Valvular Heart Disease

Features of the Metabolic Syndrome and Diabetes Mellitus as Predictors of Aortic Valve Calcification in the Multi-Ethnic Study of Atherosclerosis

Ronit Katz, PhD; Nathan D. Wong, PhD; Richard Kronmal, PhD; Junichiro Takasu, MD, PhD; David M. Shavelle, MD; Jeffrey L. Probstfield, MD; Alain G. Bertoni, MD, MPH; Matthew J. Budoff, MD; Kevin D. O’Brien, MD

Background—Calcific aortic valve disease is common in the elderly, is correlated with common cardiovascular risk factors, and is associated with increased cardiovascular event risk; however, whether metabolic syndrome is associated with an increased prevalence of aortic valve calcium (AVC) is not known.

Methods and Results—The prevalence of AVC, as assessed by computed tomography, was compared in 6780 Multi-Ethnic Study of Atherosclerosis (MESA) participants with metabolic syndrome (n=11005), diabetes mellitus (n=1016), or neither condition (n=4024). The prevalence of AVC for those with neither condition, metabolic syndrome, or diabetes mellitus was, respectively, 8%, 12%, and 17% in women (P<0.001) and 14%, 22%, and 24% in men (P<0.001). Compared with those with neither condition, the adjusted relative risks for the presence of AVC were 1.45 (95% CI 1.11 to 1.90) for metabolic syndrome and 2.12 (95% CI 1.54 to 2.92) for diabetes mellitus in women and 1.70 (95% CI 1.32 to 2.19) for metabolic syndrome and 1.73 (95% CI 1.33 to 2.25) for diabetes mellitus in men. There was a graded, linear relationship between AVC prevalence and the number of metabolic syndrome components in both women and men (both P<0.001). Similar results were obtained when the International Diabetes Federation metabolic syndrome definition was used.

Conclusions—In the MESA cohort, the metabolic syndrome and diabetes mellitus are associated with increased risk of AVC, and AVC prevalence is increased with increasing number of metabolic syndrome components. (Circulation. 2006;113:2113-2119.)

Key Words: calcium ■ diabetes mellitus ■ tomography ■ valves ■ metabolic syndrome

Aortic valve calcification (AVC) is common in the elderly, and its presence is associated with an increased risk of cardiovascular events. AVC is a characteristic of aortic sclerosis, in which the aortic valve is calcified but does not obstruct left ventricular outflow, and aortic stenosis, in which obstruction to left ventricular outflow is present. Aortic sclerosis has a prevalence of 25% in patients above the age of 65 years and has been associated with a 50% increase in risk for cardiovascular mortality. In one retrospective cohort study, subjects with aortic sclerosis were 16 times more likely to develop aortic stenosis than those with normal valves. Aortic stenosis carries an 80% 5-year risk of heart failure, valve replacement, or death. Histopathological studies have demonstrated that aortic valvular lesions have many features characteristic of atherosclerotic lesions, including chronic inflammation, lipoprotein deposition, and the presence of ACE. In addition, risk factors for atherosclerotic disease, including age, hypercholesterolemia, smoking, and male gender, also are associated with an increased AVC prevalence. The identification of factors associated with AVC may be important, because there currently are no medical therapies that have been shown conclusively either to slow AVC progression or to decrease clinical events associated with AVC.

Recently, multiple investigators have identified the insulin resistance/metabolic syndrome as a major cardiovascular risk factor. The metabolic syndrome (MetS) is identified clinically by the presence of a constellation of features, including central adiposity, dyslipidemia, hypertension, and impaired fasting glucose. The prevalence of MetS is high and is increasing, owing in part to the epidemic of obesity. Previous studies have shown that MetS and diabetes mellitus are associated with increased risk of AVC.
coronary artery calcium scores, as assessed by electron-beam computed tomography.16,17 Diabetes mellitus has been shown in echocardiographic studies to be associated with increased prevalences of aortic valve calcium18 and aortic stenosis,19 as well as with an increased rate of aortic stenosis progression.20 However, no previous studies have investigated whether MetS is associated with increased AVC prevalence, as assessed either by echocardiography or by electron-beam computed tomography.

