Aortic and Mitral Annular Calcifications Are Predictive of All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes

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OBJECTIVE—To examine the association of aortic valve sclerosis (AVS) and mitral annulus calcification (MAC) with all-cause and cardiovascular mortality in type 2 diabetic individuals.

RESEARCH DESIGN AND METHODS—We retrospectively analyzed the data from 902 type 2 diabetic outpatients, who had undergone a transthoracic echocardiography for clinical reasons during the years 1992–2007. AVS and MAC were diagnosed by echocardiography, and a heart valve calcium (HVC) score was calculated by summing up the AVS and MAC variables. The study outcomes were all-cause and cardiovascular mortality.

RESULTS—At baseline, 477 (52.9%) patients had no heart valves affected (HVC-0), 304 (33.7%) had one valve affected (HVC-1), and 121 (13.4%) had both valves affected (HVC-2). During a mean follow-up of 9 years, 137 (15.2%) patients died, 78 of them from cardiovascular causes. Compared with patients with HVC-0, those with HVC-2 had the highest risk of all-cause and cardiovascular mortality, whereas those with HVC-1 had an intermediate risk ($P < 0.0001$ by the log-rank test). After adjustment for sex, age, BMI, systolic blood pressure, diabetes duration, A1C, LDL cholesterol, estimated glomerular filtration rate, smoking, history of myocardial infarction, and use of antihypertensive and lipid-lowering drugs, the hazard ratio of all-cause mortality was 2.3 (95% CI 1.1–4.9; $P < 0.01$) for patients with HVC-1 and 9.3 (3.9–17.4; $P < 0.001$) for those with HVC-2. Similar results were found for cardiovascular mortality.

CONCLUSIONS—Our findings indicate that AVS and MAC, singly or in combination, are independently associated with all-cause and cardiovascular mortality in type 2 diabetic patients.

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A ortic valve sclerosis (AVS) is a common finding at echocardiography in the elderly population (1). AVS is defined as focal or diffuse calcification and thickening of a trileaflet aortic valve in the absence of obstruction of ventricular outflow. Approximately 30% of adults >65 years of age have AVS in Western countries. Until recently, AVS was considered an incidental echocardiographic finding of no clinical significance, as it does not significantly obstruct left ventricular outflow. However, AVS shows epidemiologic and histopathologic similarities to coronary atherosclerosis (2,3). In addition, recent large prospective studies have suggested a strong association between AVS and cardiovascular disease (CVD) outcomes both in the general population (1,4–6) and in nondiabetic high-risk patient populations such as patients with hypertension (7), coronary artery disease (8), and chronic kidney disease (9).

Mitral annulus calcification (MAC) is also a common echocardiographic finding in the elderly (10). Similar to AVS, MAC is strongly associated with an increased risk of CVD morbidity and mortality, mainly in nondiabetic populations (11,12). Notably, a recent large community-based cohort study involving 2,081 German individuals aged ≥45 years (~11% of patients with diabetes) showed that AVS and MAC were associated with a fourfold to fivefold increased risk of all-cause and CVD mortality and that the combination of AVS and MAC with a heart valve sclerosis score improved the predictability with respect to mortality (5). Similarly, patients with AVS were approximately four times more likely to develop incident coronary heart events than were those without AVS among the 2,279 middle-aged African American participants of the Jackson Atherosclerosis Risk in Community cohort (6), whereas AVS was found to be independently associated with an increase of ~50–60% in the risk of CVD events and death among the 5,621 elderly participants of the Cardiovascular Heart Study (1).

To our knowledge, no large observational studies are available on the relationship of AVS and MAC with the risk of all-cause and CVD mortality in patients with type 2 diabetes. The aim of this observational study was to evaluate the association of AVS and MAC, singly or in combination, with the risk of all-cause and CVD mortality in a sample of type 2 diabetic individuals referred for clinically indicated echocardiograms.

