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Type 2 Diabetes Mellitus Is Associated With Faster Degeneration of Bioprosthetic Valve

Results From a Propensity Score–Matched Italian Multicenter Study

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Background—The present study was aimed at determining the impact of type 2 diabetes mellitus (DM) on postoperative bioprosthetic structural valve degeneration.

Methods and Results—Twelve Italian centers participated in the study. Patient data refer to bioprosthetic implantations performed from November 1988 to December 2009, which resulted in 6184 patients (mean age 71.3±5.4 years, 60.1% male) being enrolled. Of these patients, 1731 (27.9%) had type 2 DM. The propensity score–matching algorithm successfully matched 1113 patients with type 2 DM with the same number of no-DM patients. The postmatching standard differences were less than 0.1 for each of the covariates, and 64.2% of DM patients were matched. The early (30 days) mortality rate was 7.8% (n=87) versus 2.9% (n=33) in patients with or without type 2 DM ($P<0.001$), respectively. Seven-year freedom from valve deterioration was significantly lower in patients with DM (73.2% [95% confidence interval, 61.6–85.5] versus 95.4% [95% confidence interval, 83.9–100], $P<0.001$). In Cox regression models with robust SEs that accounted for the clustering of matched pairs, DM was the strongest predictor of structural valve degeneration (hazard ratio 2.39 [95% confidence interval 2.28–3.52]). When we allowed for interaction between type 2 DM and other key risk factors, DM remained a significant predictor beyond any potentially associated variable.

Conclusions—Patients with type 2 DM undergoing bioprosthetic valve implantation are at high risk of early and long-term mortality, as well as of structural valve degeneration. **(*Circulation*. 2012;125:604-614.)**

Key Words: heart valve surgery ■ prosthetic heart valves ■ type 2 diabetes mellitus

Despite their excellent hemodynamic properties, the limited durability of bioprostheses is the major drawback in their use as a replacement for dysfunctional cardiac valves, and for this reason, their use is generally confined to older patients. The limited life span of bioprostheses is mainly caused by tissue degeneration, the pathogenesis of which is still not completely understood. Degeneration of xenografts is believed to depend on the mechanical properties of the valve and on host-related immunologic and calcification processes. Hypercholesterolemia has been associated with an increased risk of reoperation as a result of structural valve degeneration (SVD) in patients with a bioprosthetic valve.[1,2] Furthermore, it has been suggested that risk factors for atherosclerosis accelerate the degeneration of aortic pericardial valves.[2] Moreover, it has been suggested that statins could slow the progression of bioprosthetic valve degeneration.[3,4] Finally,

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the metabolic syndrome (MS), a cluster of atherogenic, inflammatory, and atherothrombotic abnormalities linked to abdominal obesity and insulin resistance, has been reported to be an independent predictor of poor prognosis in native valve disease and of faster degeneration of implanted bioprosthetic valves.[5,6]

Clinical Perspective on p 614

Among the atherosclerosis-related risk factors, type 2 diabetes mellitus (DM) has been acknowledged as a critical determinant for accelerated degeneration of both native and prosthetic tissue valves.[2,5] Nonetheless, as far as we know, no large dedicated study exists that clearly demonstrates that type 2 DM is independently associated with faster bioprosthetic valve degeneration. The objective of the present report, therefore, was to retrospectively analyze the data gathered from a national multi-institutional experience concerning the influence of type 2 DM on several major clinical outcomes after bioprosthetic valve implantation for cardiac valve replacement.

Methods

Patient Cohort and Data Collection

Twelve Italian centers participated in the study. Data were collected from patient charts for preoperative, operative, and hospital admittance details, or in the case of patients hospitalized for any cause after surgery, through direct or telephone interview with survivors, with relatives, general physicians, or hospital doctors. Patients were followed up according to each individual institutional protocol.

Patient data refer to bioprosthetic implantations performed from November 1988 to December 2009, which resulted in 6184 patients (mean age 71.3±5.4 years, 60.1% male). Of these patients, 1731 (27.9%) had type 2 DM (Table 1). All collected data were sent to a core laboratory (Cardiovascular Research Unit, Ospedale Careggi, Florence, Italy) for statistical analysis.

Ethics committee approval was waived because of the retrospective analysis of the study, according to the Italian national law regulating observational retrospective studies (law No. 11960, released on July 13, 2004). Median follow-up was 84.7 months (interquartile range 48.4–156.6 months), with a total of 26 891 years of evaluation. At the close of the follow-up (December 31, 2010), the completeness of the follow-up was 98%.

Definitions

Type II DM was diagnosed on the basis of the current recommendations of the American Diabetes Association.[7] Determination of type 2 DM status in epidemiological studies is based on measurement of the fasting plasma glucose level (FPG; ≥126 mg/dL [7.0 mmol/L]) or 2-hour postload glucose on an oral glucose tolerance test (FPG ≥200 mg/dL [11.1 mmol/L]). Patients admitted with a previous diagnosis of type 2 DM were classified on the basis of the type of treatment (oral hypoglycemic agent, non–insulin-treated diabetes [NITDM], or insulin-treated diabetes [ITDM]). The remaining patients were classified in accordance with their FPG level as having either undiagnosed type 2 DM (FPG ≥126 mg/dL), with such patients included in the DM group, or impaired fasting glucose (FPG 100–125 mg/dL [8.8–11.1 mmol/L]) or normal fasting glucose (FPG <100 mg/dL), with such patients representing the control group (no DM).[7] Glucose tolerance was not consistently investigated further in these 2 latter groups with an oral glucose tolerance test.

According to the current guidelines of the American Association for Thoracic Surgery, the Society of Thoracic Surgeons, and the European Association for Cardio-Thoracic Surgery,[8] SVD was defined as dysfunction or deterioration that involved the implanted bioprosthesis (exclusive of infection or thrombosis), such as wear, fracture, calcification, leaflet tear, stent creep, and suture-line disruption of components of a prosthetic valve. Diagnosis of SVD was made by echocardiography and confirmed at surgical reoperation.

Table 1. Diabetes History (n=1731)

Fasting preoperative glucose level, mg/dL (95% CI)	148 (130–164)
Hb A_{1c}, % (95% CI)	6.8 (6.3–7.5)
Duration of diabetes, y	10±8.9
Preoperative diabetic medication	
Diet alone	345 (20.0)
Oral hypoglycemic(s) alone	866 (50)
Insulin alone	311 (18.0)
Insulin+oral hypoglycemic(s)	209 (12.0)
Microvascular diabetic complication	538 (31.1)
Macrovascular diabetic complication	
Prior MI	519 (29.9)
Prior CVA	343 (19.8)
Peripheral PVD	311 (17.9)
Prior congestive heart failure	398 (22.9)
Recurrent hypoglycemia	474 (27.3)
Episodes of diabetic ketoacidosis	26 (1.5)

Hb A_{1c} indicates glycosylated hemoglobin; CI, confidence interval; MI, myocardial infarction; CVA, cerebrovascular accident; and PVD, peripheral vascular disease.

Values are expressed as mean±SD or n (%).

The clinical identification of patients with the features of the MS was based on the modified criteria proposed by the National Cholesterol Education Program's Adult Treatment Panel III.[9] Because waist circumference was not measured in the present sample, body mass index was substituted for waist circumference as an index of obesity.[10] Patients were considered to have the MS when 3 of the 5 following criteria were present: (1) Body mass index ≥30 kg/m^2, (2) fasting glycemia ≥110 mg/dL, (3) triglycerides ≥150 mg/dL, (4) high-density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women, and (5) systolic/diastolic blood pressures ≥130/85 mm Hg.

Statistical Analysis

Estimation of Propensity Score and Matching

Because of the significant imbalances in baseline covariates between patients with and without DM, we used propensity scores (PS) to reduce imbalance.[11] We used a multivariate logistic regression model to estimate PS for DM for all patients. Variables used in the model are displayed in Table 2.

