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Anatomic and Procedural Predictors of Paravalvular Aortic Regurgitation After Implantation of the Medtronic CoreValve Bioprosthesis

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Objectives The purpose of this study was to determine the predictors of aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI).

Background TAVI has been associated with a high rate of paravalvular regurgitation, usually mild. Nevertheless, moderate to severe regurgitations still occur and may have negative clinical consequences.

Methods Fifty patients with severe aortic stenosis were recruited and underwent successful TAVI with the Medtronic CoreValve bioprosthesis through the transfemoral route. The end point of this study is the early occurrence of significant AR, defined as the occurrence of grade II or more AR by post-procedural aortography.

Results The study population's mean age was 80.5 ± 7.9 years, with a mean aortic valve area of 0.64 ± 0.17 cm^2. Post-procedural AR was absent in 3 patients and was grade I in 27 patients, grade II in 13 patients, and grade III in 7 patients. Using univariate analysis, the chance of significant AR increased with increasing angle of left ventricular outflow tract to ascending aorta (∠LVOT-AO) (odds ratio: 1.24, $p < 0.001$). For the depth of the device in relation to the noncoronary cusp, there was a minimum chance of AR corresponding to depth = 9.5 mm (odds ratio: 1.1, $p = 0.01$). Using multivariate analysis, we found a greater chance of significant AR with a greater angle (odds ratio: 1.24, $p = 0.001$), and that the chance of significant AR is a minimum when depth of the device in relation to the noncoronary cusp is ~10 mm (odds ratio: 1.1, $p = 0.024$). A predictive model was generated, and if $2 \times$∠LVOT-AO + (depth to noncoronary cusp − 10)$^2 \geq 50$, the likelihood of occurrence of significant AR could be predicted with a sensitivity of 85% and a specificity of 87%.

Conclusions The occurrence of significant AR after TAVI can be predicted by anatomic and procedural variables. A model such as that presented can be used to select suitable patients for this procedure and guide operators during implantation of the device. (J Am Coll Cardiol 2010;56:1623–9) © 2010 by the American College of Cardiology Foundation

Trivial or mild paraprosthetic regurgitation is frequent after surgical aortic valve replacement but does not have significant impact on short- and long-term clinical outcomes (1). However, more severe paraprosthetic regurgitations might cause hemodynamic deterioration or require reintervention (1). Similarly, paravalvular aortic regurgitation (AR) is frequent after transcatheter aortic valve implantation (TAVI) using the Medtronic CoreValve bioprosthesis (Medtronic, Minneapolis, Minnesota), but is usually mild (2). Importantly, moderate to severe regurgitations do occur and may have relevant clinical consequences; nevertheless, the anatomic and procedure-related predictors of this complication after implantation of the CoreValve bioprosthesis have not been specifically studied. Therefore, we sought to shed light on these predictors and present a preliminary predictive model for this complication.

Methods

Study design. Fifty patients with severe symptomatic aortic stenosis (aortic valve area [AVA] <1 cm^2 or indexed AVA <0.6 cm^2/m^2) were recruited and underwent successful TAVI using the Medtronic CoreValve bioprosthesis through the transfemoral route. Clinical and anatomic selection criteria and device size selection were in line with the published investigational study for the third-generation (18-F) CoreValve device (2). Description of the device

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Abbreviations and Acronyms

AR = aortic regurgitation
AVA = aortic valve area
NCC = noncoronary cusp
RAO = right anterior oblique
TAVI = transcatheter aortic valve implantation
TEE = transesophageal echocardiography
∠LVOT-AO = angle of left ventricular outflow tract to ascending aorta

and technical aspects of the procedure have been previously published (2).

The end point of this study is the early occurrence of significant AR, defined as grade II or greater AR, evaluated immediately after valve implantation using qualitative angiography with visual estimation of the concentration of contrast medium in the left ventricle (3). The study protocol was approved by the ethics committee of our institution. All patients gave informed consent.