RESEARCH DESIGN AND METHODS—The study was performed within the frame of the Verona Diabetes Study, an observational longitudinal study

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on chronic complications in type 2 diabetic outpatients attending the diabetes clinic at the University Hospital of Verona (13). Briefly, for this analysis we retrospectively analyzed the electronic records of all Caucasian type 2 diabetic outpatients, who regularly attended our diabetes clinic during the years 1992–2007. Of these, we selected all patients with type 2 diabetes who had undergone a first transthoracic echocardiography for clinical reasons (e.g., dyspnea, palpitations, chest pain, heart murmur, history of myocardial infarction, electrocardiographic abnormalities, assessment of left ventricular wall thickness, presence of multiple CVD risk factors) at our institution during the same period of time. On the basis of these criteria, 937 patients with type 2 diabetes were identified and included in the final analysis.

The local ethics committee approved the study protocol. The informed consent requirement for this study was exempted by the ethics committee because researchers only accessed retrospectively a deidentified database for analysis purposes.

Clinical and laboratory data
BMI was measured as kilograms divided by the square of height in meters. A physician measured blood pressure in duplicate with a mercury sphygmomanometer (at the right upper arm using an appropriate cuff size) after the patient had been seated quietly for at least 5 min. Subjects were considered to have arterial hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any antihypertensive drugs. Information on medical history and smoking status was obtained from all patients via interviews during medical examinations.

Venous blood samples were drawn in the morning after an overnight fast. Serum lipids, creatinine, and other biochemical blood measurements were determined in the same laboratory using standard laboratory procedures (DAX 96; Bayer Diagnostics, Milan, Italy). LDL cholesterol was calculated by the Friedewald equation. A1C was measured by an automated high-performance liquid chromatography analyzer (Bio-Rad Diamat; Bio-Rad, Milan, Italy); the upper limit of normal for our laboratory was 5.6%.

Glomerular filtration rate was estimated from the four-variable Modification of Diet in Renal Disease study equation (14). Urinary albumin excretion rate was measured from a 24-h urine sample using an immunonephelometric method. The presence of abnormal albuminuria (defined as albumin excretion rate ≥30 mg/day) was confirmed in at least two of three consecutive urine samples (14). The diagnosis of diabetic retinopathy was based on fundoscopy by a single ophthalmologist.

Conventional echocardiography
All echocardiographic examinations were performed at our institution by experienced cardiologists (A.R. and S.B.). Left ventricular (LV) chamber dimensions and wall thickness were measured from M-mode recordings as suggested by the American Society of Echocardiography, and LV mass was calculated using a necropsy validated equation (15). LV ejection fraction (LV-EF) was measured from LV diameters or two-dimensional area changes in systole and diastole (16). Left atrial (LA) diameter was measured from M-mode tracing. Regional LV function was evaluated by means of wall motion score index (WMSI). The left ventricle was divided into 16 segments. Each segment was analyzed individually and scored on the basis of its motion and systolic thickening. LV segments were scored as follows: normal, 1; hypokinetic, 2; akinetic, 3; and dyskinetic or aneurysmatic, 4. WMSI was derived as the sum of all scores divided by the number of LV segments visualized (15). MAC was defined by increased echodensity located at the junction of the atrioventricular groove and posterior mitral leaflet on the parasternal long-axis, short-axis, or apical four-chamber view. AVS was defined as focal or diffuse calcification and thickening of the aortic leaflets with or without restriction of leaflet motion on echocardiography (17). A transaortic peak instantaneous velocity ≥2.5 m/s was considered as aortic stenosis.

Mortality follow-up
Vital status on 30 September 2007 was ascertained for all participants through examination of the electronic databases of the Social Health Unit of the Veneto Region, which include all records of deaths that occurred within the Veneto Region as well as the specific causes of death. Causes of death were identified in 100% of subjects. Death certificates were coded by trained nosologists using the ICD-9. Deaths were attributed to CVD causes when ICD-9 codes were 390–459. A selected sample of death certificates was reviewed manually to validate the process.