Pairs of patients with and without DM on the logit of the PS were matched by use of calipers with a width that was 0.2 SDs of the logit of the PS.[12] The resultant matched sample consisted of 1113 matched pairs. Covariate balance was measured by the standardized differences, by which an absolute standardized difference >0.1 is suggested to represent meaningful covariate imbalance.[12]

Prematched standardized differences exceeded 0.1 for 26 (53.1%) of the 49 covariates (Figure 1). The median prematching standardized difference (interquartile range) was 0.186676 (0.105739–0.332149).

The postmatching standard differences for each of the covariates are reported in Table 2. The median standardized difference was 0.036161 (interquartile range 0.016342–0.074342), and in none of the covariates did it exceed 0.1 (Figure 1).

Estimation of the Effect of DM on SVD

Postoperative data were compared between diabetic and nondiabetic subjects with the Wilcoxon signed rank test and McNemar tests. Complications were expressed as linearized rates (patients/year). Freedom from SVD was determined in the matched cohort by

Table 2. Characteristics of Propensity-Matched Pairs (n=2226)

	Type II DM (n=1113)	No Type II DM (n=1113)	Standardized Difference
Age, y	68.1±8.3	68.4±8.1	0.036
Male sex	830 (74.5)	796 (71.5)	0.067
Hypertension	1018 (91.4)	1002 (90.0)	0.048
Current smoker	280 (25.1)	289 (25.9)	0.018
BMI, kg/m^2	28.4±4.2	28.6±4.5	0.045
Obesity	579 (52.0)	530 (47.6)	0.087
Metabolic syndrome	456 (40.9)	412 (37)	0.079
Total cholesterol, mg/dL	189.6±27.7	187.8±25.6	0.067
HDL, mg/dL	52.3±13	53.4±2.5	0.086
Total cholesterol/HDL	3.6±1.1	3.5±0.9	0.029
LDL, mg/dL	113.7±28.2	114.3±27.9	0.021
Triglycerides, mg/dL	150.2±69.5	144.7±55.4	0.087
Statin use	567 (50.9)	524 (47.0)	0.077
Systolic BP, mm Hg	133.4±21.6	132.9±20.9	0.023
Diastolic BP, mm Hg	78.4±13.9	77.3±11.5	0.086
Chronic renal disease	178 (15.1)	144 (12.9)	0.085
COPD	155 (13.9)	154 (13.8)	0.002
Creatinine, mg/dL	1.3±0.7	1.2±0.5	0.082
Valvular pathology			
Aortic			
Stenosis	402 (36.1)	400 (36.0)	0.002
Insufficiency	219 (19.7)	206 (18.5)	0.030
Mixed	281 (25.2)	263 (23.7)	0.034
Mitral			
Stenosis	14 (1.2)	15 (1.3)	0.009
Insufficiency	80 (7.2)	84 (7.5)	0.013
Mixed	117 (10.6)	145 (13.0)	0.074
Etiology			
Rheumatic	345 (31.0)	329 (29.5)	0.032
Calcific	612 (54.9)	604 (54.3)	0.012
Myxomatous	101 (9.2)	124 (11.2)	0.066
Previous valve operation	42 (3.8)	44 (3.9)	0.020
Other	13 (1.1)	12 (1.1)	0.016
Pulmonary hypertension	56 (49.5)	56 (49.5)	0
NYHA ≥3	135 (12.1)	133 (11.9)	0.006
LVEF, %	44.6±12	44.7±11	0.008
Prior MI	423 (38.1)	378 (33.9)	0.087
Prior CVD	312 (28.0)	284 (25.5)	0.056
Prior PVD	248 (22.2)	206 (18.5)	0.087
Prior CHF	267 (23.9)	238 (21.3)	0.062
Surgery			
Urgent/emergent operation	111 (9.9)	84 (7.5)	0.085
Isolated AVR	691 (62.1)	670 (60.2)	0.038
Isolated MVR	134 (12)	136 (12.3)	0.009
Double valve replacement	288 (25.9)	306 (27.5)	0.036
Stentless bioprosthesis	113 (10.1)	98 (8.8)	0.044
Stented pericardial bioprosthesis	748 (67.3)	734 (65.9)	0.029
Stented porcine bioprosthesis	252 (22.6)	281 (25.3)	0.063
Bioprosthesis size, mm	23.1±0.6	23.1±0.7	0
Associated CABG	466 (41.8)	418 (37.5)	0.087
Other associated procedures	116 (10.4)	101 (10.1)	0.009
CPB time, min	125±38	124±35	0.027
CC time, min	83±23	83±20	0
Redo surgery	74 (6.6)	69 (6.2)	0.016

DM indicates diabetes mellitus; BMI, body max index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; MI, myocardial infarction; CVD, cerebrovascular disease; PVD, peripheral vascular disease; CHF, congestive heart failure; AVR, aortic valve replacement; MVR, mitral valve replacement; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; and CC, cross-clamp.

Values are expressed as mean±SD for normally distributed data, median (interquartile range) for nonnormally distributed data, or n (%).

Kaplan-Meier methodology, and a stratified log-rank test was used to compare the curves. Nonetheless, because SVD is a nonfatal event, patients can die before such an event has happened to them, so the Kaplan-Meier event-free estimate is lower than the real event-free percentage. For this reason, we used also the "actual" analysis, which provides a mortality-adjusted event-free percentage.[12]

Cumulative incidence curves were used to graphically depict valve-related and non–valve-related deaths. The competing risk analysis was used to avoid overestimation of the incidence of valve-related death, and statistical significance was tested with the Gray test.[13]

A Cox regression model with robust SEs that accounted for the clustering of matched pairs was used to estimate the association of DM with SVD.[14,15] The proportional hazard assumption was confirmed by use of Schoenfeld residuals. Covariates used in the multivariate model included age <65 years, sex, smoking, obesity, MS, total cholesterol ≥200 mg/dL, total cholesterol/HDL >4, triglycerides ≥150 mg/dL, low-density lipoprotein ≥130 mg/dL, hypertension, renal failure, type 2 DM (NITDM/ ITDM), impaired fasting glucose, use of statin, chronic obstructive pulmonary disease, valve pathology, valve etiology, pulmonary hypertension, left ventricular ejection fraction >35%, prior myocardial infarction, prior cerebrovascular accident, prior peripheral vascular disease, congestive heart failure, aortic/mitral position, valve type (pericardial versus porcine), valve size, associated coronary artery bypass grafting, other associated procedures, reoperation, cardiopulmonary bypass time ≥120 minutes, and cross-clamp time ≥80 minutes.

Optimal cutoff values of FPG and glycohemoglobin (Hb A_{1c}) were determined by receiver operating characteristic curve (ROC) analysis as the optimal threshold for predicting recurrence of SVD. We validated the results using the bootstrap method (1000 iterations) and computed the optimism-corrected estimate ("optimism" refers to absolute magnitude of bias) for sensitivity, specificity, and area under the ROC curve.

Subgroup Analysis

Subgroup analyses were performed based on age (<65 years/≥65 years), chronic renal failure (yes/no), total cholesterol/HDL (≥4/<4), total cholesterol (≥200 mg/dL/<200 mg/dL), triglycerides (≥150 mg/dL/<150 mg/dL), and MS (yes/no). We matched subjects on the PS and the subgroup variable and estimated the effect of DM in each subgroup with Cox regression using a robust variance estimator to account for clustering within matched pairs. We tested for interactions by entering interaction terms between each subgroup and DM, with an interaction $P<0.10$ considered statistically significant.

