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ARTICLE

P. D. Reaven · J. Sacks · Investigators for the VADT

Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes

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Abstract *Aims/hypothesis:* The goals of this study were to determine whether coronary calcium is associated with the presence of clinical cardiovascular disease in individuals with type 2 diabetes and if the measurement of abdominal aortic calcium may have an independent or added benefit as a surrogate marker for clinical vascular disease. *Methods:* A cross-sectional study of subjects with type 2 diabetes enrolled in seven medical centres in the USA participating in a Veterans Affairs Cooperative Study of glycaemic control. Enrolled subjects included 309 veterans over 40 years of age with type 2 diabetes, with or without stable cardiovascular disease, who had inadequate glycaemic control (HbA_1c>7.5%) on oral agents and/or insulin. The study assessed lifestyle behaviours, standard cardiovascular risk factors and coronary artery and abdominal aorta calcification by electron beam computed tomography. *Results:* Subjects with coronary artery or abdominal aorta calcification present had a strikingly higher prevalence of peripheral artery disease, coronary artery disease and all combined cardiovascular disease. Prevalence of each condition increased from 5- to 13-fold with increasing quintiles of coronary artery calcification and from 2- to 3-fold with increasing abdominal aorta calcification. These associations persisted after adjustment for lifestyle behaviours and standard cardiovascular risk factors. *Conclusions/interpretation:* These results support the notion that vascular calcium in type 2 diabetes provides additional information beyond that of standard risk factors in identifying the presence of cardiovascular disease. Subclinical measures of atherosclerosis such as arterial calcification may help more precisely stratify these individuals and alert healthcare providers to those individuals who have particularly accelerated atherosclerosis.

Keywords Aortic calcium · Arterial calcification · Atherosclerosis · Coronary calcium · Electron beam CT scan · Peripheral artery disease · Risk factors · Type 2 diabetes

Abbreviations AAC: Abdominal aortic calcium · CAC: Coronary artery calcium · CAD: Coronary artery disease · CVD: Cardiovascular disease · EBCT: Electron beam CT · MI: Myocardial infarction · PAD: Peripheral artery disease · VADT: Veterans Affairs Diabetes Trial

P. D. Reaven (✉)
Division of Endocrinology and Metabolism (CS-111E), Carl T. Hayden Veterans Affairs Medical Center,
650 East Indian School Road,
Phoenix, AZ, 85012, USA
e-mail: peter.reaven@med.va.gov
Tel.: +1-602-2775551
Fax: +1-602-2006004

J. Sacks
Cooperative Studies Program, Hines VA Hospital,
Hines, IL, USA

Introduction

Coronary calcification has been demonstrated to be an excellent estimate of the burden of atherosclerosis in epicardial vessels [1]. In the general population, coronary artery calcium (CAC) is also strongly associated with the prevalence of cardiovascular disease (CVD), and the prevalence and amount of CAC are consistently higher in those with clinical coronary artery disease [2, 3]. High levels of CAC have also been associated with increased risk for future development of CVD in most, but not all, studies [4–10].

Diabetes is a frequent and strong risk factor for CAC [3, 11, 12] and individuals with diabetes consistently have higher levels of CAC than do those without diabetes [3, 11–14]. However, the association between CAC and clinical CVD has not been well studied and appears less consistent in subjects with diabetes. Several studies have shown that diabetes subjects with known vascular disease have higher levels of CAC than those without these conditions [3, 15], yet, these studies were conducted in cohorts of type 1 or both type 1 and 2 diabetes subjects. Moreover, the relationship of calcium with clinical cardiovascular disease was only examined in subjects with type 1 diabetes [15]. Given the younger age of subjects with type 1 diabetes and the

resulting tendency to have zero or low scores of CAC in type 1 diabetes, it has been difficult to assess whether the relationship of CAC with CVD is graded or perhaps threshold dependent. In a recent study of self-referred subjects, calcium scanning demonstrated that all-cause mortality over 5 years was increased in individuals with and without diabetes in proportion to the extent of CAC [16]. Outcomes in this latter study were determined via the National Death Index, therefore, relationships between CAC and total CVD events, as well as with distinct CVD categories, were not evaluated. In addition, classification of diabetes included both type 1 and type 2 diabetes and detailed baseline assessments of risk factors, including laboratory data were not available. In the one community based prospective cohort study of vascular calcium and cardiovascular disease reported to date, CAC was not an independent predictor of future cardiovascular events in individuals with diabetes [17].