Statistical analysis
Data are expressed as means ± SD or percentages. Skewed variables were logarithmically transformed to improve normality prior to analysis (duration of diabetes, triglycerides, and albuminuria). In accord with a previous study (5), we calculated a heart valve calcium (HVC) score combining the presence of calcium at the level of aortic and mitral valve as follows: HVC-0, absence of any thickening or calcification; HVC-1, presence of either isolated AVS or isolated MAC; and HVC-2, coexistence of AVS and MAC. Patients were stratified according to the HVC score. Comparisons between groups were made using one-way ANOVA (for continuous variables) and the χ^2 test (for categorical variables). Univariate survival analysis was performed by the Kaplan-Meier analysis, and the overall significance was calculated by the log-rank test. Cox regression analysis was used to study the association between the HVC score and the risk of all-cause and CVD mortality after adjustment for potential confounders. The model assumptions for the Cox proportional hazards regression models were checked by visual inspection of proportional hazard assumption, Schoenfeld residuals, and covariance matrix. Four forced-entry Cox regression models were performed: an unadjusted model; a model adjusted for age and sex (model 1); a model adjusted for age, sex, BMI, duration of diabetes, smoking status, systolic blood pressure, A1C, LDL cholesterol, estimated glomerular filtration rate (eGFR), history of myocardial infarction, and use of any antihypertensive and lipid-lowering medications (model 2, where the number of subjects with available data for analysis was 792); and a model adjusted for age, sex, LV mass, LV-EF <50%, WMSI, and LA diameter (model 3, where all subjects had available data for analysis). The covariates included in these multivariate regression models were chosen as potential confounding factors on the basis of their significance in univariate analysis or on the basis of their biological plausibility. Results of Cox proportional hazards models are presented as HR (95% CI). All analyses were performed using statistical package SPSS 19.0, and statistical significance was assessed at the two-tailed 0.05 threshold.

RESULTS

Baseline characteristics
Of the initial sample of 937 type 2 diabetic patients, 35 who had either aortic valve prosthesis or rheumatic or congenital aortic valve disease were excluded from analysis.

Thus, 902 (362 women) patients with type 2 diabetes represent the final analytical sample.

Overall, 477 (52.9%) patients were free of any thickening or calcification at the valvular level (i.e., HVC-0), and 304 (33.7%) patients had either isolated MAC or isolated AVS (HVC-1); i.e., 43 (4.8%) patients had isolated MAC and 261 (28.9%) patients had AVS, and 17 of them had aortic stenosis. The remaining 121 (13.4%) patients had combined AVS and MAC (HVC-2), and 39 of them had aortic stenosis.

As shown in Table 1, age, systolic blood pressure, LDL cholesterol, albuminuria, and the prevalence of hypertension significantly increased, whereas BMI, triglycerides, and eGFR decreased across the HVC score. Sex, smoking history, duration of diabetes, frequency of diabetic retinopathy, fasting plasma glucose, A1C, and HDL cholesterol did not significantly change across the HVC score. Among the echocardiographic parameters, only LA diameter increased across the HVC score, whereas LV mass, LV-EF, and WMSI were not significantly different among the groups.

Survival analysis

During a mean follow-up period of 9 years (median 7.6 years), 137 (15.2% of total) patients died (78 of these from CVD causes). As shown in Fig. 1A, the HVC score was strongly associated with an increased risk of death from all causes and from CVD causes. During the follow-up period, patients with HVC-2 had an ~20% overall survival rate compared with ~80% of those with HVC-0 and with an intermediate survival rate (~40%) in those with HVC-1. The differences among these curves were statistically significant ($P < 0.0001$ by the log-rank test). Similar results were found for CVD mortality (Fig. 1B).

In Cox univariate survival analysis (see unadjusted models in Tables 2 and 3), both HVC-1 and HVC-2 were associated with an increased risk of all-cause and CVD mortality. As also shown in Tables 2 and 3, the results remained essentially unchanged after adjustment for age, sex, BMI, smoking status, systolic blood pressure, duration of diabetes, A1C, LDL cholesterol, eGFR, history of myocardial infarction, and current use of any antihypertensive and lipid-lowering medications (regression models 1 and 2) or after adjustment for age, sex, and other baseline echocardiographic parameters, such as LV mass, LV-EF <50%, WMSI, and LA diameter (model 3).

Notably, other independent predictors of CVD and all-cause mortality ($P < 0.01$–0.001) were older age, longer duration of diabetes, smoking status, lower eGFR, and greater LV mass (data not shown). The significant, graded association between the HVC score and the risk of both all-cause and CVD mortality was consistent in men versus women (as shown in Supplementary Tables 1–4) and in younger versus older individuals (data not shown).