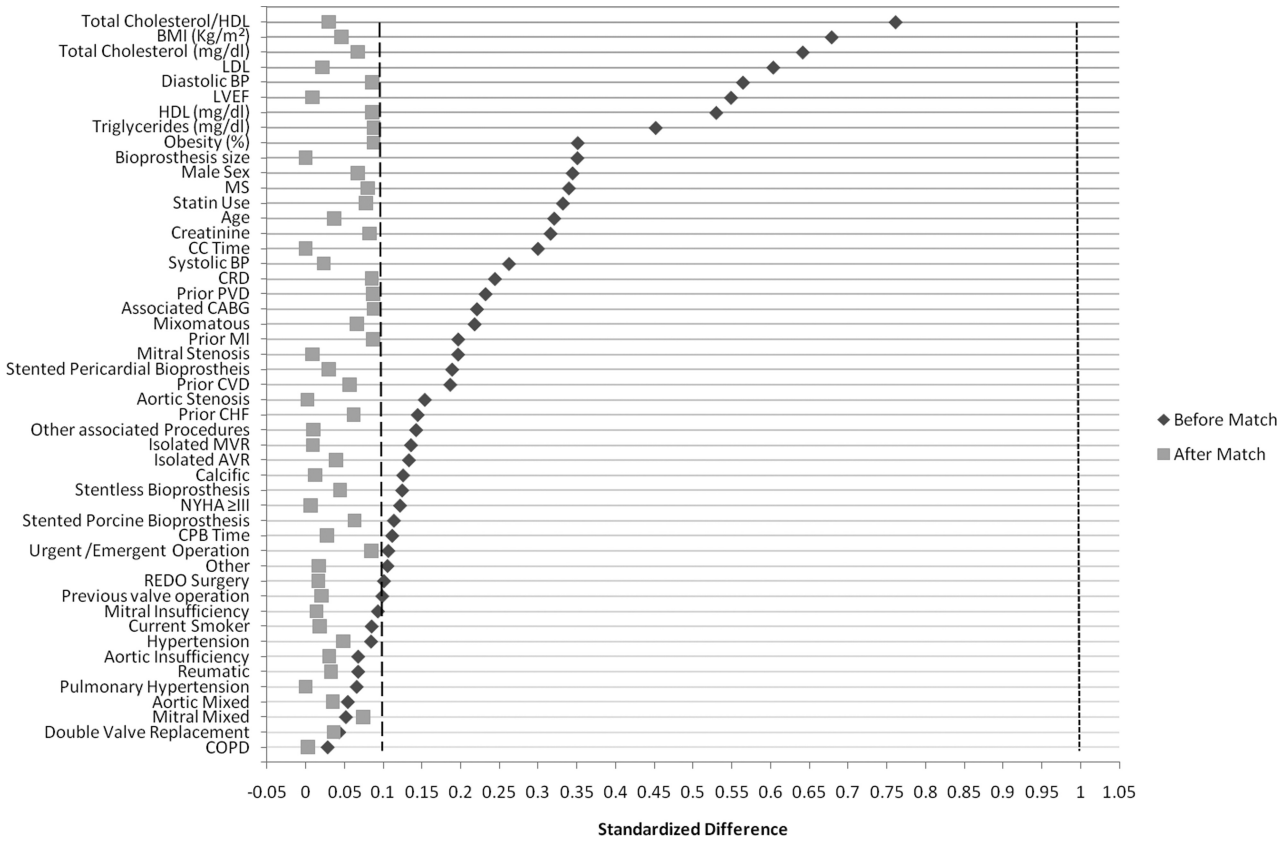

Figure 1. Absolute standardized differences before and after propensity score matching comparing covariate values for patients with or without diabetes mellitus (DM). HDL indicates high-density lipoprotein; BMI, body mass index; LDL, low-density lipoprotein; BP, blood pressure; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; CC, cross-clamp; CRD, chronic renal disease; PVD, peripheral vascular disease; CABG, coronary artery bypass graft; MI, myocardial infarction; CVD, cerebrovascular disease; CHF, congestive heart failure; MVR, mitral valve replacement; AVR, aortic valve replacement; NYHA, New York Heart Association; CPB, cardiopulmonary bypass; and COPD, chronic obstructive pulmonary disease.

Software

Analyses were performed with SAS, release 9.2 (SAS Institute, Cary, NC), SPSS 12.0 (SPSS, Chicago, IL), and Graph Pad Prism release 5 (Graph Pad Software Inc, La Jolla, CA) statistical packages. Cumulative incidence analyses were performed with an SAS macro.[16] ROC curve optimism analysis was conducted with S-plus statistical software, release 6.0 (Insightful Corp, Seattle, WA).

Results

Matched-Pairs Clinical Outcome

Early and long-term outcomes are shown in Table 3. Patients with type 2 DM had higher 30-day mortality, longer intensive care unit stay, longer assisted ventilation time, and higher incidence of early postoperative complications.

During follow-up, there were 262 late deaths (196 among patients with type 2 DM [18 valve related] and 66 in the control group [8 valve related]). Linearized rates were 1.5 patient-years (95% confidence interval [CI] 1.3–2.0) and 0.4 patient-years (95% CI, 0.1–0.7) in the type 2 DM group and no-DM group, respectively. Non–valve-related death rates at 5 and 10 years (Figure 2) were 15.2% (95% CI, 14.7%–15.8%) and 20.9% (95% CI, 19.5%– 21.7%) for DM versus 5.9% (95% CI, 4.5%–6.3%) and 8.7% (95% CI, 5.2%–9.4%) for no DM ($P<0.001$), respectively. Valve-related death rates were 4.6% (95% CI, 4.1%–5.2%) and 6.4% (95% CI, 5.8%–6.9%) for DM versus 1.1% (95% CI, 0.8%–1.6%) and 2.2% (95% CI, 1.9%–2.7%) for no DM ($P<0.001$). Finally, New York Heart Association (NYHA) functional class was, at follow-up, significantly higher in nondiabetic patients.

Matched-Pairs SVD

One hundred twenty-one patients (10.8%) in the type 2 DM group and 43 (3.8%) in the no-DM group had reoperation as result of primary tissue valve failure. Linearized rates were 3.3 patient-years (95% CI, 1.8–5.0) and 0.8 patient-years (95% CI, 0.4–1.8) in the type 2 DM group and no-DM group, respectively. Seven-year freedom from SVD was 95.4% (95% CI, 83.9%– 100% [actual 98.7%, 95% CI, 88.9%–100%]) and 73.2% (95% CI, 61.6% –85.5% [actual 81.2%, 95% CI, 70.7%– 91.4%]) in patients without or with type 2 DM, respectively (Figure 3A; $P<0.001$). Among patients without DM, SVD occurred in 18 (47.3%) without MS and 24 (52.7%) with associated MS ($P=0.8$). In contrast, among patients with DM and SVD, there was a significant difference between those with (n=33; 27.2%) or without (n=88; 72.8%; $P=<0.001$) MS. Kaplan-Meier plots for SVD in patients with or without MS are displayed in Figure 3B.

Among patients without DM, 7-year freedom from SVD was 96.8% (95% CI, 84.6%– 100% [actual 98.7%, 95% CI, 85.5%–100%]) in patients without MS and 86.3% (95% CI, 74.5%–98.1% [actual 91.3%, 95% CI, 80.0%–100%]) in

Table 3. Hospital and Long-Term Outcome (n=2226)

	Type II DM (n=1113)	No Type II DM (n=1113)	P
30-d mortality	87 (7.8)	33 (2.9)	<0.001
ICU stay ≥3 d	93 (8.3)	39 (3.5)	0.001
Assisted ventilation time ≥1 d	222 (19.9)	56 (5.6)	<0.001
Low-output syndrome	49 (4.4)	54 (4.8)	0.8
Bleeding	22 (1.9)	18 (1.6)	0.55
Myocardial infarction	24 (2.1)	20 (1.7)	0.4
Multiorgan failure	7 (0.6)	8 (0.7)	0.9
Mediastinitis	45 (4.0)	10 (0.9)	<0.001
Renal failure	53 (4.7)	43 (3.8)	0.81
Transient	30 (2.6)	27 (2.4)	
CVVH	15 (1.3)	10 (10.9)	
Dialysis	8 (0.7)	6 (0.5)	
Cerebrovascular accidents	28 (2.5)	21 (1.8)	0.44
TIA	20 (1.7)	16 (1.4)	
Stroke	8 (0.7)	5 (0.4)	
Overall complications	533 (47.8)	295 (26.5)	<0.001
Long-term results			
Survivors	830 (74.5)	1014 (91.1)	<0.001
NYHA at follow up	3 (2–4)	2 (1–3)	<0.001
I	238 (28.7)	465 (45.8)	
II	199 (24.0)	357 (35.3)	
III	246 (29.6)	122 (12.0)	
IV	147 (17.7)	70 (6.9)	
LVEF, %	47.9±12	52.7±11	0.8

DM indicates diabetes mellitus; ICU, intensive care unit; CVVH, continuous venovenous ultrafiltration; TIA, transient ischemic attack; NYHA, New York Heart Association functional class; and LVEF, left ventricular ejection fraction.

