62	< .001	4.19	0.44–39.51	.211	2.11	2.11–4.32	.410
	Cox model: $p < .001$			Cox model: $p < .001$			Cox model: $p < .047$			Cox model: $p < .001$		

All models were adjusted for age, diabetes duration and the number of risk factors.

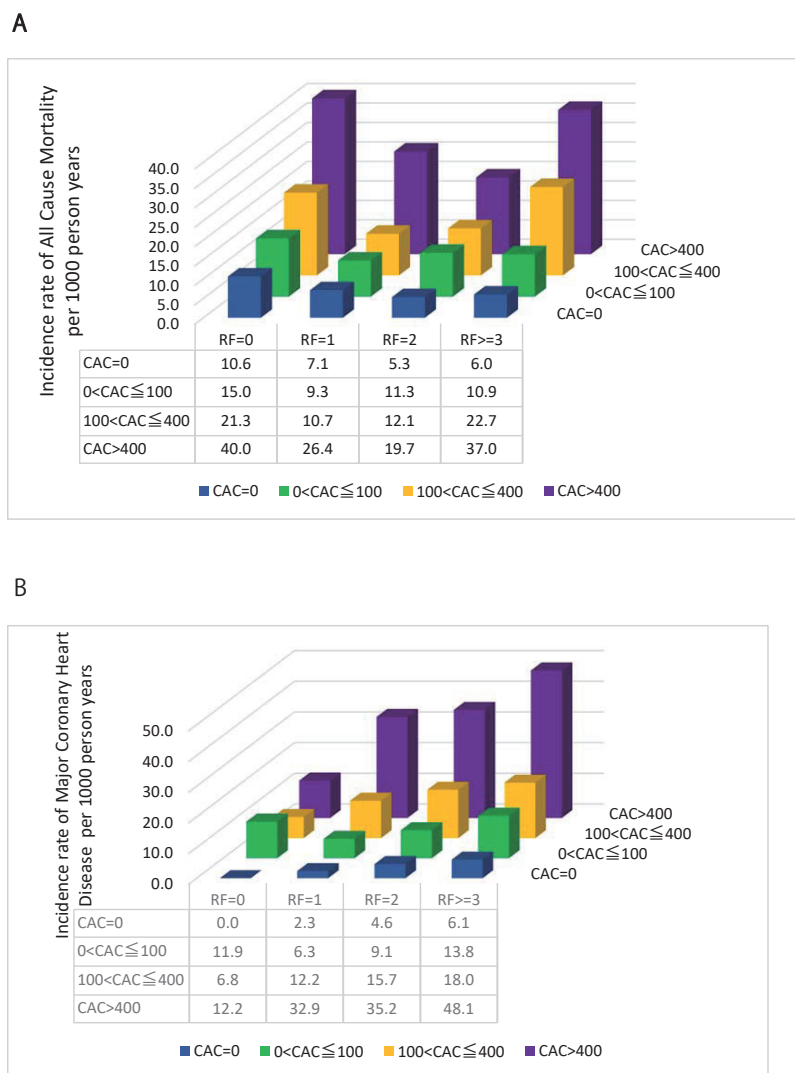


Fig. 3.

Incidence rates of all-cause mortality (A) and major coronary heart disease (B) among subgroups of risk factor burden and CAC category.

outcome and severity of CAC in asymptomatic T2DM patients. Of the included patients, 23.5% had a CAC score of zero and severe CAC (CAC score > 400) was present in 14.7%. Those patients of older age, male sex, longer diabetic history, and multiple traditional risk factors tended to have a higher CAC score. Increasing severity of CAC significantly predicted higher long-term all-cause mortality and major CHD events irrespective of risk factor burden. Diabetic patients without CAC had very low event rate.