Echocardiographic assessment. Transthoracic echocardiography was performed before and immediately after valve implantation. The severity of aortic stenosis was assessed by the mean transvalvular gradient, and AVA calculated with the continuity equation (4). The AR was quantified using color-flow techniques that included measurement of the width and area of the AR jet at the junction of the left ventricular outflow tract (LVOT) and the aortic annulus in the parasternal long-axis view in relation to the maximum width and area of the LVOT at the same location (5). The AR was graded as I for trivial/mild, II for moderate, III for moderate to severe, and IV for severe (6,7). The aortic valve annulus diameter (mm) was measured using transesophageal echocardiography (TEE) in the long-axis view. Aortic valve calcification relied on visualization of bright echoes at the base of the aortic valve leaflets using TEE, and was graded as mildly calcified when calcification appeared as small isolated spots, moderately calcified when multiple larger spots were present, and heavily calcified when extensive thickening and calcification of all cusps was seen (8). The thickness of both the noncoronary cusp (NCC) and the right coronary cusp was measured in the long-axis view using TEE. Moreover, distribution and localization (symmetric or asymmetric) of calcification and number of cusps (tricuspid or bicuspid) were reported. Noteworthy, bicuspid aortic valves were excluded during screening of patients according to the anatomic boundaries that guide patient selection (9). The annulus was considered oval if the difference between the anteroposterior diameter and the transverse diameter was >2 mm measured in short-axis view using TEE. Postoperatively, the presence, degree, and type (paravalvular vs. transvalvular) of AR were recorded in all patients using transthoracic echocardiography.

Angiographic assessment. All patients underwent left ventriculography in 30° right anterior oblique (RAO) and 50° left anterior oblique projections and aortic root injection in 50° left anterior oblique within 1 week before the procedure together with coronary angiography. The sinus of Valsalva diameter was measured as the largest width (mm) of the aortic root at the level of the aortic sinuses. The diameter of the ascending aorta was measured 45 mm above the plane of the aortic annulus. Immediately after valve deployment, aortography, to assess the degree of AR, in 30° RAO and 50° left anterior oblique projections was recorded over several cardiac cycles.

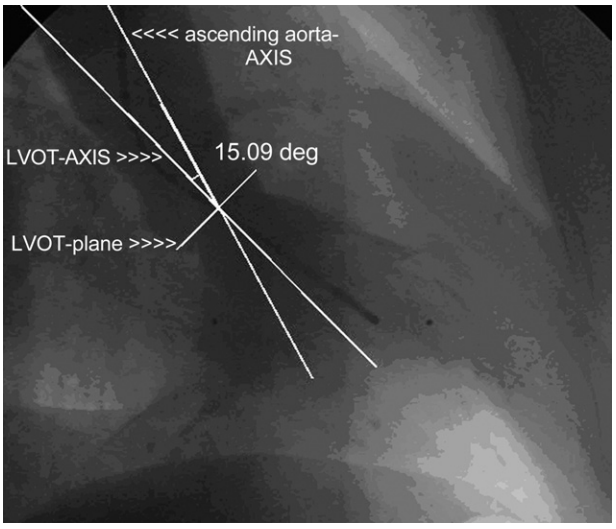

Figure 1 **Measurement of ∠LVOT-AO Using Left Ventriculography in RAO 30°**

The ∠LVOT-AO is the angle between the axis of the first 4 cm of the ascending aorta (AO), representing the contact surface with the upper part of the bioprosthesis, and the left ventricular outflow tract (LVOT) axis, representing the landing zone of the prosthesis. This angle was assessed using left ventriculography in right anterior oblique (RAO) projection 30° during preparation of the patients for the procedure.