Normally distributed data are expressed as mean±SD, nonnormally distributed data as median (interquartile range), and categorical variables as frequencies.

patients with MS. In patients with DM and without MS, 7-year freedom from SVD was 64.2% (95% CI, 51.7%–75.5% [actual 70.2%, 95% CI, 62.9%–73.4%]), whereas in patients with DM and MS, it was 47.5% (95% CI, 36.2%–59.8% [actual 54.0%, 95% CI, 43.7%–63.2%]).

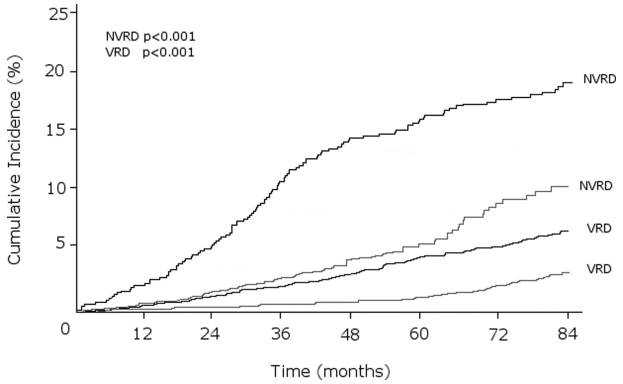

Figure 2. Cumulative incidence plots depicting no valve-related death (NVRD) and valve-related death (VRD) in patients with diabetes mellitus (black lines) or no diabetes mellitus (green lines).

Seven-year freedom from SVD was significantly lower in patients with ITDM (53.4%, 95% CI, 41.7%–65.5% [actual 63.5%, 95% CI, 52.8%–75.8%]) than in those with NITDM (80.6%, 95% CI, 67.7%–93.1% [actual 87.3%, 95% CI, 75.8% –98.9%]) and impaired fasting glucose (81.5%, 95% CI, 69.8%–94.6% [actual 87.8%, 95% CI, 76.6% –98.9%]; $P<0.001$; Figure 3C). Finally, 7-year freedom from SVD did not differ among diabetic patients by age (Figure 3D).

Multivariate Analysis

On Cox regression (Table 4), type 2 DM (hazard ratio [HR] 2.39, 95% CI, 2.28–3.52), age <65 years (HR 1.41; 95% CI, 1.35–2.27), chronic renal failure (HR 1.36; 95% CI, 1.31–2.23), total cholesterol/HDL ratio ≥4 (HR 1.19; 95% CI, 1.14–2.00), total cholesterol >200 mg/dL (HR 1.18; 95% CI, 1.12–1.93), and triglycerides ≥150 mg/dL (HR 1.16; 95% CI, 1.07–2.03) were independent predictors of SVD. Compared with patients with ITDM, those with NITDM had a 21.4% lower risk of SVD. Among patients with impaired fasting glucose, those with MS without DM, and those without DM and MS, the risk of SVD was 48.5%, 71.0%, and 88.2% lower than in patients with ITDM, respectively (Figure 4).

The ROC curve analysis showed that a cutoff value of FPG ≥142 mg/dL (95% CI, 134–161 mg/dL) was predictive of SVD. The model showed an area under the ROC curve of 0.84 (95% CI, 0.79–0.86 [optimism-corrected 0.82; 95% CI, 0.77–0.85]) with 0.87 (95% CI, 0.83–88) sensitivity (optimism-corrected 0.85; 95% CI, 0.84–0.86) and with 0.82 (95% CI, 0.80–0.84) specificity (optimism-corrected 0.79; 95% CI, 0.78–0.80). The optimal cutoff value of Hb A_{1c} to predict SVD was ≥6.5% (48 mmol/mol; 95% CI, 6.2%–6.8%). The model showed an area under the ROC curve of 0.93 (95% CI, 0.92–0.94; optimism-corrected 0.90 [95% CI, 0.89–0.91]) with 0.90 (95% CI, 0.88–0.91) sensitivity (optimism-corrected 0.87 [95% CI, 0.86–0.87]) and with 0.87 (95% CI, 0.85–0.89) specificity (optimism-corrected 0.85 [95% CI, 0.84–0.86]).

Subgroup Analysis

Associations between DM and SVD were observed in various subgroups of patients (Figure 5). Patients with DM were associated with increased SVD regardless of age, chronic renal failure, cholesterol/HDL, total cholesterol, triglycerides, and MS. There were no apparent significant interactions between DM and any of the covariates.

Discussion

The main result of the present multicenter, retrospective PS study is that type 2 DM is a strong predictor of bioprosthetic SVD independent of other risk factors and, above all, of other metabolic factors. Indeed, type 2 DM was, in our experience, the strongest predictor of SVD (HR 2.39; 95% CI, 2.68–3.52). This finding is clinically relevant because of the high prevalence of DM (≈30%) in patients undergoing heart valve replacement.[17]

It has been suggested that the process of heart valve degeneration is associated with the risk factors of atherosclerosis and shares many of its histological and molecular

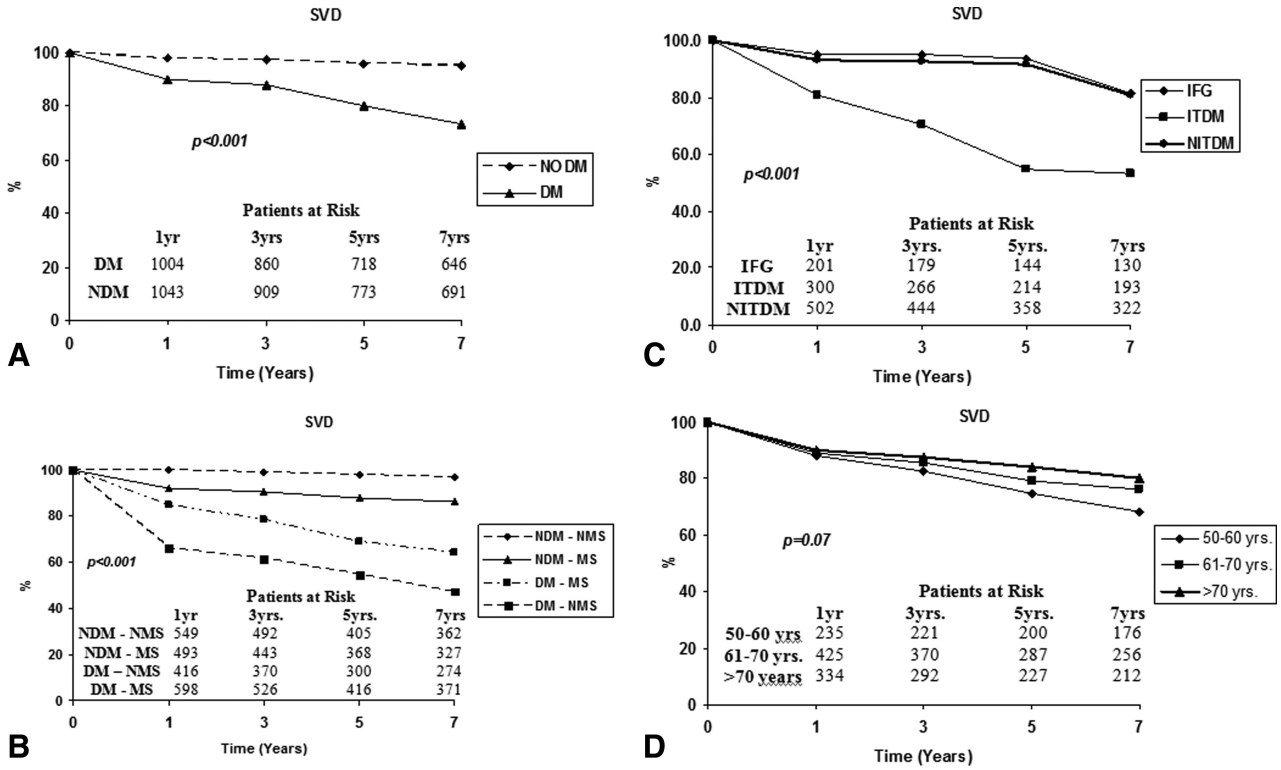

Figure 3. Actual freedom from structural valve degeneration (SVD) in the matched cohort. **A**, Actuarial freedom from SVD in patients with diabetes mellitus (DM) and without DM (NDM). **B**, Actuarial freedom from SVD in patients with DM and no metabolic syndrome (DM – NMS), with DM and associated metabolic syndrome (DM – MS), without DM or metabolic syndrome (NDM – NMS), and with metabolic syndrome without DM (NDM – MS). **C**, Actuarial freedom from SVD in patients with insulin-treated type 2 DM (ITDM), non–insulin-treated type 2 DM (NITDM), and impaired fasting glucose (IFG). **D**, Age-adjusted actuarial freedom from SVD in patients with type 2 DM.