We analyzed data from the Multi-Ethnic Study of Atherosclerosis (MESA) to determine whether, at baseline, features of MetS (waist circumference, blood pressure, low HDL cholesterol, high triglycerides, and impaired fasting glucose) were associated, either individually or collectively, with increased AVC scores. We also determined the prevalence and quantity of AVC among persons with MetS, diabetes mellitus, or neither condition.

Methods

Study Population

The MESA cohort consists of 6814 men and women aged 45 to 84 years who were recruited from 6 US communities (Baltimore, Md; Chicago, Ill; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, NY; and St. Paul, Minn) and who were free of clinically evident cardiovascular disease at the time of enrollment. The main objective of MESA is to determine the characteristics of subclinical cardiovascular disease and its progression. In MESA, participants were free of clinical CVD at baseline. Participants were excluded if they had a history of any of the following procedures: coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker or defibrillator implantation, or any other cardiac surgery. Of the 6780 participants, 168 (2.5%) had self-reported rheumatic fever; the exclusion of these people from the analysis did not change the results. The study was designed to include whites, blacks, Hispanics, and Chinese. Sampling and recruitment procedures have been described in detail previously.21 Participants were enrolled between August 1, 2000, and July 30, 2002. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

Questionnaires were used to obtain information about socioeconomic status, medical history, medication, and tobacco use. Smoking was defined as current, former, or never. Waist circumference at the umbilicus was measured to the nearest 0.1 cm with a steel measuring tape (standard 4-oz tension). Resting blood pressure was measured 3 times with participants in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon/GE Healthcare; Giles, Bucks, United Kingdom). The average of the last 2 measurements was used in analysis. Total and HDL cholesterol, triglycerides, and glucose levels were measured from blood samples obtained after a 12-hour fast. LDL cholesterol was calculated with the Friedewald equation.22 Diabetes was defined as fasting glucose ≥126 mg/dL or use of hypoglycemic medication. Impaired fasting glucose was defined as fasting glucose 110 to 125 mg/dL.

MetS Definitions

MetS was defined with the Third Adult Treatment Panel of the National Cholesterol Education Program (ATP III)23 modified criteria as the presence of 3 or more of the following: large waist circumference (women ≥88 cm and men ≥102 cm); elevated triglycerides (≥150 mg/dL); low HDL cholesterol (men <40 mg/dL and women <50 mg/dL); impaired fasting glucose (110 to 125 mg/dL); and elevated blood pressure (≥130/85 mm Hg or self-reported use of medications for hypertension). The American Diabetes Association recently recommended that the range for impaired fasting glucose be changed from 110 to 125 mg/dL to 100 to 125 mg/dL24; the effect of this modification on the population prevalence of MetS has not been fully explained. Therefore, a revised definition of MetS that applied the lower threshold for impaired fasting glucose (100 to 125 mg/dL) was created to assess the effect of this change on the prevalence of MetS and its association with AVC. As a secondary analysis, we also examined the International Diabetes Federation (IDF) criteria for MetS,13 which recommend large waist circumference (for whites, blacks, and Hispanics: ≥80 cm if female or ≥84 cm if male; for Chinese, ≥80 cm if female or ≥90 cm if male) and 2 or more of the following: elevated triglycerides (≥150 mg/dL); low HDL cholesterol (men <40 mg/dL and women <50 mg/dL); impaired fasting glucose (100 to 125 mg/dL); and elevated blood pressure (≥130/85 mm Hg or self-reported use of medications for hypertension).

Computed Tomography Techniques

All participants underwent 2 computed tomography (CT) scans at the same time for evaluation of coronary artery calcium. CT studies were performed with either an Imatron C-150XL computed tomographic scanner (GE-Imatron, South San Francisco, Calif) in 3 sites or multidetector CT scanners (4-slice) in 3 sites. The exact scanning methodology employed in the MESA study has been reported elsewhere.25

All studies were analyzed at the MESA CT reading center at Harbor-UCLA Research and Education Institute. The calcium score of each lesion was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield units within this area, as described by Agatston et al.26 The density factor was assigned in the following manner: 1 for lesions for which the maximal density was 130 to 199 HU, 2 for lesions 200 to 299 HU, 3 for lesions 300 to 399 HU, and 4 for lesions >400 HU. A total calcium score (for both Agatston and volume) was determined by summing individual lesion scores at each anatomic site. Volume of calcium was also measured (in mm3) as the volumetric score.27 AVC was measured and quantified with the same lesion definition as for coronary calcification. Any calcified focus seen that extended to the aortic root was deemed aortic valve calcium, by methodology described previously.28 Calcification that involved either the aortic or mitral annuli was not included. AVC score (Agatston and volume) was assessed in every patient. The absence of AVC was deemed a score of 0.