Angle of LVOT to ascending aorta measurement (∠LVOT-AO). We considered the angle between the axis of the first 4 cm of the ascending aorta representing the contact surface with the upper part of the bioprosthesis and the LVOT axis representing the landing zone of the prosthesis. This angle was assessed using left ventriculography in RAO 30° during preparation of the patients for the procedure. The ∠LVOT-AO was measured using commercially available software (JiveX Dicom Viewer, version 4.0.2, VISUS Technology Transfer GmbH, Bochum, Germany) as follows: the LVOT-axis was considered as a line perpendicular to the plane of the LVOT; the aorta-axis is the line passing in the first 4 cm and parallel to the aortic wall (Fig. 1).

Evaluation of device position. Depth of final device position in the LVOT was measured using a final aortogram of the deployed bioprosthesis in RAO projection, displaying the aortic valve in optimal alignment with all 3 leaflets visible in the same plane. The depth of delivery was defined as the distance from the native aortic annular margin on the side of the NCC to the most proximal edge on the corresponding side (deepest in the left ventricle) of the deployed stent-frame (Fig. 2). In addition, the depth of

delivery from the annular margin of the left coronary cusp to the corresponding side was measured (Fig. 2).

Statistical analysis. Statistical analysis was done using Minitab software (Minitab, Release 13.1, State College, Pennsylvania). Data were expressed as mean ± SD or percent. Comparisons of baseline and procedure-related characteristics of patients according to AR ≥2 or <2 were performed using the *t* test or chi-square test as appropriate. All potential predictors for the occurrence of significant AR were studied using univariate logistic regression analysis. Some relationships were not completely linear, yet a curvilinear and a quadratic relationship could exist, so we have also checked whether a quadratic relationship with an intermediate optimum in each of the variables is present, but we have only reported details of the quadratic term when it was significant. Promising variables in the univariate analysis ($p < 0.1$) were included in a multivariate logistic regression with a backward selection approach, with a significant level of $p < 0.05$. Adjusted odds ratio is presented with 95% confidence interval. The logistic regression model was used to determine a preliminary prognostic score for AR; the receiver-operating characteristic curve for this score (i.e., a plot of sensitivity against 1-specificity for each cut-off value) was plotted, the area under the curve determined, and a 95% confidence interval for the area under the curve found using the bootstrap method. The correlation between angiographic and echocardiographic grading of AR was studied using Spearman rho correlation.

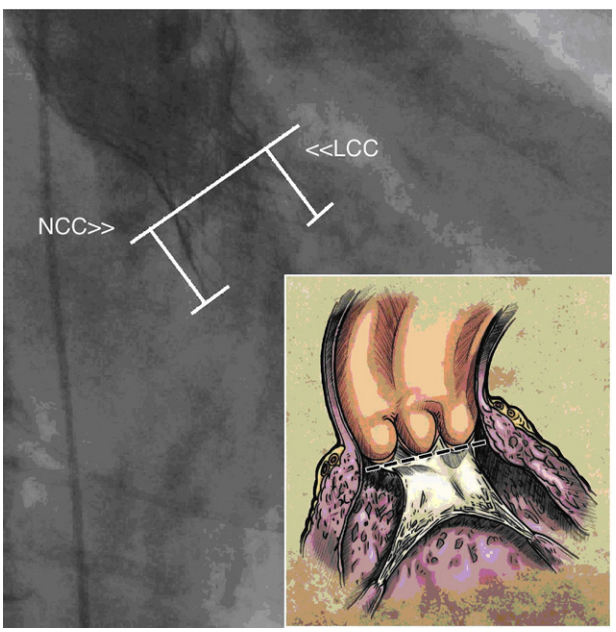

Figure 2 **Measurement of Depth of Medtronic CoreValve Bioprosthesis Using Fluoroscopy in Relation to NCC and LCC**

The depth of the final device position in the left ventricular outflow tract measured using the final aortogram of the deployed bioprosthesis in the right anterior oblique projection is shown. The depth of delivery is defined as the distance from the native aortic annular margin on the side of both the noncoronary cusp (NCC) and the left coronary cusp (LCC) to the most proximal edge on the corresponding side of the deployed stent-frame. Figure was created by Craig Skaggs.