Thus, there remains uncertainty regarding the relationship of CVD with increasing CAC in type 2 diabetes and whether this association is independent of lifestyle behaviours and conventional CVD risk factors. In fact, it has been suggested that the presence of vascular calcification may be less closely related to the burden of soft (and more vulnerable) noncalcified lesions in individuals with diabetes than in those without diabetes, and therefore may have different implications for plaque rupture and clinical events [18].

Although aortic calcification may also be associated with the overall burden of atherosclerosis in this vessel [19, 20], its relationship to cardiovascular disease has been even less frequently studied. Given the known relationship between aortic atherosclerosis and peripheral artery disease, it is of interest to know whether abdominal calcification is related to vascular disease and, in particular, peripheral artery disease. This is of increased importance in individuals with type 2 diabetes, where the prevalence of peripheral artery disease (PAD) is relatively high.

The goals of this study were therefore to (1) more carefully examine the nature of the relationship between CAC and the presence of clinical cardiovascular disease in individuals with type 2 diabetes and (2) assess whether the measurement of abdominal aortic calcium (AAC) may have an independent or added benefit as a surrogate marker for clinical vascular disease and in particular, for peripheral artery disease. To achieve these goals, the current study examines the relationship between vascular calcification in both the coronary arteries and the abdominal aorta with the presence of PAD, coronary artery disease or all combined CVD in a well-characterized group of individuals participating in the Risk Factors, Atherosclerosis and Clinical Events in Diabetes (RACED) study, a seven-site substudy of the Veterans Affairs Cooperative Study of "Glycemic Control and Complications in Diabetes Mellitus Type 2" (VADT) [21].

Methods

Enrolled subjects included male and female veterans over 40 years of age with type 2 diabetes (with or without chronic CVD) who remained inadequately controlled (HbA_1c>7.5%) on oral agents and/or insulin. Additional exclusion and inclusion criteria have been previously described in detail [21]. As part of the baseline exams for the VA Cooperative Study, all subjects were queried regarding their past medical history, current health, medication use, basic socioeconomic information and completed questionnaires to assess typical lifestyle behaviours, including alcohol and tobacco use. Subjects also received physical exams and had blood drawn in the fasting state (no food after 10 P.M.) for assessment of baseline health and a variety of cardiovascular risk factors. Three hundred and nine subjects at seven sites (representing over 95% of all subjects recruited into the parent study at these sites over the time frame of the substudy) also agreed to receive coronary and abdominal calcium scans during the baseline period. At the enrolment visit, subjects were provided sufficient information regarding the study goals and methodology to permit them to provide an informed consent. The study protocol was approved by the institutional committee on human research for each study site participating in this substudy.

Height and weight were measured to the nearest 0.1 cm or 0.5 kg, respectively, and body mass index (kg/m^2) was calculated. Resting blood pressure was measured three times in the right arm after 5 min in the seated position. While in the fasting state, blood was drawn and plasma and serum aliquots prepared and frozen at −80°C for measurement of standard cardiovascular risk factors. Cardiovascular disease was defined as the presence of prior myocardial infarction (MI), stroke, coronary bypass or other invasive intervention procedures for coronary artery disease or peripheral vascular disease, as assessed and defined as previously described [21]. Coronary artery disease (CAD) was defined as the presence of prior myocardial infarction (MI), coronary bypass or other invasive intervention procedures for coronary artery disease. Peripheral vascular disease for this study was defined as an ankle brachial index of ≤0.9.

All subjects underwent electron beam computer tomography (EBCT) cardiac scanning using an Imatron C150XL scanner (GE Imatron, South San Francisco, CA). Thirty to 40 adjacent axial scans of slice thickness of 3 mm were obtained by table incrementation starting at the level of the carina and continuing to the level of the diaphragm. Tomographic images were electrocardiographically triggered to 80% of the RR interval (near the end of diastole) to minimize cardiac motion as previously described [22]. To reduce inter-assay variability of CAC scans, two scans were done in succession on each subject at baseline and averaged. Abdominal aortic scans were obtained by scanning a section of the aorta extending from the upper pole of the right kidney to the iliac bifurcation with 30 adjacent axial slices each of 6-mm thickness. A calibration phantom was scanned under the chests and abdomens of each participant at each scanning centre to allow calibration of the images to identical standards.