Data Analyses

The study population for the present analysis includes all MESA participants who had no missing data on any component of MetS. After the application of these criteria, 6780 individuals remained for analysis.

All analyses were stratified by gender. Comparisons between MetS, diabetes mellitus, and neither condition (and across number of MetS risk factors) with demographic measures and cardiovascular risk factors are expressed with means and proportions. We used the χ2 test for proportions and ANOVA for comparison of levels of continuous risk factors.

Because the prevalence of calcification was >10% in the cohort, ORs overestimate the relative risk (RR). Therefore, RR estimates are presented from the regression model y = exp(βxβ). The exponentiated parameters β are interpreted as RRs. We assumed gaussian error and used robust standard error estimates. Using this method, we examined the prevalence of AVC >0 (ie, the percent with scores >0) among the 3 disease groups (MetS, diabetes mellitus, and neither condition) by gender, adjusted for age and ethnicity and additionally for other non-MetS risk factors (LDL cholesterol, lipid-lowering medications, and smoking). Among those with detectable calcium, the natural logarithm of the AVC score was used as a continuous variable in a linear regression. For all nondiabetic subjects, we further examined the number of MetS risk factors (from none to all 5) and their association with prevalence of AVC and examined the RR of AVC >0 by number of MetS risk factors using those with 0 MetS risk factors as the reference group. For the RR regression, participants who had 4 and 5 risk factors were grouped together owing to the relatively small numbers. Two-way interactions be-
and 21% in men, with substantial differences by gender and ethnicity subgroups (from a low of 13% in Chinese-American men to a high of 31% in Hispanic women). Elevated blood pressure was the most common component for men, ranging from 81% in subjects with MetS to 80% in subjects with diabetes. Large waist circumference was much more prevalent in women (94% for those with MetS and 87% for those with diabetes) than in men (75% for MetS and 51% for diabetes). With the IDF definition of MetS, 2239 participants (33%) had MetS, with MetS prevalences of 35% in women and 31% in men. With the IDF definition, the prevalence of MetS also differed by ethnicity, ranging from 11% in Chinese-American women to 32% in both black women and white women and from 8% in Chinese men to 38% in white men.

**Results**

**Participant Characteristics**

The mean age of the cohort was 62 years (range 45 to 85 years); 53% were female; 12% were Chinese-American, 28% were black, and 22% were Hispanic. Of the 6780 participants, 1550 (23%) met the ATP III definition for MetS and an additional 1026 (15%) met the definition for diabetes mellitus. There were significant differences in all coronary risk factors between those without either MetS or diabetes, those with MetS, and those with diabetes (Table 1). The prevalence of MetS in participants without diabetes was 30% in women and 21% in men, with substantial differences by gender and ethnicity subgroups (from a low of 13% in Chinese-American men to a high of 31% in Hispanic women). Elevated blood pressure was the most common component for men, ranging from 81% in subjects with MetS to 80% in subjects with diabetes. Large waist circumference was much more prevalent in women (94% for those with MetS and 87% for those with diabetes) than in men (75% for MetS and 51% for diabetes). With the IDF definition of MetS, 2239 participants (33%) had MetS, with MetS prevalences of 35% in women and 31% in men. With the IDF definition, the prevalence of MetS also differed by ethnicity, ranging from 11% in Chinese women to 32% in both black women and white women and from 8% in Chinese men to 38% in white men.

**Relationships of MetS and Diabetes Mellitus to AVC Prevalence**

The prevalence of AVC in women with MetS was significantly lower (12%) than in those with diabetes (17%) and significantly higher than in those with neither condition (8%; both $P<0.001$). In men, the prevalence of AVC in those with MetS was 22% compared with 24% in those with diabetes.
and 14% in those with neither condition (P < 0.001; Figure 1A). Similar results were observed with the IDF criteria for MetS (Figure 1B).