Results

Baseline characteristics. Baseline clinical, echocardiographic, angiographic, and procedural characteristics are shown in Table 1. All 50 patients (age 80.5 ± 7.9 years; 40% males) had severe aortic stenosis (mean AVA 0.64 ± 0.17 cm^2).

Early assessment of AR after TAVI. Angiographic grading of AR revealed absence of AR in 3 patients (6%), grade I in 27 patients (54%), grade II in 13 patients (26%), and grade III in 7 patients (14%). Therefore, according to post-procedural angiography, 20 patients had significant AR (40%). Post-procedural transthoracic echocardiography showed absence of paravalvular AR in 9 patients (18%), grade I in 24 patients (48%), grade II in 13 patients (26%), and grade III in 4 patients (8%). No cases with grade IV or transvalvular AR were reported. The echocardiographic grading of AR correlated well with the angiographic grading ($r = 0.8$, $p < 0.001$) (Fig. 3). The mean value of ∠LVOT-AO was significantly higher in patients with significant AR compared with patients with no/mild AR (25.6 ± 8.2° vs. 15.7 ± 4.7°, respectively). The mean distance from the ventricular end of the frame of the prosthesis to the lower edge of both the NCC and the left coronary cusp was comparable in both groups (Table 1).

Predictors of significant AR. Univariate and multivariate predictors of significant post-procedural AR are shown in Table 2. Using univariate analysis, we found a significant evidence of an increased chance of significant AR with increasing ∠LVOT-AO ($p < 0.001$). For the depth of the device in relation to the NCC, there was a quadratic relationship, with the minimum chance of significant AR corresponding to depth = 9.5 mm. There was also a quadratic relationship for the depth of the device in relation to the left coronary cusp, with the minimum chance of significant AR corresponding to depth = 10.42 mm. The occurrence of significant AR was unrelated to septum thickness, shape of annulus, ascending aorta diameter, pulmonary hypertension, degree of leaflet calcification, pattern of calcium distribution, annulus diameter, valve size, and baseline AR. Using multivariate analysis, we found a greater chance of significant AR with greater angle, and that the chance of significant AR is a minimum when depth of the device in relation to NCC is ~10 mm, and tends to take larger values when the depth is either smaller or larger.

Predictive model for occurrence of significant AR. The test suggested by the preceding analysis is as follows: test positive if $0.21314 \times$ ∠LVOT-AO $- 1.8242 \times$ depth to NCC $+ 0.091 \times (\text{depth to NCC})^2 \geq k$. The number k is the cut-off point. To decide on a good value for k, we plotted a receiver-operating characteristic curve and looked

for values of k where the curve is close to the point (0, 1) (Fig. 4). This method suggested using $k = -4.0459$, so that the test is positive if: $0.21314 \times \angle$LVOT-AO $- 1.8242 \times$ depth $+ 0.091 \times$ (depth to NCC)$^2 \geq -4.0459$, with a sensitivity of 90% and a specificity of 86.7%. However, this test is rather complicated. We did simplify the model to the following: $2 \times \angle$LVOT-AO + (depth to NCC $- 10)^2$. An appropriate cut-off point is 50, so that the test is positive if $2 \times \angle$LVOT-AO + (depth to NCC $- 10)^2 \geq 50$. With this test, we obtained a sensitivity of 85% and a specificity of 86.7%. The cost of simplifying was to reduce the sensitivity a little. The relationship between the calculated score and the degree of post-procedural AR in the whole cohort is shown in Figure 5.

To address the contribution of the quadratic fit for depth to NCC over ∠LVOT-AO, we then looked at the sensitivity and specificity of the test just based on the angle. This resulted in a sensitivity of 85% and a specificity of 70% (compared with 90% and 87%, respectively, when depth to NCC is included). Therefore, it seems that including depth to NCC does improve the test to a worthwhile extent, especially regarding its specificity.