Readers at the centralised reading centre who were blinded to the demographic, clinical and electrocardiographic information performed calcium scoring. Before reading, the brightness of the image was adjusted to a standard brightness using linear regression against the brightness measured in regions of interest inside of the hydroxyapatite bars in the calibration phantom. A CT volume threshold was utilized for identification of calcific lesions as previously described [23]. Each focus exceeding the minimum volume criteria and having greater than 130 Hounsfield units was scored using the algorithm developed by Agatston et al. [24] as previously described [23]. Total coronary or aortic calcium scores were determined by summing individual lesion scores from each of four anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries) or along the scanned region of the aorta, respectively.

Plasma total cholesterol, triglycerides, and HDL cholesterol concentrations were measured using standard enzymatic methods and reagents obtained from Roche Diagnostics (Indianapolis, IN) on a Hitachi 911 analyser.

Statistical methods Categorical data are presented as a percentage and continuous data as mean values±SD. Calcium scores and log transformed calcium scores (after adding 1 to each CAC or AAC score) were analysed. Comparisons between groups were tested by unpaired *t*-tests or by chi-square tests for categorical variables. Multiple linear regression analyses were performed with Agatston calcium score as the dependent variable to evaluate the importance of known covariates of CAC or AAC. All tests of significance were two-tailed and statistical significance was defined as probability equal or less than 0.05.

Results

Three hundred and nine subjects with type 2 diabetes have baseline CAC and AAC data available for analysis. The majority of subjects were male (94%) and Caucasian (65%). Other than having a slightly greater percent of female subjects (6% vs 3%, $p<0.05$), this cohort was representative of individuals in the larger VADT study and was, as previously described [23], on average middle aged (61±9 years), overweight (BMI 31.5±4.3 kg/m^2) and in poor glycaemic control (HbA1c 9.2±1.4%). Approximately 35% had baseline evidence of CVD including myocardial infarctions, strokes, bypass surgery, revascularization procedures or PAD. Coronary artery disease prevalence and PAD prevalence were 27 and 13%, respectively. Current smoking was relatively infrequent (15%) but the majority had been smokers (72%) at some time in the past. Baseline medication use was common, with almost 85% taking aspirin, 70% taking statins or other hypolipidaemic medications and 85% receiving hypertension medication. Insulin, oral sulphonylurea, thiazolinedinedione, and metformin use in this population was 57, 54, 11 and 68%, respectively. The presence of CAC or AAC (defined as values>0) was common in this study group, with only 16 and 10% of subjects not demonstrating any calcium, respectively.

To ascertain which risk factors may confound the relationship between vascular calcification and CVD we explored the association between risk factors and CAC and AAC. We first created two groups, 59 with CAC scores equal to zero (CAC=0) and 250 with scores greater than zero (CAC>0). Similar groups were created according to the presence (n=55) or absence (n=249) of AAC. We then calculated risk factor means for each CAC (or AAC) group and these are shown in Table 1. Mean values for the demographic factors of age, duration of diabetes, and years smoking differed ($p<0.05$) between the CAC=0 and CAC>0 groups. Lower values for total cholesterol (p=0.05), were present in those with CAC>0, whereas other risk factors, including current alcohol use and level of education obtained were not different between CAC groups. Similar patterns of risk factor distribution were seen among the AAC groups, although the lower values for BMI, diastolic blood pressure and triglycerides among those with AAC>0 did reach significance.

In data not shown, these two calcium categories were also expanded by creating quintiles of CAC (and AAC) scores and mean levels of risk factors were also examined across these quintiles. Mean values for the demographic factors of age, duration of diabetes, and years of smoking

Table 1 Mean levels of risk factors dichotomised by CAC and AAC scores

	CAC=0	CAC>0	AAC=0	AAC>0
Number	59	250	55	249
Age (years)	55	63[a]	54	63[b]
Duration of diabetes (years)	9	12[a]	9	12[b]
BMI (kg/m^2)	31	32	32.9	31.2[b]
Alcohol				
None (%)	55	53	54	53
<1 drink/day (%)	45	41	42	42
1+/day (%)	0	6	4	5
Education				
Grade school (%)	5	7	7	7
High school (%)	37	34	32	35
College (%)	58	59	52	59
Past smoker (%)	70	72	58	75[b]
Current smoker (%)	16	14	9	16
Years smoking	19	26[a]	12	27[b]
Systolic BP (mmHg)	132	133	130	133
Diastolic BP (mmHg)	78	75	78	74[b]
HbA_1c (%)	9.7	9.3	9.7	9.1[b]
Total cholesterol (mmol/l)	5.1	4.8[a]	5.1	4.8
HDL cholesterol (mmol/l)	1.1	1.0	1.1	1.0
LDL cholesterol (mmol/l)	2.9	2.7	2.7	2.8
Triglycerides (mmol/l)	2.4	2.3	2.6	2.3[b]