Subclinical Atherosclerosis and Risk Factor Burden

Measuring atherosclerotic plaque burden must take into account the aggregated effect of all known and unknown risk factors. The extent of CAC has

been shown to be closely related with total coronary artery atherosclerotic plaque burden, and CAC scanning provided a direct means of measuring atherosclerosis²⁵). Incidence of CAC is strongly associated with traditional atherosclerotic risk factors such as age, sex, race, body mass index, waist-hip ratio, diabetes, history of hypertension, and family history of CHD²⁶⁻²⁸). But the distribution of CAC is heterogeneous across age and risk factor burden in the general population^{18, 19, 29}). High atherosclerotic burden is not an obligatory finding in older patients or those with multiple risk factors. Likewise, young patients and those with no or one risk factor may have increased burden of atherosclerosis. Results from the Multi-Ethnic Study of Atherosclerosis (MESA) revealed a direct relationship between Framingham

risk score (FRS) and the prevalence and amount of CAC, but the distribution of CAC within FRS groups remains heterogeneous³⁰. This heterogeneity between traditional risk factors and atherosclerosis burden was also observed in our diabetic patients. Our study showed there was no difference in the distribution of CAC severity in diabetic patients with two or fewer risk factors. Only clustering of three or more risk factors predict more severe CAC, but still one-fifth of the patients with high risk-factor burden had no CAC.

CAC and CHD Events in the General Population

In several prospective or retrospective, population-based, or patient-referred studies, CAC score has consistently been shown to predict cardiac events in the asymptomatic general population with significant incremental value over conventional risk factor-based assessment^{14-17, 31-33}. In a large cohort of 25,253 asymptomatic subjects, Budoff *et al.* showed that an increasing CAC score was associated with increased risk of all-cause mortality after a mean follow-up of 6.8 years³³. From the MESA analysis, the HRs for a coronary event was 7.73 for those with a CAC score of 101 to 300, and 9.67 for a CAC score >300 as compared with patients with a CAC score of 0¹⁵. CAC score was superior to FRS in the prediction of total CHD events after a mean follow-up of 4.3 years with the area under the curve for CAC score being 0.79 as compared to 0.68 for FRS ($p < 0.001$)³². A CAC score >400 is considered as a CHD risk equivalent, with the 10-year event rate exceeding 20% in asymptomatic patients. The annual event rate in patients with a CAC score of zero is very low (0.11% to 0.17%), making a CAC score of zero a strong negative predictor of CHD events³⁴. The 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease has suggested class IIa recommendation for CAC score measurement to guide clinician-patient risk discussion in borderline-to-intermediate-risk groups and certain subgroups, such as women and young adults³⁵.

CAC and Cardiovascular Risk in T2DM Patients

For the asymptomatic T2DM population, there were a few studies demonstrating increased prevalence and severity of CAC, wide variability of cardiovascular risk in different CAC categories, and worse prognosis associated with increasing CAC severity^{21-24, 36, 37}. In a 8.5-year follow-up of 1,343 T2DM patients from the MESA and Heinz-Nixdorf-Recall studies, Yeboah *et al.* showed that CAC score was a better predictor of incident cardiovascular events compared with FRS and the United Kingdom Prospective Diabetes Study score (area under the curve, 0.76, 0.70, and 0.69,

respectively; all $p < 0.05$)²³. Our study showed similar findings; progressively higher incidence of all-cause mortality and major coronary heart events were observed with increasing severity of CAC under various risk factor burden in this largest T2DM cohort over the mean 8.4 years (Fig. 2, 3A, 3B). After confounding factors adjustment, patients with a CAC score >400 had a significant higher HR for all-cause mortality (2.08), cardiac mortality (8.67), and major CHD (10.5) as compared with patients with a zero CAC score (Table 3). Patients without CAC account for 13.4% to 39.3% of the study population in various studies^{23, 24, 28, 36}, being 24.2% in our report. They had the lowest incidence rate of all-cause mortality and major CHD events (6.4 and 3.9 per 1000 person-year, respectively) under various risk factor burden (Table 2, Fig. 3A, 3B). Even patients with three or more risk factors but zero CAC had a lower major CHD event rate than patients with CAC >400 and no or one risk factor (6.1 versus 12.2 or 32.9 per 1000 person-year). Our study and prior reports provide strong evidence that diabetes per se is not a CHD risk equivalent and CAC determination is a better strategy for risk stratification in mid-to-long-term cardiovascular outcome.