Discussion

This study represents the first step toward a predictive model for the occurrence of significant AR after implantation of the Medtronic CoreValve bioprosthesis. The results suggest that the occurrence of significant AR is strongly related to the ∠LVOT-AO and the final depth of the bioprosthesis.

The only study that addressed the predictors for AR after TAVI was conducted by Detaint et al. (10), who related the occurrence of significant AR to prosthesis/annulus discongruence in patients treated with the Edwards-Sapien valve. The Medtronic CoreValve bioprosthesis is a long device (53 mm for the 26-mm inflow device, and 55 mm for the 29-mm

Table 1 Baseline Clinical, Echocardiographic, Angiographic, and Procedural Characteristics of 50 Patients Who Underwent Successful Implantation of the Medtronic CoreValve Bioprosthesis

Characteristics	All (n = 50)	AR <2 (n = 30)	AR ≥2 (n = 20)	p Value
Age, yrs	80.52 ± 7.85	80.50 ± 7.99	80.55 ± 7.83	0.98
Height, cm	169.96 ± 8.52	170.96 ± 8.78	168.45 ± 8.10	0.31
Weight, kg	76.66 ± 15.09	78.60 ± 17.04	73.75 ± 11.36	0.27
BSA, m^2	1.91 ± 0.22	1.94 ± 0.25	1.87 ± 0.17	0.22
BMI, kg/m^2	26.56 ± 4.66	26.93 ± 5.31	26.00 ± 3.52	0.49
Echocardiographic parameters				
Mean pressure gradient, mm Hg	50.38 ± 17.22	50.23 ± 14.81	50.60 ± 20.70	0.94
AVA, cm^2	0.64 ± 0.17	0.64 ± 0.18	0.64 ± 0.16	0.92
iAVA, cm^2/m^2	0.34 ± 0.09	0.33 ± 0.10	0.34 ± 0.09	0.72
Annulus, mm	23.26 ± 1.41	23.50 ± 1.48	22.90 ± 1.25	0.14
Degree of leaflet calcification				
Mild/moderate	27 (54.0%)	17 (56.7%)	10 (50.0%)	0.64
Severe	23 (46.0%)	13 (43.3%)	10 (50.0%)	
Asymmetric calcification	28 (56.0%)	16 (53.3%)	12 (60.0%)	0.62
NCC thickness, mm	5.49 ± 1.85	5.09 ± 1.63	6.11 ± 2.02	0.055
RCC thickness, mm	5.61 ± 1.83	5.38 ± 1.70	5.97 ± 2.00	0.27
IVS thickness, mm	14.26 ± 2.91	13.73 ± 2.60	15.05 ± 3.23	0.12
Baseline AR grade	0.88 ± 0.69	0.80 ± 0.66	1.00 ± 0.72	0.32
Annulus shape, oval	19 (38.0%)	12 (40.0%)	7 (35.0%)	0.73
Ejection fraction, %	46.96 ± 13.14	47.30 ± 13.38	46.45 ± 13.09	0.82
LVEDD, mm	52.36 ± 10.40	52.66 ± 8.89	51.90 ± 12.56	0.80
Angiographic and procedural parameters				
∠LVOT-AO	19.66 ± 7.94	15.70 ± 4.71	25.60 ± 8.19	<0.01
Sinus of Valsalva diameter, mm	29.74 ± 3.37	29.73 ± 3.40	29.75 ± 3.41	0.98
Ascending aorta diameter, mm	30.04 ± 4.47	30.06 ± 4.95	30.00 ± 3.75	0.95
Depth to NCC, mm	10.42 ± 3.72	9.75 ± 2.49	11.43 ± 4.94	0.17
Depth to LCC, mm	11.35 ± 3.72	11.00 ± 2.69	11.81 ± 4.93	0.47
Balloon diameter, mm	22.34 ± 1.61	22.43 ± 1.73	22.20 ± 1.43	0.62
Valve size				
29 mm	20 (40.0%)	13 (43.3%)	7 (35.0%)	0.57
26 mm	30 (60.0%)	17 (56.7%)	13 (65.0%)	0.56
Post-procedural AVA, cm^2	1.89 ± 0.15	1.88 ± 0.15	1.90 ± 0.15	0.65
Post-procedural iAVA, cm^2/m^2	1.00 ± 0.14	0.99 ± 0.14	1.01 ± 0.15	0.68