Almost identical results were also found when separate analyses were performed in those with ($n = 210$) and those without ($n = 692$) a previous history of myocardial infarction. In both of these subgroups, increasing HVC score predicted all-cause and CVD mortality, independently of potential confounders. In particular, among those with a history of myocardial infarction, the HVC score was associated with both all-cause mortality (HR 4.9 [95% CI 2.4–10.4], $P < 0.001$ for HVC-1, and 7.5 [2.7–20.6], $P < 0.001$ for HVC-2) and CVD mortality (4.2 [1.7–10.9], $P < 0.005$, and 9.0 [2.6–31.1], $P < 0.001$) even after adjustment for age, sex, LV mass, LV-EF <50%, WMSI, and LA diameter.

The strong association between the HVC score and mortality was further reinforced by the finding of a positive, graded relationship between the extent of mitral and aortic annular calcification and the clinical outcomes. Indeed, the HR for all-cause mortality was more than doubled in those with both valves affected (unadjusted HR 7.2 [95% CI 4.5–11.4] for those with HVC-2) compared with those with either isolated AVS (3.2 [2.2–4.8]) or isolated MAC (2.4 [1.3–4.1]), respectively. In addition, a stronger association with the risk of mortality was also observed with the amount of calcium at the level of aortic valve; the HR for all-cause mortality increased from 3.2 (95% CI 2.2–4.8) in those with isolated AVS to 4.4 (2.2–7.7) in those with aortic stenosis at baseline. Notably, after exclusion of patients who had aortic stenosis at baseline ($n = 56$) or developed aortic stenosis during the follow-up ($n = 13$), the value of HVC score in predicting all-cause mortality remained essentially unchanged (adjusted HR 2.3 [95% CI 1.5–3.5] for HVC-1 and HR 5.1 [3.1–8.5] for HVC-2, respectively). Consistent results were observed for CVD mortality (data not shown).

Table 1—Baseline clinical, biochemical, and echocardiographic characteristics of type 2 diabetic patients, stratified by HVC score

	HVC-0	HVC-1	HVC-2	P
n	477	304	121	
Female sex	38	41	47	0.18
Age (years)	66 ± 9	71 ± 8	73 ± 8	<0.001
BMI (kg/m^2)	29 ± 5	28 ± 5	28 ± 5	<0.05
Current smokers	26	26	28	0.81
Diabetes duration (years)	15 ± 9	16 ± 9	17 ± 8	0.09
Hypertension	91	93	94	<0.05
Systolic blood pressure (mmHg)	137 ± 19	139 ± 18	143 ± 20	<0.01
Diastolic blood pressure (mmHg)	80 ± 9	80 ± 9	80 ± 10	0.84
Fasting glucose (mmol/L)	9.0 ± 2.6	8.7 ± 2.7	9.1 ± 2.8	0.54
A1C	7.6 ± 1.6	7.6 ± 1.5	7.9 ± 1.5	0.28
LDL cholesterol (mmol/L)	4.9 ± 0.9	5.1 ± 1.0	5.2 ± 0.9	<0.01
Triglycerides (mmol/L)	1.75 ± 1.1	1.71 ± 1.4	1.50 ± 0.7	<0.05
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	0.16
eGFR (ml/min/1.73 m^2)	66 ± 19	63 ± 19	63 ± 18	<0.05
Albuminuria (mg/day)	53 ± 124	75 ± 157	94 ± 180	<0.05
Diabetic retinopathy	30	33	41	0.18
LA diameter (mm)	39 ± 5	40 ± 5	42 ± 5	<0.01
LV ejection fraction	59 ± 13	58 ± 12	60 ± 12	0.61
WMSI	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	0.86
LV mass (g)	246 ± 77	243 ± 92	259 ± 99	0.58