Education refers to highest level completed. To convert from mmol/l to mg/dl divide by 0.02586

[a]Significantly different from CAC=0 ($p<0.05$)

[b]Significantly different from AAC=0 ($p<0.05$)

increased monotonically with increasing quintile of CAC. Baseline levels of other demographic factors, triglycerides, and blood pressure remained fairly flat across CAC quintiles and were not significantly different. The patterns of risk factor associations with increasing quintiles of AAC were in general quite similar to those for CAC.

Medication use was common in this population and tended to be more frequent in those with increased vascular calcification. Those with CAC>0 were more frequently receiving insulin, thiazolidinediones, alpha and beta blockers, diuretics and statin medications than those in the CAC=0 group and these differences were statistically significant ($p<0.05$). In contrast, oral sulphonlyureas and metformin were used less frequently in the CAC>0 group ($p<0.05$). No differences were seen in use of aspirin, angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists. Patterns of medication use for individuals with and without AAC were similar to those for the categories of CAC but only the differences in use of statins (higher in those with AAC>0) achieved statistical significance. These data indicate that those with measurable vascular calcification (CAC or AAC) were not being treated less aggressively with anti-lipid, anti-hypertensive or diabetes medications.

The prevalence of PAD, CAD and combined CVD events are presented in Table 2 for *all* subjects. Diabetic subjects with either CAC or AAC>0 had a strikingly higher prevalence of PAD, CAD and CVD ($p<0.05$ for each). To determine whether increases in prevalence of CVD with increasing CAC and AAC scores were a reflection of underlying differences between the groups (as illustrated in Table 2) in age, duration of diabetes, years of smoking, or level of glucose control, stratification analyses were also performed (Table 2). Subjects were divided into two strata (low and high) according to the median values for these variables and the prevalence of PAD, CAD and CVD was computed and presented in a two-way analysis of strata by calcium levels (CAC=0 and CAC>0 or AAC=0 and AAC>0). For example, for age<61 years, PAD prevalence increases from 4 to 14% over the two levels of CAC whereas for age>61, PAD prevalence increases from 0 to 16%. Substantial and statistically significant ($p<0.05$) increases in prevalence were associated with positive CAC or AAC scores for subjects both above and below the median of each variable. The magnitudes of the change in each strata were similar to the change seen for all subjects.

Even more impressive was the consistent increase in prevalence of clinical vascular disease across quintiles of CAC and AAC, as shown in Fig. 1. Prevalence of each condition increased from 5- to 13-fold with increasing quintiles of CAC and from 2- to 3-fold with increasing AAC. The same consistent increases were seen when definitions of CAD included angina (data not shown).

In addition to stratification by important confounder variables, logistic regression adjusted prevalence levels were calculated adjusting for age, BMI, duration of diabetes, years of smoking and several variables that had shown more modest univariate relationships with CAC or AAC (total cholesterol, HDL cholesterol and HbA_1c levels). The adjusted prevalence of PAD (4.4% vs 14.5%, $p<0.05$), CAD (10.9% vs 29.8%, $p<0.05$) and CVD (15.9% vs 38.8%, $p<0.05$) remained strikingly higher in those with CAC>0 after adjusting for these potential confounder variables. Similarly, the adjusted prevalence of PAD (3.6% vs 13.9%, $p<0.05$), CAD (16.7% vs 27.9%, $p<0.05$) and CVD (20.4% vs 36.7%, $p<0.05$) remained higher in those with AAC>0.