Values are mean ± SD or n (%).

AR = aortic regurgitation; AVA = aortic valve area; BMI = body mass index; BSA = body surface area; iAVA = indexed aortic valve area; IVS = interventricular septum; LCC = left coronary cusp; LVEDD = left ventricular end-diastolic diameter; ∠LVOT-AO = angle between ascending aorta and left ventricular outflow tract; NCC = noncoronary cusp; RCC = right coronary cusp.

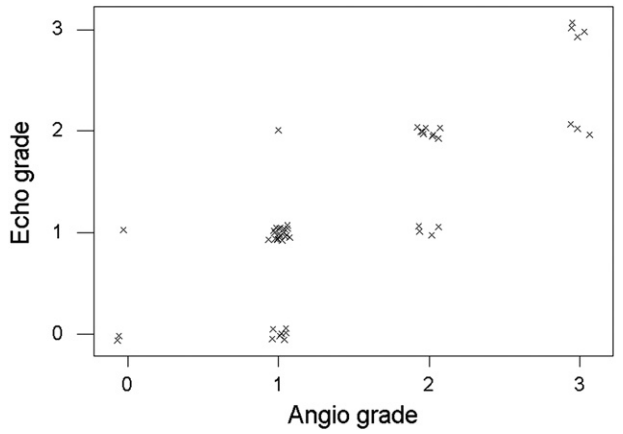

Figure 3 **Correlation Between Angiographic and Echocardiographic Grading of Post-Procedural AR**

Using Spearman rho correlation, the angiographic grading of aortic regurgitation (AR) correlated well with the echocardiographic grading ($r = 0.8$, $p < 0.001$). "Jitter" has been used to show multiple plots.

inflow device) and allows for a wide range of implant depths. Moreover, the hemodynamic performance of the prosthesis within the aortic annulus may depend on a number of factors relating to the ascending aorta, the LVOT, annulus shape, degree of contact with the aortic annulus, degree of calcification and thickness of the aortic valve leaflets, and the ability of the nitinol stent to provide a radial force. It is quite obvious that these parameters in combination determine the hemodynamic results of implantation.

In our series, we found that the ∠LVOT-AO is the strongest independent determinant contributing to the occurrence of significant AR after implantation of the CoreValve bioprosthesis. A greater angle may affect the radial force of the prosthesis and its ability to completely seal the paravalvular space. Moreover, nitinol stent deformation, helped by the stiffness of the aorta and the calcific nature of the aortic root and valve, may be another factor in this context. The net result will be inability of the prosthesis to seal the gap between it and the aortic annulus, causing paravalvular AR.

The depth of the device is also an important factor. Very deep implantation results in severe AR, because the covered skirt would be situated below the native annulus, allowing blood to regurgitate through the holes of the uncovered portion of the stent frame (11). Likewise, high implantation results in malapposition of the prosthesis, allowing blood to flow in the space between prosthesis and annulus. Jilaihawi et al. (11) recently underscored the importance of final device depth in avoiding patient-prosthesis mismatch. They defined an "optimal" depth of 5 mm to 10 mm below the native NCC as measured on fluoroscopy. We have found that the optimal depth of the device that correlates with a minimal chance of AR is ~10 mm; deeper or shallower implantations result in more degrees of AR. Therefore, we believe that implantation of the device at that depth can result in optimal hemodynamics, taking into consideration the