Data are means ± SD or percent. Cohort size, $n = 902$. P values refer to one-way ANOVA or the χ^2 test (for categorical variables). Hypertension was defined as blood pressure ≥140/90 mmHg or use of any antihypertensive drug treatment.
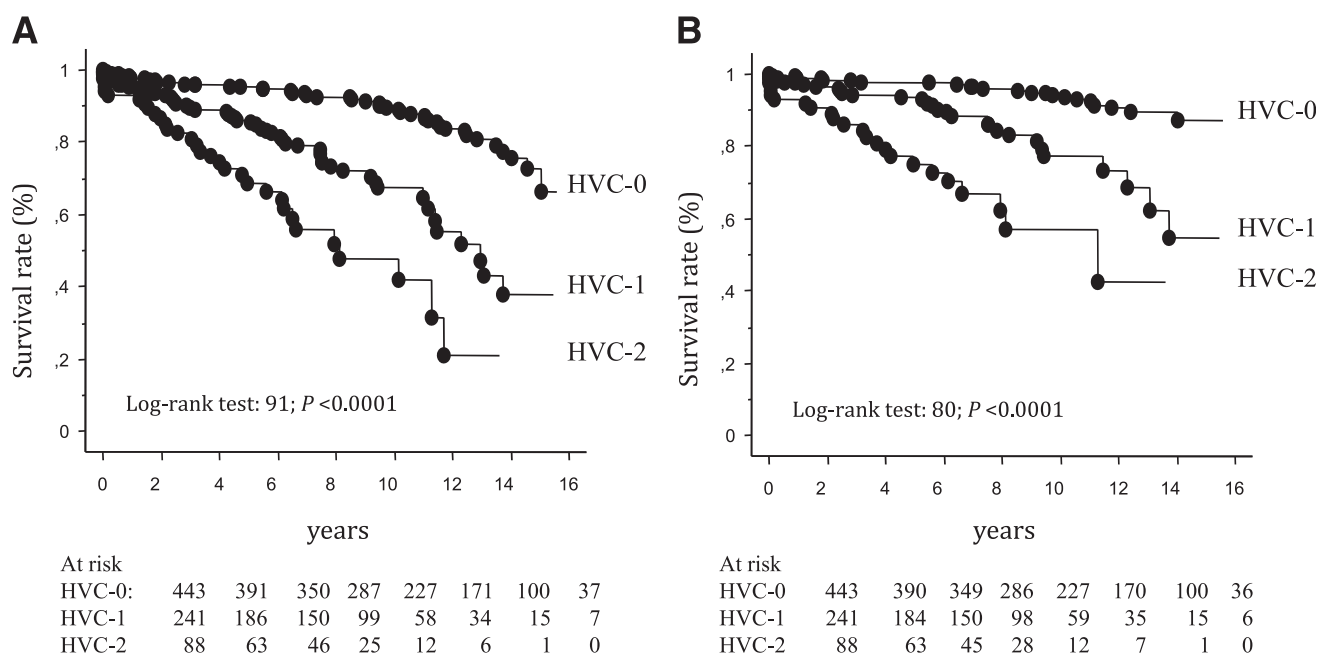
Figure 1—*Kaplan-Meier survival analysis for all-cause* (A) *and cardiovascular* (B) *mortality in 902 type 2 diabetic patients, stratified by the HVC score.*

CONCLUSIONS—To our knowledge, this study is the first to specifically address the value of AVS and MAC in predicting all-cause and CVD mortality in a large sample of type 2 diabetic patients referred for clinically indicated echocardiograms.

The major finding of this "real-world" study is that AVS and MAC, singly or in combination, predicted an increased risk of CVD and all-cause mortality, independently of traditional risk factors, diabetes-related variables, kidney function parameters (eGFR), and other baseline echocardiographic variables (LV mass, LV-EF, WMSI, and LA diameter). Notably, the combined presence of AVS and MAC was more strongly associated with an increased risk of all-cause and CVD mortality than the presence of either item alone. Collectively, the results of

this study complement and expand previous observations on the value of AVS and MAC for predicting mortality both in the general population and in other nondiabetic high-risk patient populations (1,4–9,18).