Among women with detectable calcium who had neither MetS nor diabetes, the mean of ln(AVC) was 3.76 (SD = 1.28); the mean for those with MetS was 3.80 (SD = 1.68) compared with the mean among diabetic subjects of 4.00 (SD = 1.15). The difference between these means was not significant (P = 0.407). For men, these figures were 4.16 (SD = 1.63), 4.21 (SD = 1.53), and 4.28 (SD = 1.55), respectively (P = 0.779). We tested for interactions between MetS and either age or ethnicity in the prediction of the presence of AVC. There were no significant interactions with age or ethnicity (all P > 0.10).

Relationship of AVC Prevalence to Number of MetS Components

There was a graded, linear association between the prevalence of AVC and the number of metabolic risk factors (excluding persons with diabetes) for both genders (Figure 2A). For women, AVC prevalence ranged from 3% in those without any metabolic risk factors to 7%, 11%, 12%, 15%, and 17% in those with 1, 2, 3, 4, and 5 metabolic risk factors, respectively (P < 0.001 for trend). For men, the prevalence of AVC was higher and ranged from 9% in those without any metabolic risk factors to 15%, 17%, 22%, 23%, and 30% in those with 1, 2, 3, 4, and 5 metabolic risk factors, respectively (P < 0.001 for trend). Similar results were obtained when the IDF definition of MetS was used (Figure 2B).

Regression Analyses of MetS, Diabetes Mellitus, and AVC Risk

From RR regression analyses, the RR of AVC (compared with those with neither MetS nor diabetes mellitus), adjusted for age and ethnicity, was significantly higher in both women and men among those with MetS (women: RR 1.49, 95% CI 1.14 to 1.96; men: RR 1.70, 95% CI 1.32 to 2.18) and diabetes (women: RR 2.20, 95% CI 1.61 to 3.01; men: RR 1.72, 95% CI 1.33 to 2.23). Additional adjustment for LDL cholesterol, lipid-lowering medication use, and cigarette smoking showed these relations to persist (women with MetS: RR 1.45, 95% CI 1.11 to 1.90; men with MetS: RR 1.70, 95% CI 1.32 to 2.19; women with diabetes: RR 2.12, 95% CI 1.54 to 2.92; and men with diabetes: RR 1.73, 95% CI 1.33 to 2.25; Table 2). For the IDF definition of MetS, the RR of AVC adjusted for age, gender, LDL cholesterol, lipid-lowering medication use, and cigarette smoking was still significantly higher in both men and women than in those with neither condition (women: RR 1.43, 95% CI 1.10 to 1.86; men: RR 1.40, 95% CI 1.12 to 1.76). The IDF definition of MetS also had no effect on the severity of AVC (women: RR 1.89, 95% CI 0.99 to 3.62; men: RR 1.19, 95% CI 0.77 to 1.85).
TABLE 2. Multivariable RR Estimates (95% CI) of AVC >0 and Diabetes Mellitus, MetS (ATP III and IDF Definitions), or Neither Condition

<table>
<thead>
<tr>
<th></th>
<th>Women (n=3581)</th>
<th></th>
<th>Men (n=3199)</th>
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<td>Neither Condition</td>
<td>MetS</td>
<td>Diabetes Mellitus</td>
<td>Neither Condition</td>
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<tr>
<td>ATP III MetS definition, n</td>
<td>2159</td>
<td>927</td>
<td>495</td>
<td>2045</td>
</tr>
<tr>
<td>Model 1*</td>
<td>1.0 (Ref)</td>
<td>1.49 (1.14–1.96)</td>
<td>2.20 (1.61–3.01)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1.0 (Ref)</td>
<td>1.45 (1.11–1.90)</td>
<td>2.12 (1.54–2.92)</td>
<td>1.0 (Ref)</td>
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<tr>
<td>IDF MetS definition, n</td>
<td>1834</td>
<td>1252</td>
<td>495</td>
<td>1681</td>
</tr>
<tr>
<td>Model 1*</td>
<td>1.0 (Ref)</td>
<td>1.50 (1.15–1.95)</td>
<td>2.33 (1.68–3.23)</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1.0 (Ref)</td>
<td>1.43 (1.10–1.86)</td>
<td>2.22 (1.59–3.09)</td>
<td>1.0 (Ref)</td>
</tr>
</tbody>
</table>

Ref indicates referent category.
*Adjusted for age and ethnicity.
†Adjusted for age, ethnicity, LDL, smoking, and lipid-lowering medication use.