Finally, to determine whether the knowledge of both CAC and AAC status provides additional information regarding the probability of having vascular disease, PAD, CAD and CVD rates were computed for the four combinations of CAC and AAC as shown in Table 3. PAD prevalence was highest when both CAC and AAC were greater than 0. In contrast, MI, CAD and CVD prevalence

Table 2 Prevalence of PAD, CAD, and CVD for all subjects, and those stratified by low and high age, DM duration, years of smoking and HbA_1c, according to dichotomised CAC and AAC scores

		CAC=0	CAC>0	AAC=0	AAC>0
PAD (%)	All patients	4	15[a]	4	14[b]
	Age<61 years	4	14[a]	5	13[b]
	Age≥61 years	0	16[a]	8	16
	DM duration<10 years	6	11	3	12
	DM duration≥10 years	0	18[a]	7	18
	Smoking<18 years	6	15	6	16
	Smoking≥18 years	0	15[a]	0	14[b]
	HbA_1c<9.0%	0	14[a]	7	13
	HbA_1c≥9.0%	6	16	4	16[b]
CAD (%)	All patients	2	32[a]	14	28[b]
	Age<61 years	4	32[a]	14	28[b]
	Age≥61 years	0	33[a]	15	31
	DM duration<10 years	3	30[a]	7	28[b]
	DM duration≥10 years	5	34[a]	21	32
	Smoking<18 years	3	23[a]	13	20
	Smoking≥18 years	5	41[a]	20	37
	HbA_1c<9.0%	0	31[a]	11	30
	HbA_1c≥9.0%	6	33[a]	17	29
CVD (%)	All patients	6	41[a]	17	37[b]
	Age<61 years	9	39[a]	18	35[b]
	Age≥61 years	0	44[a]	15	43[b]
	DM duration<10 years	9	37[a]	10	35[b]
	DM duration≥10 years	4	45[a]	24	43[b]
	Smoking<18 years	8	33[a]	17	31
	Smoking≥18 years	5	50[a]	20	45
	HbA_1c<9.0%	0	39[a]	14	38
	HbA_1c≥9.0%	12	44[a]	21	41[b]

DM duration Duration of diabetes
[a]Significantly different compared to CAC=0 ($p<0.05$)
[b]Significantly different compared to AAC=0 ($p<0.05$)

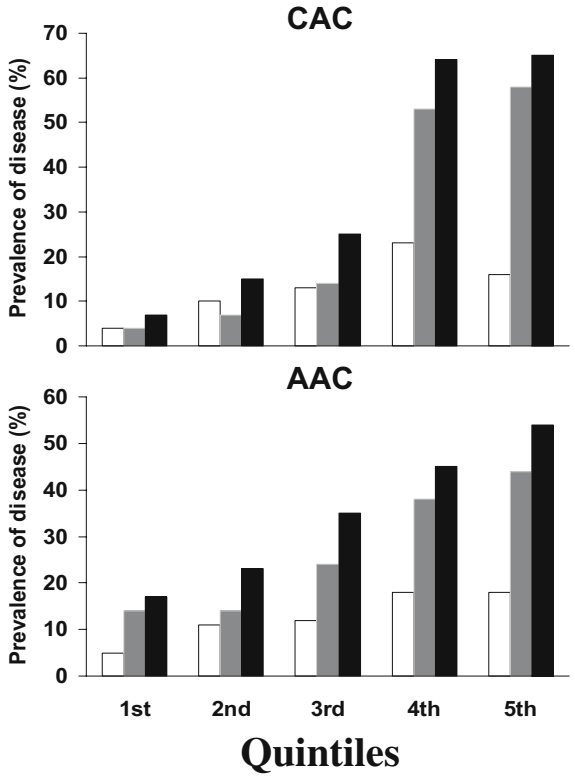

Fig. 1 Prevalence of PAD, CAD and CVD by quintiles of calcium. Prevalence of PAD (*open bars*), CAD (*shaded bars*) and combined CVD (*filled bars*) is expressed according to quintile of CAC (*top panel*) or AAC (*bottom panel*)

increased when CAC was greater than 0 irrespective of the AAC level. These results suggest CAC is more reliably associated with MI, CAD and CVD prevalence whereas PAD prevalence is determined by both CAC and AAC status. These prevalence patterns remained even when other individual CAD outcomes such as cardiac bypass surgery or percutaneous intervention (data not shown) were examined or when angina was included in the definition of CAD or CVD.