The biological mechanisms accounting for the association of AVS and MAC with an increased risk of all-cause and CVD mortality have still not been fully elucidated. Patients with MAC or AVS, especially those with AVS, may progress to aortic stenosis, which is a pathologic condition that is associated with an increased risk of mortality (19). However, it should also be noted that in our study the strength of the association between the HVC score and the clinical outcomes remained essentially unaltered even after exclusion of patients who either had aortic stenosis at baseline or developed aortic

stenosis during the follow-up. Thus, in accord with the results of previous studies (1–3,20,21), we believe that a plausible explanation for our findings is that AVS and MAC are reliable markers of the severity of systemic atherosclerosis. It is known that there are similarities in the histopathologic lesions of AVS, MAC, and coronary atherosclerosis and that these three diseases share multiple CVD risk factors (e.g., hypertension, smoking, dyslipidemia, and diabetes) and common pathophysiologic mechanisms (1–3,18,21). More recent studies suggested that AVS and MAC are not only associated with coronary atherosclerosis but also with atherosclerosis in other vascular beds (21–25). However, since in our study the HVC score strongly predicted CVD mortality independently of traditional CVD risk

Table 2—*Association between HVC score and the risk of all-cause mortality in patients with type 2 diabetes*

	HVC-0	HVC-1	HVC-2	P for trend
n	477	304	121	
Deaths	51 (10.7)	54 (17.8)	32 (26.4)	<0.0001
Unadjusted model	1.0 (ref.)	3.3 (2.2–4.8), P < 0.001	7.2 (4.5–11.4), P < 0.001	<0.0001
Adjusted model 1	1.0 (ref.)	2.5 (1.6–3.7), P < 0.001	5.3 (3.3–8.5), P < 0.001	<0.0001
Adjusted model 2	1.0 (ref.)	2.3 (1.1–4.9), P < 0.01	9.3 (3.9–17.4), P < 0.001	<0.0001
Adjusted model 3	1.0 (ref.)	2.5 (1.5–4.2), P < 0.005	5.5 (2.9–10.5), P < 0.001	<0.0001

Data are n (%) or HR (95% CI) as determined by means of univariate and multivariate Cox proportional hazards models. Cohort size, n = 902 (except for regression model 2, in which 792 subjects with available data were included). Regression model 1: adjusted for age and sex. Regression model 2: model 1 plus BMI, diabetes duration, smoking history, systolic blood pressure, A1C, LDL cholesterol, eGFR, previous history of myocardial infarction, and use of any antihypertensive and lipid-lowering drugs. Regression model 3: model 1 plus LV mass, LV-EF <50%, WMSI, and LA diameter as detected by means of echocardiography.

Table 3—*Association between HVC score and the risk of cardiovascular mortality in patients with type 2 diabetes*

	HVC-0	HVC-1	HVC-2	*P* for trend
n	477	304	121	
CVD deaths	25 (5.2)	30 (9.9)	23 (19)	<0.0001
Unadjusted model	1.0 (ref.)	3.7 (2.1–6.3), P < 0.001	10.3 (5.7–18.6), P < 0.001	<0.0001
Adjusted model 1	1.0 (ref.)	2.5 (1.4–4.4), P < 0.001	6.8 (3.7–12.7), P < 0.001	<0.0001
Adjusted model 2	1.0 (ref.)	2.7 (0.9–7.4), P = 0.069	15.0 (5.9–34.6), P < 0.001	<0.0001
Adjusted model 3	1.0 (ref.)	2.5 (1.5–5.1), P < 0.01	6.5 (2.8–15.3), P < 0.001	<0.0001

Data are *n* (%) or HR (95% CI), as determined by means of univariate and multivariate Cox proportional hazards models, unless otherwise indicated. Cohort size, *n* = 902 (except for regression model 2, in which 792 subjects with available data were included). Regression model 1: adjusted for age and sex. Regression model 2: model 1 plus BMI, diabetes duration, smoking history, systolic blood pressure, A1C, LDL cholesterol, eGFR, previous history of myocardial infarction, and use of any antihypertensive and lipid-lowering drugs. Regression model 3: model 1 plus LV mass, LV-EF <50%, WMSI, and LA diameter as detected by means of echocardiography.

factors and other potential confounders, it is also possible to speculate that AVS and MAC, singly or in combination, reflect not only the burden of systemic atherosclerosis (1–3,21,26,27) but also the presence of other underlying conditions, which may predispose patients to active and accelerated atherosclerosis, such as systemic chronic inflammation (21,28), platelet aggregation abnormalities (21,29), and genetic predisposition (30).