Application of the new, lower limit of fasting glucose (100 mg/dL) resulted in a nearly 3-fold increase in the prevalence of impaired fasting glucose (from 12% to 35%) and an additional 7% for the total population classified as having MetS. Furthermore, fully adjusted RRs estimated from the revised criteria of MetS that used the 100 to 125 mg/dL range for fasting glucose were very similar to those estimated when we used the original impaired fasting glucose criteria (when the adjusted model [model 2] from Table 2 was used, AVC >0 yielded a 1.43 RR in women [95% CI 1.10–1.86] and 1.73 RR in men [95% CI 1.19 to 1.89]).

In age- and ethnicity-adjusted models performed separately for each component of the MetS (Table 3), elevated blood pressure, high triglycerides, and abdominal obesity were significantly associated with AVC, with approximately 45%, 45% to 60%, and 35% to 60% increases, respectively, in AVC prevalence. Remaining components were less strongly associated with AVC. When all 5 of the components of MetS were included in a single model, the RR for elevated blood pressure was attenuated slightly but still exhibited the strongest association with AVC relative to the other components (results not shown).

### Regression Analyses of the Relationship of Number of MetS Components to the Presence of AVC

To examine the association between the number of components and presence of AVC, sex-specific models were fit with categories that represented the presence of 1, 2, 3, and ≥4 components, with 0 components as the referent (Table 4). Women and men with 4 to 5 components were 3.32 (95% CI 1.77 to 6.21) and 2.26 (95% CI 1.72 to 3.86) times more likely to have AVC than participants with 0 components. Furthermore, the presence of any 2 components was positively associated with presence of AVC (women: 2.44, 95% CI 1.32 to 4.50; men: 1.46, 95% CI 1.01 to 2.11). When the new lower limit of fasting glucose (100 mg/dL) was used, the magnitude of association between each number of remaining components and prevalence of AVC remained nearly the same (for 4 to 5 components, the RR in women was 3.32 [95% CI 1.71 to 6.45], and in men, the RR was 2.32 [95% CI 1.54, 3.52]). When we applied the IDF definition, sex-specific models were fit that represented the abdominal obesity criteria plus the presence of 0, 1, 2, or ≥3 components, with no abdominal obesity present as the referent (Table 4). Women and men with abdominal obesity plus 3 to 4 components were 1.72 (95% CI 1.01 to 2.90) and 1.92 (95% CI 1.39 to 2.66) times more likely to have AVC than participants with no abdominal obesity; however, the presence of fewer components plus abdominal obesity had no significant association with AVC in either men or women.

#### Discussion

Our report of a large, population-based multiethnic cohort shows an increased and graded likelihood of AVC with the presence of MetS and diabetes mellitus, as well as with the

<table>
<thead>
<tr>
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<th>Women (n=3086)</th>
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<th>Men (n=2668)</th>
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<td></td>
<td>Model 1*</td>
<td>Model 2†</td>
<td></td>
<td>Model 1*</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>1.50 (1.10–2.04)</td>
<td>1.44 (1.06–1.97)</td>
<td>1.46 (1.14–1.87)</td>
<td>1.35 (1.05–1.74)</td>
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<tr>
<td>Low HDL</td>
<td>1.32 (1.00–1.74)</td>
<td>1.09 (0.80–1.47)</td>
<td>1.28 (1.00–1.63)</td>
<td>1.15 (0.89–1.50)</td>
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<tr>
<td>High triglycerides</td>
<td>1.56 (1.18–2.07)</td>
<td>1.36 (1.00–1.85)</td>
<td>1.62 (1.26–2.08)</td>
<td>1.45 (1.11–1.91)</td>
</tr>
<tr>
<td>Impaired fasting glucose (≥110 mg/dL)</td>
<td>0.99 (0.61–1.60)</td>
<td>0.83 (0.51–1.35)</td>
<td>1.09 (0.78–1.52)</td>
<td>0.96 (0.69–1.35)</td>
</tr>
<tr>
<td>Impaired fasting glucose (≥100 mg/dL)</td>
<td>1.06 (0.80–1.41)</td>
<td>0.87 (0.65–1.17)</td>
<td>0.99 (0.78–1.24)</td>
<td>0.86 (0.67–1.09)</td>
</tr>
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<td>Abdominal obesity (ATP III criteria)</td>
<td>1.63 (1.20–2.21)</td>
<td>1.41 (1.03–1.94)</td>
<td>1.34 (1.06–1.69)</td>
<td>1.20 (0.94–1.53)</td>
</tr>
<tr>
<td>Abdominal obesity (IDF criteria)</td>
<td>1.57 (0.99–2.50)</td>
<td>1.22 (0.76–1.96)</td>
<td>1.51 (1.18–1.95)</td>
<td>1.35 (1.04–1.75)</td>
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</table>