characteristics. Results of MESA (Multi-Ethnic Study of Atherosclerosis)[18] showed that type 2 DM and MS are associated with increased risk of valve calcification. Briand and coworkers[5] found that type 2 DM was associated with a faster progression of mean gradient and noted that the association of type 2 DM with MS led to a mean gradient-progression rate 2.5-fold higher than in those without these 2 factors. Moreover, Nollert et al[2] showed that the risk factors for atherosclerosis might play a substantial role in the degeneration of aortic bioprosthetic valves and that type 2 DM was a risk factor for reoperation for aortic valve replacement. Nonetheless, all of these studies shared the limitation of having a small number of patients and considered type 2 DM in conjunction with other confounding metabolic factors potentially responsible for structural bioprosthetic failure. For this reason, we allowed for interaction between type 2 DM and other significant risk factors, and we found that the effect of type 2 DM on postoperative outcomes was similar or even higher in low- versus high-risk patients. Moreover, we failed to find any significant interactions between DM and any of the other risk factors, which demonstrates that type 2 DM remains a critical determinant of SVD beyond any other potentially associated predictor.

Table 4. Multivariate Cox Model*

	HR (95% CI)	*P*
Diabetes	2.39 (2.28–3.52)	<0.001
Age <65 y	1.41 (1.35–2.27)	0.009
Chronic renal failure	1.36 (1.31–2.23)	0.01
Total cholesterol/HDL ≥4	1.19 (1.14–2.00)	0.02
Total cholesterol >200 mg/dL	1.18 (1.12–1.93)	0.02
Triglycerides ≥150 mg/dL	1.16 (1.07–2.03)	0.03
Metabolic syndrome	1.10 (1.02–1.94)	0.08
LDL cholesterol >130 mg/dL	1.05 (0.94–1.75)	0.1
Mitral position	1.00 (0.89–1.70)	0.3
Pericardial bioprosthesis	0.94 (0.81–1.64)	0.6

HR indicates hazard ratio; CI, confidence interval; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Model with a robust variance estimate that accounts for clustering within matched pairs.

It has also been suggested that statin treatment may slow the progression of bioprosthetic degeneration,[3] and this action was hypothesized to be attributable to its pleiotropic effects, including anti-inflammatory properties, which could be beneficial in preventing the postoperative degeneration of bioprostheses.[4] In the present study, the use of statin therapy did not appear to significantly influence the degeneration of bioprosthetic valves; however, controversy remains about this issue,[19] and controlled prospective, randomized trials would be advisable to draw any conclusive information in this regard.

Regarding other proatherosclerotic conditions, multivariate analysis did not show MS to be an independent predictor of

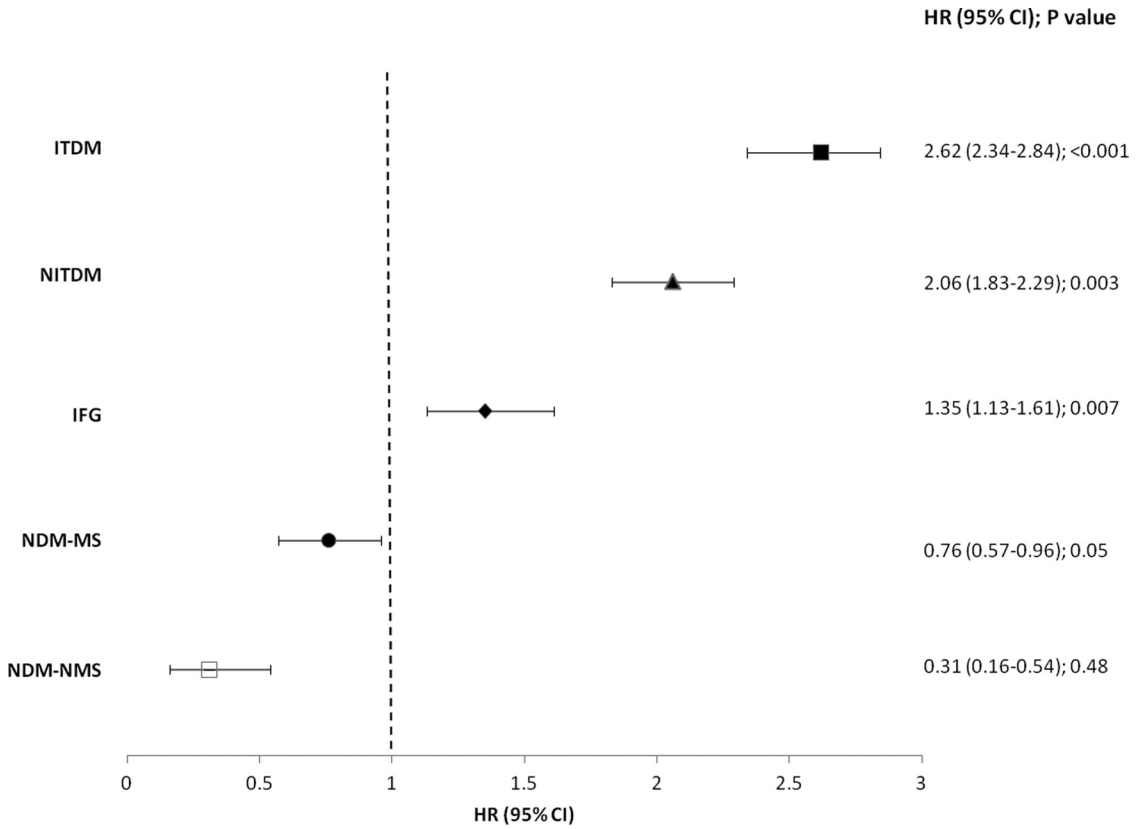

Figure 4. Hazard ratios (HR) and 95% confidence intervals (CIs) for structural valve degeneration in patients with insulin-treated type 2 diabetes mellitus (ITDM), non–insulin-treated type 2 diabetes mellitus (NITDM), impaired fasting glucose (IFG), metabolic syndrome without diabetes mellitus (NDM-MS), and without metabolic syndrome or diabetes mellitus (NDM-NMS).

SVD. This lack of association between MS and SVD and the strong association between DM and SVD observed in the present study appear to suggest that hyperglycemia rather than insulin resistance may play a major role in bioprosthesis deterioration. Alternatively, one may hypothesize that because only some (hyperglycemia and, to a lesser extent, triglycerides) but not all components of the syndrome may predict SVD, this may weaken the overall impact of MS when evaluated with stringent statistical analysis. Nevertheless, specific work is needed to explore the possible role of insulin resistance in SVD. Finally, total cholesterol levels, as well as a high total cholesterol/HDL cholesterol ratio, were a very strong independent predictor of SVD. Total cholesterol levels are not included in the definition of the MS and are not correlated with the presence of type 2 DM because they are not significantly affected by insulin resistance.[20] Therefore, the fact that total cholesterol was associated with SVD independent of DM appears to confirm findings from previous studies[1,2] and to suggest that an accelerated atherosclerotic process, of which hyperglycemia and hypercholesterolemia[21] are among the main determinants, may play a key role in SVD.