Our findings may have important clinical implications. CVD risk stratification is of paramount importance in routine clinical practice. The use of risk estimation systems such as the Framingham Risk Score has been recommended as the cornerstone for the estimation of the CVD risk in persons without previous CVD events (31,32), but their ability to identify patients who will develop future CVD events and death remains limited, particularly in those with type 2 diabetes (33,34).

Imaging techniques have been proposed to improve specificity of CVD risk stratification. Great attention has recently been paid to coronary artery calcium (CAC) score, as measured by computed tomography (35,36). However, the CAC evaluation has some important disadvantages such as its high costs and radiation exposure. Moreover, the incremental value of CAC score to the prediction of major CVD events and death is marginal (37). Conversely, the echocardiographic evaluation of AVS and MAC is easy, reproducible, safe, and cheap (15). Overall, our findings provide strong evidence that AVS and MAC, singly or in combination, are powerful independent predictors of all-cause and CVD mortality in patients with type 2 diabetes. The echocardiographic detection of "asymptomatic" MAC and AVS can identify a subgroup of patients with higher likelihood of

diffuse vascular atherosclerotic processes and should prompt a careful evaluation of conventional CVD risk factors and the institution of proper prevention or treatment strategies.

The major limitations of this study are its retrospective, longitudinal design (which does not allow us to draw any firm conclusion about causality) and a possible selection bias of excluding the patients who had missing echocardiographic data at baseline. There was also a relatively small number of clinical events during the follow-up (i.e., the cumulative incidence of all-cause mortality in the whole sample was ~15% [137 deaths]), and, therefore, the results should be interpreted with some caution. In addition, although our statistical models were extensive, unmeasured confounders (e.g., plasma inflammatory biomarkers) could potentially explain the observed associations. Finally, because our sample comprised white type 2 diabetic individuals who were followed at an outpatient diabetes clinic and who were referred for echocardiography for clinical reasons, our results may not necessarily be generalizable to other diabetic populations. The strengths of our study include the relatively large number of participants of both sexes, the long duration of the follow-up, the complete nature of the dataset, and the ability to adjust for several established risk factors and potential confounders.

In conclusion, this study is the first to demonstrate a graded and independent association of AVS and MAC with the risk of all-cause and CVD mortality in a sample of type 2 diabetic patients referred for clinically indicated echocardiograms. Further follow-up studies on larger cohorts of patients are needed to confirm the reproducibility of our results and to determine whether intervening in the

progression of calcific annular or valvular disease can reduce the incidence of CVD events and death in patients with type 2 diabetes.

References
1. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–147
2. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90:844–853
3. Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in non-rheumatic stenotic aortic valves. Arterioscler Thromb Vasc Biol 1999;19:1218–1222
4. Barasch E, Gottdiener JS, Marino Larsen EK, Chaves PH, Newman AB. Cardiovascular morbidity and mortality in community-dwelling elderly individuals with calcification of the fibrous skeleton of the base of the heart and aortosclerosis (The Cardiovascular Health Study). Am J Cardiol 2006;97:1281–1286
5. Völzke H, Haring R, Lorbeer R, et al. Heart valve sclerosis predicts all-cause

and cardiovascular mortality. Atherosclerosis 2010;209:606–610

6. Taylor HA Jr, Clark BL, Garrison RJ, et al. Relation of aortic valve sclerosis to risk of coronary heart disease in African-Americans. Am J Cardiol 2005;95:401–404

7. Olsen MH, Wachtell K, Bella JN, et al. Aortic valve sclerosis and albuminuria predict cardiovascular events independently in hypertension: a losartan intervention for endpoint-reduction in hypertension (LIFE) substudy. Am J Hypertens 2005;18:1430–1436

8. Shah SJ, Ristow B, Ali S, Na BY, Schiller NB, Whooley MA. Acute myocardial infarction in patients with versus without aortic valve sclerosis and effect of statin therapy (from the Heart and Soul Study). Am J Cardiol 2007;99:1128–1133

9. Hüting J. Predictive value of mitral and aortic valve sclerosis for survival in end-stage renal disease on continuous ambulatory peritoneal dialysis. Nephron 1993;64:63–68