Table 2 **Predictors of Significant Aortic Regurgitation in 50 Patients After Implantation of the Medtronic CoreValve Bioprosthesis**

Variable	Estimated Coefficient, β_i	Standard Error	OR (95% CI)	p Value
Univariate regression model				
∠LVOT-AO	0.21	0.06	1.24 (1.10–1.39)	<0.01
Depth to NCC, mm	−1.76	0.71	0.02 (0.04–0.70)	0.01
Depth to NCC squared	0.09	0.03	1.10 (1.02–1.18)	0.01
Depth to LCC, mm	−1.33	0.63	0.26 (0.08–0.90)	0.035
Depth to LCC squared	0.06	0.03	1.07 (1.01–1.13)	0.03
NCC thickness, mm	0.32	0.17	1.38 (0.98–1.95)	0.07
Asymmetric calcification	−0.21	0.37	0.81 (0.40–1.67)	0.57
Ejection fraction, %	−0.005	0.02	0.99 (0.95–1.04)	0.82
Degree of leaflet calcification	0.23	0.49	1.26 (0.49–3.28)	0.63
IVS diameter, mm	0.16	0.11	1.18 (0.95–1.46)	0.13
Ascending aorta diameter, mm	−0.004	0.06	1.00 (0.88–1.13)	0.96
Sinus of Valsalva diameter, mm	0.002	0.09	1.00 (0.85–1.19)	0.99
LVEDD diameter, mm	−0.01	0.03	0.99 (0.94–1.05)	0.80
Baseline AR	0.43	0.43	1.54 (0.66–3.60)	0.32
Oval annulus	0.39	0.62	1.48 (0.44–5.04)	0.53
Valve size	−0.35	0.59	0.70 (0.22–2.27)	0.56
Multivariate regression model for the independent predictors				
∠LVOT-AO	0.21	0.06	1.24 (1.09–1.41)	<0.01
Depth to NCC, mm	−1.82	0.85	0.16 (0.03–0.85)	0.03
Depth to NCC squared	0.09	0.04	1.10 (1.01–1.19)	0.02

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

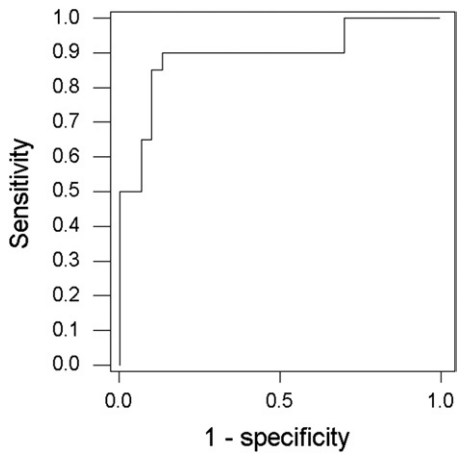

Figure 4 **ROC Curve for Predictive Model for Occurrence of Post-Procedural AR**

The receiver-operating characteristic (ROC) curve of the predictive model for the occurrence of significant post-procedural aortic regurgitation (AR) is shown. Area under the curve: 0.89; 95% confidence interval (obtained using the bootstrap method): 0.78 to 0.98. To decide on a good value for k, an ROC curve was plotted, and we looked for values of k where the curve is close to the point (0, 1). This method suggested using $k = -4.0459$, so that the test is positive if: $0.21314 \times \angle$LVOT-AO $- 1.8242 \times$ depth $+ 0.091 \times$ (depth to NCC)$^2 \geq -4.0459$, with a sensitivity of 90% and a specificity of 86.7%. $\angle$LVOT-AO = angle of left ventricular outflow tract to ascending aorta; NCC = noncoronary cusp.

$\angle$LVOT-AO. Moreover, in this sense, we found that a difference of ~3.4 mm in the depth above or below the NCC is equivalent to an angle difference of 5° (data not shown).