CAC and Aspirin for Primary Prevention in T2DM

The benefits and harms of aspirin for primary prevention of cardiovascular disease in the diabetic population have been widely studied in the past decades but remain controversial^{38, 39}. Recommendations from various guidelines for aspirin use have also been inconsistent. A recent meta-analysis including 12 randomized controlled trials based on 34,227 diabetic participants with a median treatment duration of 5 years showed that there was a significant reduction in risk of major adverse cardiovascular events with a HR of 0.89 (0.83–0.95), comparing aspirin use with no aspirin intake. Aspirin use had no effect on all-cause mortality and other endpoints, and had also no influence on major bleeding⁴⁰. Another meta-analysis including 10 studies and 30,448 participants showed that aspirin use was associated with a decrease in primary composite cardiovascular outcome with a HR of 0.89 (0.80–1.00), but no effect on secondary cardiovascular outcomes. Significant increase in major bleeding (HR, 1.29) and major gastrointestinal bleeding (HR, 1.35) were described as being associated with aspirin use⁴¹. Therefore, the use of low-dose aspirin for primary prevention in diabetes should be individualized according to personal baseline cardiovascular and bleeding risk as per recommendation from latest American Diabetes Association (ADA) standards of medical care in

diabetes. An analysis of aspirin use for primary prevention of CHD from the MESA study showed nondiabetic individuals with a CAC score ≥ 100 had an estimated net benefit regardless of their traditional risk status while individuals with zero CAC were estimated to receive net harm from aspirin use⁴²⁾. In an observation of 2,384 diabetic patients after a follow-up of 5.6 ± 2.6 years, Silverman *et al.* reported that CAC can help risk stratification and a CAC score ≥ 100 may aid in the selection of patients who may benefit from aspirin therapy within the low and intermediate-risk groups based on age and risk factors profile⁴³⁾. Among our study population, aspirin use could be suggested in 96.5% of the participants according to ADA's risk factors criteria, but may be beneficial only in 34.3% as per CAC score >100 criteria. Accordingly, CAC scoring may help decision-making for aspirin use in primary prevention.

Limitations

The major limitation of our study was that all cardiovascular endpoints were ascertained by a study nurse via telephone interview with the patient or family retrospectively after a mean 8.4 years' interval. Only 31.3% of the patients' outcomes were confirmed by formal hospital chart records, but were not adjudicated by an independent committee. There were probably missing nonfatal cardiovascular events in some patients, but the accuracy of all-cause mortality and cardiac mortality may be less affected by the method of data acquisition.

Conclusions

Among the asymptomatic T2DM population, there is significant heterogeneity between traditional coronary risk factors and atherosclerotic burden, represented by the CAC score. Only multiple risk factors predict increasing severity of CAC. Increasing severity of CAC was associated with higher all-cause mortality, cardiac mortality, and incident cardiovascular events. A CAC score >400 or zero can identify high- or low-risk subsets irrespective of risk factor burden. Measurement of CAC provides better prognostication of adverse cardiovascular events than traditional risk factors in asymptomatic T2DM patients. Additional research is needed to confirm the utility of CAC screening to guide selection of diabetic patients for aspirin therapy in the primary prevention of cardiovascular disease.

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Author Contribution

MHL, SLC, CCC, WCC, and YCH contributed to the conception and design of the work. MHL, YLW, SLC, WCC, and YCH contributed to the acquisition, analysis and interpretation of data for the work. MHL and YLW drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring accuracy and integrity.

Disclosure of Potential Conflicts of Interest

All authors declare that they have no conflict of interest.

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Ethical Approval

The institutional review board at Lo-Tung Poh-Ai Hospital approved the study with review board number (OMCP-97-013).

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