*Model 1: RRs are estimated from RR regression models of each component of MetS, adjusted for age and ethnicity.
†Model 2: RRs for each component of MetS, adjusted for age, ethnicity, LDL, and use of lipid-lowering medication.
The mechanisms by which MetS might mediate increased valvular calcification are not known. However, MetS is associated with increased oxidant and inflammatory stress, and both oxidized cholesterol and inflammatory cytokines, each of which is present in human aortic valve lesions,\(^9,29\) have been shown to increase calcific nodule formation by valvular fibroblasts in vitro.\(^{30}\)

This study has several limitations: (1) It is cross-sectional, which limits conclusions about causality; (2) the study may be subject to survival bias in that individuals with cardiovascular disease did not participate in MESA; (3) because MESA was a population-based, multiethnic cohort, that MetS and diabetes,\(^16,17\) which underscores the potential similarities in the pathogeneses of atherosclerosis and AVC. The present investigation is the first to demonstrate, in a large, population-based, multiethnic cohort, that MetS and diabetes are independently associated with AVC. Moreover, there was a graded, linear relationship between the number of MetS components and RR for the presence of AVC, which further strengthens the association of MetS with AVC.

In conclusion, results from this adult population–based cohort provide support for a link between the presence of MetS and the presence of AVC. They further underscore the importance of recognizing and treating individual components of MetS, particularly elevated blood pressure and dyslipidemia. Further study is warranted to determine whether screening for aortic valve disease should be recommended in those with MetS or diabetes. Also, given differing findings with regard to the efficacy of either statin therapy or ACE inhibitors in calcific aortic valve disease,\(^{32–36}\) further investigation is needed to define whether those interventions, as well as interventions that directly target insulin resistance in MetS, might retard or reverse AVC.

Acknowledgments
This research was supported by R01-HL-63963-01A1, contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169, and grant DK02456 from the National Heart, Lung, and Blood Institute.

Disclosures
Dr Wong has received research grants from Pfizer and Bristol-Myers Squibb and is on the speakers’ bureau of Pfizer, Bristol-Myers Squibb, Takeda Pharmaceutical Company Limited, and Sanofi-Aventis. Dr Budoff has received honoraria from and is on the speakers’ bureau of General Electric. Dr O’Brien is on the speakers’ bureau of Takeda Pharmaceutical Company Limited and has served as a consultant for Sanofi-Aventis.

References
Calcific aortic valve disease, which includes aortic sclerosis and aortic stenosis, is present in >25% of elderly subjects. Several common cardiovascular risk factors, including age, male gender, diabetes mellitus, and elevated levels of both LDL cholesterol and lipoprotein(a), have been associated with increased prevalence of aortic valve calcium (AVC). Metabolic syndrome is a risk factor for cardiovascular disease, but whether metabolic syndrome is associated with an increased prevalence of AVC is not known. This study examined the relationship of metabolic syndrome with AVC, as assessed by electron-beam computed tomography, in 6780 participants in the Multi-Ethnic Study of Atherosclerosis (MESA). MESA is a large, multiethnic cohort of subjects without clinical cardiovascular or valvular heart disease at baseline. AVC was present at baseline in 908 MESA participants (13.4%). Metabolic syndrome was associated with a significantly higher adjusted relative risk (RR) of AVC in both women (RR = 1.45, 95% CI 1.11 to 1.90) and men (RR = 1.70, 95% CI 1.32 to 2.19). In addition, there was a graded, linear relationship between AVC prevalence and the number of metabolic syndrome components in both women and men (both P < 0.001). These findings suggest that, as has been shown for atherosclerosis, metabolic syndrome is also a significant risk factor for calcific aortic valve disease.
Features of the Metabolic Syndrome and Diabetes Mellitus as Predictors of Aortic Valve Calcification in the Multi-Ethnic Study of Atherosclerosis

_Circulation._ 2006;113:2113-2119; originally published online April 24, 2006; doi: 10.1161/CIRCULATIONAHA.105.598086

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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