10. Boon A, Cheriex E, Lodder J, Kessels F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. Heart 1997;78:472–474

11. Fox CS, Vasan RS, Parise H, et al.; Framingham Heart Study. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. Circulation 2003;107:1492–1496

12. Benjamin EJ, Plehn JF, D'Agostino RB, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374–379

13. de Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. Diabetes Care 1999;22:756–761

14. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473–2483

15. Lang RM, Bierig M, Devereux RB, et al.; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79–108

16. Quinones MA, Pickering E, Alexander JK. Percentage of shortening of the echocardiographic left ventricular dimension. Its use in determining ejection fraction and stroke volume. Chest 1978;74:59–65

17. Gharacholou SM, Karon BL, Shub C, Pellikka PA. Aortic valve sclerosis and clinical outcomes: moving toward a definition. Am J Med 2011;124:103–110

18. Rodriguez CJ, Bartz TM, Longstreth WT Jr, et al. Association of annular calcification and aortic valve sclerosis with brain findings on magnetic resonance imaging in community dwelling older adults: the cardiovascular health study. J Am Coll Cardiol 2011;57:2172–2180

19. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation 1982;66:1105–1110

20. Carabello BA. Aortic sclerosis—a window to the coronary arteries? N Engl J Med 1999;341:193–195

21. Adler Y, Fink N, Spector D, Wiser I, Sagie A. Mitral annulus calcification—a window to diffuse atherosclerosis of the vascular system. Atherosclerosis 2001;155:1–8

22. Agmon Y, Khandheria BK, Meissner I, et al. Aortic valve sclerosis and aortic atherosclerosis: different manifestations of the same disease? Insights from a population-based study. J Am Coll Cardiol 2001;38:827–834

23. Yamaura Y, Nishida T, Watanabe N, Akasaka T, Yoshida K. Relation of aortic valve sclerosis to carotid artery intima-media thickening in healthy subjects. Am J Cardiol 2004;94:837–839

24. Adler Y, Vaturi M, Herz I, et al. Non-obstructive aortic valve calcification: a window to significant coronary artery disease. Atherosclerosis 2002;161:193–197

25. Rossi A, Bertagnolli G, Cicoira M, et al. Association of aortic valve sclerosis and coronary artery disease in patients with severe nonischemic mitral regurgitation. Clin Cardiol 2003;26:579–582

26. Tolstrup K, Roldan CA, Qualls CR, Crawford MH. Aortic valve sclerosis, mitral annular calcium, and aortic root sclerosis as markers of atherosclerosis in men. Am J Cardiol 2002;89:1030–1034

27. Hamirani YS, Nasir K, Blumenthal RS, et al. Relation of mitral annular calcium and coronary calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol 2011;107:1291–1294

28. Chandra HR, Goldstein JA, Choudhary N, et al. Adverse outcome in aortic sclerosis is associated with coronary artery disease and inflammation. J Am Coll Cardiol 2004;43:169–175

29. Sucu M, Davutoglu V, Sari I, Ozer O, Aksoy M. Relationship between platelet indices and aortic valve sclerosis. Clin Appl Thromb Hemost 2010;16:563–567

30. Nordström P, Glader CA, Dahlén G, et al. Oestrogen receptor alpha gene polymorphism is related to aortic valve sclerosis in postmenopausal women. J Intern Med 2003;254:140–146

31. Gibbons RJ, Jones DW, Gardner TJ, Goldstein LB, Moller JH, Yancy CW; American Heart Association. The American Heart Association's 2008 statement of principles for healthcare reform. Circulation 2008;118:2209–2218

32. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–187

33. Mazzone T. Reducing cardiovascular disease in patients with diabetes mellitus. Curr Opin Cardiol 2005;20:245–249

34. Saito I, Folsom AR, Brancati FL, Duncan BB, Chambless LE, McGovern PG. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Ann Intern Med 2000;133:81–91

35. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210–215

36. Raggi P, Gongora MC, Gopal A, Callister TQ, Budoff M, Shaw LJ. Coronary artery calcium to predict all-cause mortality in elderly men and women. J Am Coll Cardiol 2008;52:17–23

37. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–1345