Potential Mechanisms Responsible for SVD in DM

The pathogenesis of postoperative calcification of bioprosthetic heart valves is not fully understood. Calcification and mineralization occur in virtually all bioprosthetic valves, but the extent and characteristics vary a great deal and are especially pronounced in young adults.[22] The mechanisms of accelerated calcification in young patients remain mostly unknown. It might involve an immune-mediated reaction and an increased adsorption of proteins related to bone formation.[23,24] Another important mechanism of bioprosthetic degeneration is mechanical stress. The design of the valve and its stent are considered the 2 most important features to cope with mechanical stress. In the vast majority of explanted tissue valves, inflammatory cells were found to either cover the surfaces at almost a monolayer density or focally infiltrate into the tissue. The 3 possible mechanisms that can explain these phenomena are the immune response theory, the glutaraldehyde intrinsic proinflammatory effect, and the shear stress theory. It is realistic that all 3 mechanisms work together to determine postimplantation prosthetic tissue degradation.[4] The potential mechanism responsible for SVD in type 2 DM patients is still largely unclear; however, oxidative stress leading to DNA damage is implicated in progressive chronic degenerative process secondary to DM. Indeed, increased production of highly aggressive reactive oxygen species under hyperglycemic conditions is considered the main trigger of severe chronic complications such as degenerative valve disease.[25] Similar to diabetic patients, smokers also have highly increased production of reactive oxygen species, which leads to an enhanced incidence of degenerative valve disease,[22] although the specific pathophysiological mechanisms require further clarification. A repair capacity in the presence of increased production and the damaging

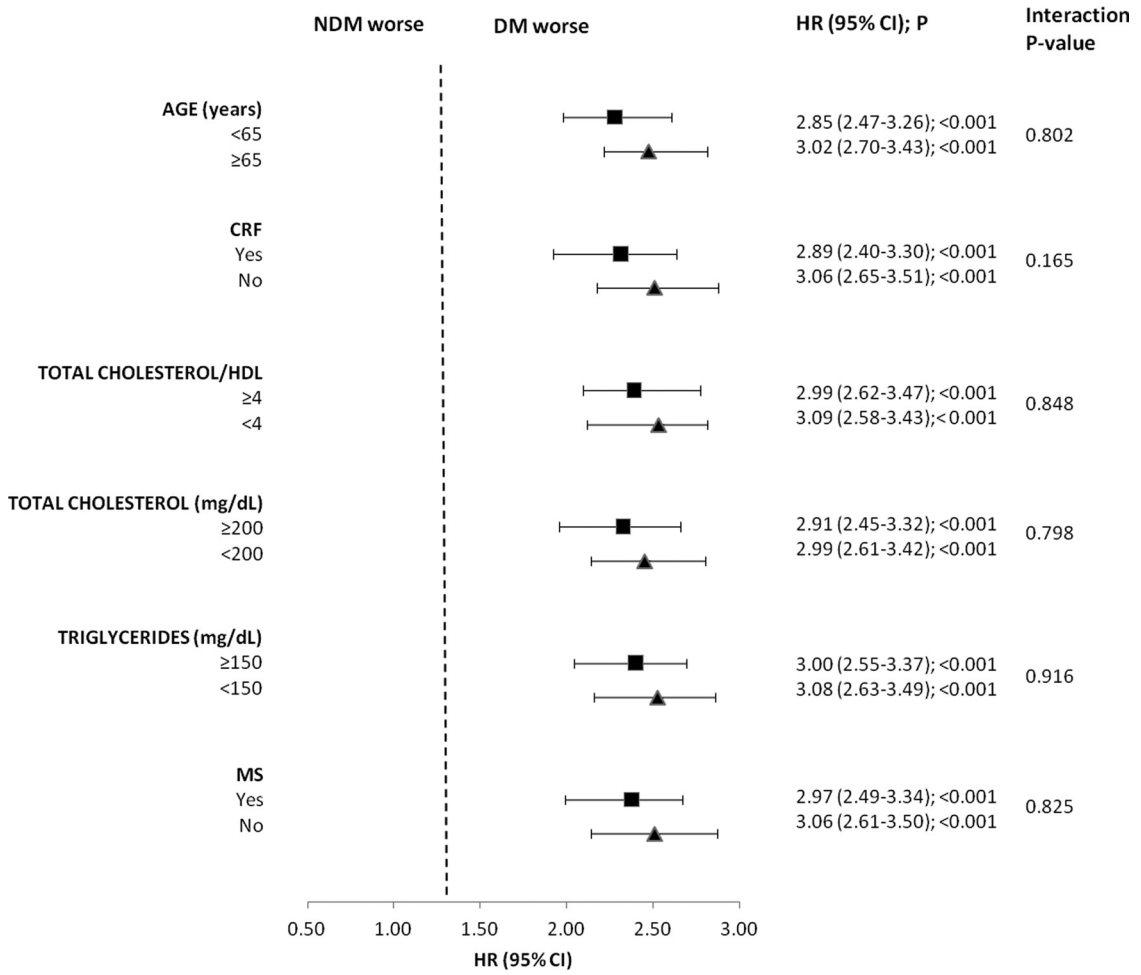

Figure 5. Risk of structural valve deterioration in various subgroups in patients with diabetes mellitus (DM) and without diabetes (NDM). HR indicates hazard ratio; CRF, chronic renal failure; HDL, high-density lipoprotein; and MS, metabolic syndrome.

effects of reactive oxygen species in patients with DM or corresponding animal models is now under intensive investigation as a parameter or even a biomarker of differential cell resistance to diabetic complications.[26–30] Furthermore, oxidative stress has been proposed to be the pathogenic mechanism linked to taurine depletion, which is associated with the development of cardiomyopathy.[26] Thus, the relevance in tissue valve degeneration of molecular events caused by both type 2 DM and taurine depletion might represent a fertile area for further investigation.

Furthermore, patients with DM are a high-risk group for infectious disorders. Increased prevalence of infectious endocarditis in patients with type 2 DM contributes considerably to both acute valve insufficiency and chronic progressive degeneration of valvular tissue.[25]

Mechanical stress, induced by unfavorable transvalvular flow conditions, may play an adjunctive role in SVD development. Indeed, Flameng and coworkers[31] recently indicated patient/prosthesis mismatch as another potential determinant of tissue valve SVD. Although transvalvular flow characteristics exert an undisputed impact on bioprosthetic tissue integrity,[32] current knowledge of factors and the mean of calculations of parameters that generate an unfavorable patient/prosthesis interplay and clinical conditions or postoperative effects are still unclear or poorly defined.[33–37] The interplay between undue mechanical stress and type 2 DM may exacerbate the unfavorable working environment of the prosthetic biological tissue. Further research in this area and in the relationship between mechanical stress and type 2 DM–related effects on tissue valves is therefore mandatory, particularly in light of improving intraoperative strategy (appropriate valve choice, myectomy in association with valve replacement, stented versus stentless, etc) and postoperative results.[38]

Clinical Considerations

In the present study, type 2 DM had a significant impact on in-hospital and long-term survival after heart valve replacement. These findings are in accordance with the experience of Halkos and associates,[38] who showed, in a study of 2964 patients submitted to isolated primary cardiac valve operation, a worse outcome in diabetic patients (in-hospital mortality of 8.0% versus 3.9% and 10-year mortality of 58.5% versus 29.5%, respectively) and who showed that among patients with DM, insulin-treated subjects had the worst long-term results.

Furthermore, the present data indicated that in addition to the confirmed negative impact on life expectancy, type 2

ITDM conveyed a higher risk of SVD, whereas NITDM treated with oral hypoglycemic agents conveyed an intermediate risk compared with the lower risk of SVD with no DM.