Table 3 Prevalence of PAD, MI, CAD and CVD according to dichotomised CAC and AAC scores

		CAC=0	CAC>0	Comment
PAD (%)	AAC=0	6	0	PAD increases only when
	AAC>0	3	15	both CAC and AAC are positive
MI (%)	AAC=0	0	27	MI increases when
	AAC>0	0	20	CAC>0 irrespective of AAC
CAD (%)	AAC=0	0	33	CAD increases when
	AAC>0	3	31	CAC>0 irrespective of AAC
CVD (%)	AAC=0	6	33	CVD increases when
	AAC>0	7	41	CAC>0 irrespective of AAC

Discussion

A major finding of this study is that accumulation of CAC was associated with a higher prevalence of CVD in individuals with type 2 diabetes. Importantly, this relationship appeared "dose" related, with greater CAC scores associated with greater rates of vascular disease. This relationship held for each category of CVD evaluated, including MI, angioplasty or bypass surgery, or stroke as well as the combined CVD endpoint. Similar associations were also seen even when the relatively "soft" diagnosis of angina was included in the definition of CVD. CAC was also related to PAD and was not much different than AAC in its association with PAD. Individuals with either a CAC score greater than zero or an AAC score greater than zero had over a threefold increase in PAD. These data suggest that CAC may be a relatively good measure of systemic arterial disease.

A strength of the current study was the relatively comprehensive assessment of lifestyle behaviours, medication use, socioeconomic status, and standard cardiovascular risk factors. The potential for these variables to confound or explain the difference in disease prevalence between those with differing levels of vascular calcification was explored by both stratification and by regression analysis approaches. The positive relationship between calcium accumulation and presence of vascular diseases was not explained by differences in medication usage, life style behaviours or other standard cardiovascular risk factors. Of note, even in this cohort of subjects with poorly controlled diabetes, HbA_1c values were not positively related to the presence of calcium. Consistent with this result, prevalence of PAD, CAD and CVD were similar in individuals with HbA_1c levels below or above the median at baseline. These data support the notion that glycaemia by itself may play a relatively modest role in the development of atherosclerosis and/or expression of clinical disease in this older population with type 2 diabetes [25]. This is now being directly tested in this same population in the parent study "Glycemic Control and Complications in Diabetes Mellitus Type 2" [21].

Calcium in the abdominal aorta was also related to increased prevalence of PAD, CAD and CVD and these patterns were even more impressive when prevalence of these conditions was stratified according to quintiles of AAC or CAC (demonstrating an impressive monotonic increase with disease prevalence). Again, the positive relationship of AAC with vascular disease was not a simple consequence of different lifestyle behaviours, increased levels of standard risk factors or decreased use of medications with potential beneficial vascular effects. As the current study was able to quantitate more precisely the extent of abdominal calcium and to determine the relationship of increasing burdens of AAC with CVD, these data add substantially to earlier reports that calcium seen in the abdominal aorta on standard radiographs may be a useful predictor of clinical CVD [26–28]. Moreover, this study demonstrates that AAC is also related to vascular disease in patients with type 2 diabetes.

However, CAC appeared to be more strongly associated with CVD than did AAC. When CAC=0, rates of coronary artery disease and CVD in general were quite low irrespective of AAC scores, and the prevalence of MI, CAD and CVD was relatively high if CAC>0, even when AAC=0. The only exception to this pattern was PAD: in this instance, the highest prevalence was present when both CAC and AAC were >0. Therefore, at least in this population, the combination of these two calcium scores is better than either alone only in the association with PAD.

An additional finding of interest is that measures of smoking appeared to be more strongly related to extent of AAC than to the extent of CAC. Differences in relationships of risk factors, and in particular, cigarette smoking, to the extent of atherosclerosis in different vascular beds has been previously suggested [29, 30] and this notion gains further support from the findings in this study. Identifying and understanding these different risk factor-vascular pathology location interactions may provide insight into basic mechanisms of atherosclerosis and suggest potential strategies for more focused interventions for vascular disease at specific sites.

In summary, the results from this study strongly support the notion that assessment of vascular calcium in type 2 diabetes provides additional information beyond that of standard risk factors in identifying the presence of CVD. While individuals with type 2 diabetes are as a group considered at high risk for CVD, not all such individuals develop macrovascular complications. Subclinical measures of atherosclerosis such as arterial calcification may help to stratify these individuals more precisely and alert healthcare providers to those individuals who have particularly accelerated atherosclerosis. Although we have performed a careful assessment of lifestyle behaviours and risk factors, we recognize that these factors could have been modified in some instances as a result of a prior diagnosis of CVD; and these data may not be applicable to women with diabetes or to younger individuals with diabetes. Although our data are consistent with results from a large observational study of CAC and all-cause mortality in subjects with diabetes [16], these cross-sectional relationships must be verified in a prospective study of the same population before we can confidently promote the value of measuring vascular calcification in type 2 diabetes to predict future CVD events.

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