In addition, the increased risk associated with the ITDM group was >2.5 times higher than with MS without DM. This latter finding appears to confirm that hyperglycemia per se may be the strongest predictor of SVD and is also supported by the greater risk of SVD observed in patients treated with oral hypoglycemic agents than in those with untreated hyperglycemia. That insulin treatment was associated with the highest risk of SVD in patients in the present study may also be consistent with this view, because insulin-treated type 2 DM patients were likely those with more difficult glycometabolic control, and therefore, severity of type 2 DM would be confirmed to play a key role in SVD. Alternatively, one can argue that patients treated with insulin were those more likely to have a relevant degree of insulin resistance,[39] whereas those treated with oral hypoglycemic agents, mainly insulin sensitizers,[40] were those more likely to have an improved insulin sensitivity. Therefore, on the basis of these considerations, a possible role for insulin resistance in the determinism of SVD cannot be excluded and, as alluded above, should be investigated specifically. The most recent glycemic goal recommended by the American Diabetes Association, selected on the basis of epidemiological and interventional studies, is in general an Hb A_{1c} level of <7%. Recently, a joint position statement of the American Heart Association with the American Diabetes Association and the American College of Cardiology also endorsed this Hb A_{1c} target as being associated with long-term reduction in the risk of diabetic macrovascular disease.[41] However, this issue, particularly in type 2 DM, remains debated, and in the same statement, the authors suggest that for some patients, individualized glycemic targets other than the general goal may be appropriate.

The findings of the present study would indicate the need for caution with regard to the choice of a biological prosthesis for cardiac valve replacement in patients with DM and advises the use of mechanical prostheses. Limited published data, however, do not support the superiority of mechanical valves versus tissue valves in patients with DM in terms of early or late postoperative results.[38] Furthermore, the influence of DM on valve-related complications after heart valve replacement that are usually linked to mechanical substitutes (eg, hemorrhage, thromboembolism, pannus formation) has also been poorly explored. Evaluation of postoperative complications in patients with artificial valves has suggested that DM may predispose to different patterns of adverse events after surgery according to the type of prosthesis used, particularly with regard to non–SVD-related events.[42] Therefore, the impact of what is currently known as the "diabetic disadvantage,"[43] particularly in patients requiring an artificial valve, warrants further studies to better elucidate whether and how type 2 DM might affect the patient postoperative outcome depending on the presence of a mechanical or a biological prosthesis.

On the basis of the present data, stricter metabolic control than recommended in the general diabetic population with a target Hb A_{1c} <6.5% might be advisable in patients with a bioprosthesis, and improved implementation of current guidelines[41] should be taken into consideration, particularly in patients with ITDM, who have an exceedingly high risk of SVD with respect to those with NITDM.

Interestingly, on the basis of the present data, patients with DM thought to be reasonably well controlled, according to current guidelines[42] (Hb A_{1c} <7% but >6.5%), or with mild DM (FPG slightly >140 mg/dL) still appear to bear a significant risk of valve degeneration. Moreover, SVD risk appears to be exceedingly high in ITDM with respect to NITDM. Finally, the use of oral hypoglycemic insulin-sensitizer agents may be hypothesized to be able to attenuate the risk of SVD in type 2 DM.

Study Limitations

This study retains the obvious limitations related to the multicenter and retrospective format of data collection. In particular, the clinical evaluation and procedures were performed at different centers by different surgeons. However, the main limitation of the present study is its retrospective nature.

To reduce the bias, we used the PS analysis, a technique that has been used in other recent clinical studies.[11,13] Nonetheless, inexact or incomplete matching might affect the results of the present study. However, we matched nondiabetic patients with 64.2% of patients with DM, with the worst matching having a PS difference of 0.016 and with a median standardized difference after matching of 0.003, which indicates a satisfactory matching. In addition, patients not undergoing active hypoglycemic treatment were categorized with respect to glucose tolerance on the basis of fasting glucose levels and not on their response to an oral glucose tolerance test. This may be another limitation inherent to the nature of the study in that the definitions, particularly of the no-DM group, may not be totally accurate. However, this approach is validated by other previous large cohort studies with cardiovascular end points.[44,45]

With regard to statin therapy, data were extremely variable with respect to doses, type, duration and onset of treatment, and adherence to therapy throughout the follow-up. Furthermore, no data were available about the actual effect of the ongoing lipid-lowering therapy. Interpretation of these findings, therefore, may be difficult in terms of the effects of such hypocholesterolemic agents on postoperative valve degeneration.

Unfavorable transvalvular flow conditions, for instance, generated by inappropriate balance between prosthetic size/design and patient anatomic or functional features (patient/prosthesis mismatch, among others), may play a critical role in SVD development.[32,33] This information was not reviewed in the present analysis and hence represents a limitation of our study. However, mechanically related SVD of tissue valves remains to be defined, because current knowledge on this topic and the elucidation of the factors and extent of such a pathogenetic phenomenon are still controversial.[34–37]

Finally, because of the retrospective nature of the study, which included patients operated on during a 21-year period, we failed to report information about the mode of failure (stenosis/regurgitation/mixed). It would have been important

to perform some analysis in this regard because the determinants of SVD may differ depending on the underlying mechanism. Finally, patients could not be followed up with the same follow-up interval but according to each individual institutional protocol.

Conclusions

We conclude that type 2 DM exerts a significant impact on postoperative outcome in patients undergoing cardiac valve replacement with tissue valves. Specifically, type 2 DM was shown to be a strong predictor of SVD. Moreover, risk appears to increase for patients treated with insulin, for those with Hb A_{1c} >6.5%, and for those with FPG >142 mg/dL. Therefore, even patients with apparently well-controlled or mild DM need to be included in the high-risk group for SVD. Whether postoperative strict (target Hb A_{1c} >6.5%) glycemic control in patients with type 2 DM undergoing tissue valve implantation should be implemented must be demonstrated in intervention studies.

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Disclosures

None.

References

1. Farivar RS, Cohn LH. Hypercholesterolemia is a risk factor for bioprosthetic valve calcification and explantation. *J Thorac Cardiovasc Surg*. 2003;126:969–975.
2. Nollert G, Miksch J, Kreuzer E, Reichart B. Risk factors for atherosclerosis and the degeneration of pericardial valves after aortic valve replacement. *J Thorac Cardiovasc Surg*. 2003;126:965–968.
3. Antonini-Canterin F, Zuppiroli A, Popescu BA, Granata G, Cervesato E, Piazza R, Pavan D, Nicolosi GL. Effect of statins on the progression of bioprosthetic aortic valve degeneration. *Am J Cardiol*. 2003;92:1479–1482.
4. Colli A, Gherli T, Mestres CA, Pomar JL. Degeneration of native and tissue prosthetic valve in aortic position: do statins play an effective role in prevention? *Int J Cardiol*. 2007;116:144–152.
5. Briand M, Pibarot P, Després JP, Voisine P, Dumesnil JG, Dagenais F, Mathieu P. Metabolic syndrome is associated with faster degeneration of bioprosthetic valves. *Circulation*. 2006;114:S512–S517.
6. Briand M, Lemieux I, Dumesnil JG, Mathieu P, Cartier A, Després JP, Arsenault M, Couet J, Pibarot P. Metabolic syndrome negatively influences disease progression and prognosis in aortic stenosis. *J Am Coll Cardiol*. 2006;47:2229–2236.
7. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2004;27:S5–S14.
8. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW; Councils of the American Association for Thoracic Surgery; Society of Thoracic Surgeons; European Association for Cardio-Thoracic Surgery; Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *J Thorac Cardiovasc Surg*. 2008;135:732–738.
9. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2492.
10. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004;109:2818–2825.
11. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiade M, Allman RM, Meleth S, Bourge RC. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J*. 2006;27:1431–1439.
12. Grunkemeier GL, Jamieson WR, Miller DC, Starr A. Actuarial versus actual risk of porcine structural valve deterioration. *J Thorac Cardiovasc Surg*. 1994;108:709.
13. Gray. RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Statist*. 1988;16: 1141–1154.
14. Austin PC. A tutorial case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. *Multivariate Behav Res*. 2011;46:119–151.
15. Lin DY, Wei LJ. The robust inference for the Cox proportional hazard model. *J Am Stat Assoc*. 1989;84:1074–1078.
16. Anderson WN. Algorithms for actuarial and actual analysis. In: Sloan FJ, ed. Proceedings of the Eight Annual Western Users of SAS Software Conference; September 2000; Scottsdale, AZ.
17. Bonow RO, Grundy SM, Howard B, Smith S Jr, Eckel R, Redberg R. Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary conference proceeding for healthcare professionals from a special writing group of the American Heart Association. *Circulation*. 2002;105:2231–2239.
18. Katz R, Budoff MJ, Takasu J, Shavelle DM, Bertoni A, Blumenthal RS, Ouyang P, Wong ND, O'Brien KD. Relationship of metabolic syndrome with incident aortic valve calcium and aortic valve calcium progression: the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes*. 2009;58:813–819.
19. Gring CN, Houghtaling P, Novaro GM, Roselli E, Smedira N, Banbury M, Blackstone E, Griffin BP. Preoperative cholesterol levels do not predict explant for structural valve deterioration in patients undergoing bioprosthetic aortic valve replacement. *J Heart Valve Dis*. 2006;15:261–268.
20. Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. *Am J Cardiovasc Drugs*. 2005;5:379–387.
21. Lorusso R, Pentiricci S, Raddino R, Scarabelli TM, Zambelli C, Villanacci V, Burattin A, Romanelli G, Casari S, Scelsi R, Giustina A. Influence of type 2 diabetes on functional and structural properties of coronary artery bypass conduits. *Diabetes*. 2003;52:2814–2820.
22. Rahimtoola SH, Braunwald E, eds. *Atlas of Heart Diseases: Valvular Heart Disease, Volume XI*. Philadelphia, PA: Current Medicine; 1997.
23. Human P, Zilla P. Characterization of the immune response to valve bioprostheses and its role in primary tissue failure. *Ann Thorac Surg*. 2001;71:S385–S388.
24. Shen M, Marie P, Farge D, Carpentier S, De Pollak C, Hott M, Chen L, Martinet B, Carpentier A. Osteopontin is associated with bioprosthetic heart valve calcification in humans. *C R Acad Sci III*. 1997;320:49–57.
25. Yeghiazaryan K, Bauriedel G, Schild HH, Golubnitschajal O. Prediction of degeneration of native and bioprosthetic aortic valves: issue-related particularities of diabetes mellitus. *Infect Disord Drug Targets*. 2008;8:88–99.
26. Hinokio Y, Suzuki S, Hirai M, Chiba M, Hirai A, Toyota T. Oxidative DNA damage in diabetes mellitus: its association with diabetic complications. *Diabetologia*. 1999;42:995–998.
27. Sardaş S, Yilmaz M, Oztok U, Cakir N, Karakaya AE. Assessment of DNA strand breakage by comet assay in diabetic patients and the role of antioxidant supplementation. *Mutat Res*. 2001;490:123–129.
28. Taniguchi N, Kaneto H, Asahi M, Takahashi M, Wenyi C, Higashiyama S, Fujii J, Suzuki K, Kayanoki Y. Involvement of glycation and oxidative stress in diabetic macroangiopathy. *Diabetes*. 45:S81–S83.
29. Krauss H, Koźlik J, Grzymisławski M, Sosnowski P, Mikrut K, Piatek J, Paluszak J. The influence of glimepiride on the oxidative state of rats with streptozotocin-induced hyperglycemia. *Med Sci Monit*. 2003;9:BR389–BR393.
30. Gazzaruso C, Solerte SB, Pujia A, Coppola A, Vezzoli M, Salvucci F, Valenti C, Giustina A, Garzaniti A. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: a potential protective role for statins and 5-phosphodiesterase inhibitors. *J Am Coll Cardiol*. 2008;51:2040–2044.
31. Flameng W, Herregods MC, Velcalsteren M, Herijgers P, Bogaerts K, Meuris B. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. *Circulation*. 2010;121:2123–2129.

32. Carpentier A. Factors affecting the fate of valvular bioprosthesis. *Circulation*. 2010;121:2083–2084.
33. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic position and its prevention. *J Am Coll Cardiol*. 2000;36:1131–1141.
34. Sakamoto Y, Yoshitake M, Naganuma H, Kawada N, Kinouchi K, Hashimoto K. Reconsideration of patient-prosthesis mismatch definition from the valve indexed effective orifice area. *Ann Thorac Surg*. 2010;99: 1951–1955.
35. Howell NJ, Keogh BE, Ray D, Bonser RS, Graham TR, Mascaro J, Rooney SJ, Wilson IC, Pagano D. Patient-prosthesis mismatch in patients with aortic stenosis undergoing isolated aortic valve replacement does not affect survival. *Ann Thorac Surg*. 2010;89:60–64.
36. Cotoni DA, Palac RT, Dacey LJ, O'Rourke DJ. Defining patient-prosthesis mismatch and its effect on survival in patients with impaired ejection fraction. *Ann Thorac Surg*. 2011;91:692–699.
37. Cohen RG, Bourne ET. Industry-generated charts fir the selection of stented aortic valve prostheses: clinical tool or marketing ploy? *Ann Thorac Surg*. 2011;91:1001–1002.
38. Halkos ME, Kilgo P, Lattouf OM, Puskas JD, Cooper WA, Guyton RA, Thourani VH. The effect of diabetes mellitus on in-hospital mortality and long-term outcomes after heart valve operations. *Ann Thorac Surg*. 2010; 90:124–130.
39. Gazzaruso C, Solerte SB, De Amici E, Mancini M, Pujia A, Fratino P, Giustina A, Garzaniti A. Association of the metabolic syndrome and insulin resistance with silent myocardial ischemia in patients with type 2 diabetes mellitus. *Am J Cardiol*. 2006;97:236–239.
40. Mazziotti G, Bossoni S, Orini S, Salimbeni P, Gazzaruso C, Solerte BS, Vescovi P, Romanelli G, Giustina A. Treatment with metformin is protective against limitations in instrumental activities of daily living in older subjects with type 2 diabetes mellitus. *J Am Geriatr Soc*. 2009;57: 562–564.
41. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation.* 2009;119:351–357.
42. Lee JH, Burner KD, Fealey ME, Edwards WD, Tazelaar HD, Orszulak TA, Wright AJ, Baddour LM. Prosthetic valve endocarditis: clinicpathological correlates in 122 surgical specimens from 116 patients (1985–2004). *Cardiovasc Pathol*. 2011;20:26–35.
43. Brown JR, Edwards FH, O'Connor GT, Ross CS, Furnary AP. The diabetic disadvantage: historical outcomes measures in diabetic patients undergoing cardiac surgery. *Semin Thorac Cardiovasc Surg*. 2006;18: 281–288.
44. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol*. 2010; 55:1310–1317.
45. Fisman EZ, Motro M, Tenenbaum A, Boyko V, Mandelzweig L, Behar S. Impaired fasting glucose concentrations in nondiabetic patients with ischemic heart disease: a marker for a worse prognosis. *Am Heart J*. 2001;141:485–490.

CLINICAL PERSPECTIVE

Biological prostheses are increasingly implanted to treat disparate cardiac valve diseases. Postoperative structural valve degeneration represents the most relevant drawback of such artificial valves, sometimes leading to substantial leaflet tissue derangement, clinical deterioration and ultimately, reoperation. The causes and pathogenetic mechanisms of artificial valve structural impairment are not yet fully understood. Atherosclerosis-related risk factors have been suggested recently, through analysis of postoperative outcome in limited patient experiences, to play a role in postimplantation bioprosthetic failure. This multicenter retrospective study sought to investigate specifically the early and long-term influence of type 2 diabetes mellitus in terms of composite outcome in patients undergoing bioprosthetic heart valve implantation in the aortic or mitral position. Propensity score analysis enabled a 1:1 match in 2226 diabetic and nondiabetic subjects among 6184 patients submitted to cardiac valve replacement with biological valves during a 21-year period. In this study, type 2 diabetes mellitus was shown to be an independent predictor of unfavorable outcome, either in terms of reduced life expectancy or in terms of structural bioprosthetic valve degeneration, with the insulin-treated subjects showing the most unfavorable postoperative results. Furthermore, diabetes mellitus was shown to negatively affect postoperative tissue valve performance, irrespective of other associated cardiovascular risk factors. Additional studies are needed to disclose the pathogenetic mechanisms by which such a metabolic disorder may affect the structural integrity of tissue valves and to investigate methods to reduce such an adverse event. Meanwhile, strict clinical surveillance is advised on the basis of the currently witnessed higher rate of structural valve degeneration in diabetic patients submitted to cardiac valve replacement with a biological prosthesis.