Clinical implications. To prevent AR after TAVI, first, we should pay more attention to the $\angle$LVOT-AO, which could be simply measured during the pre-procedural preparatory phase. Second, we should try to deploy the prosthesis as discussed in the preceding text. Using imaging modalities like TEE in addition to fluoroscopy may be warranted (12). Based on the data presented and the predictive model we developed, patients with angles >25° may be offered other options. In patients with smaller angles, the final depth of the implanted bioprosthesis should be properly checked.

So far, there is no study that has addressed the short- and long-term clinical impact of significant AR after TAVI. In an experimental model, Azadani et al. (13) found that, owing to the paravalvular leaks, TAVI imposes a significantly higher workload on the left ventricle than an equivalently sized surgically implanted bioprosthesis. Future studies with long-term follow-up periods are needed to study the clinical impact of this complication.

Study limitations. The values for sensitivity and specificity of the predictive model are quite promising. However, we need to be aware that we have tailored the predictive model specifically to this dataset, and that the sensitivity and specificity for the same test used on independent data may be different. Although the multivariable model has been obtained using a standard method and seems in accord with clinical expectations, further studies are required to confirm its form. However, it is often the case that models with entirely different sets of prognostic variables can provide almost as good a fit. Another limitation is that the $\angle$LVOT-AO was not determined reproducibly or blindly, and the model requires a blinded analysis in another dataset for confirmation. Finally, owing to different designs of the available TAVI devices, the presented model is applied only to the Medtronic CoreValve bioprosthesis and not to other devices.

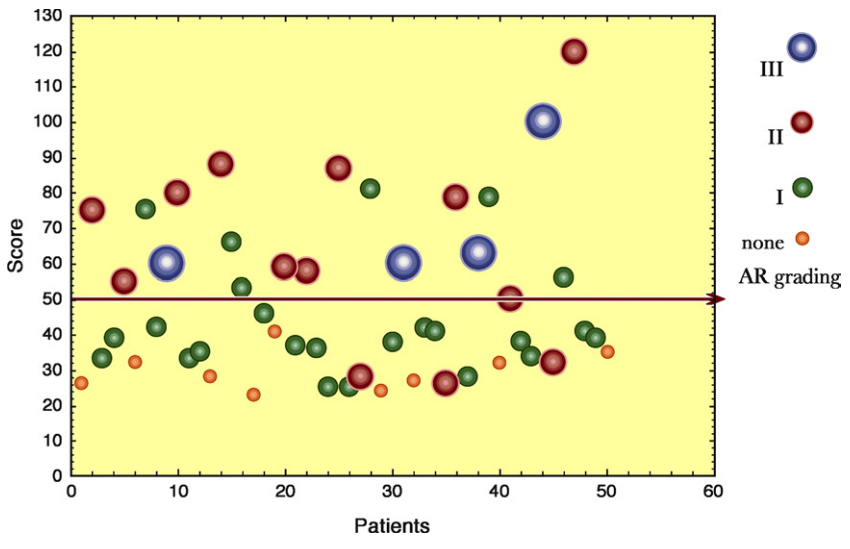

Figure 5 **Scatter Plot of Calculated Score and Degree of AR in the Whole Cohort**

Of note, all patients with aortic regurgitation (AR) grade III **(blue spheres)** and all but 3 patients with AR grade II **(red spheres)** have a score ≥50. Conversely, 6 patients with AR grade I **(green spheres)** have a score ≥ 50. **Orange spheres** indicate no AR.

Conclusions

The occurrence of significant AR after TAVI remains a safety concern. We found that occurrence of AR after TAVI using the Medtronic CoreValve bioprosthesis depends on an interaction between anatomic and procedural variables. A model such as that presented, after validation in larger series, could be used to select the suitable patients for this procedure and guide the operators during implantation of the device.

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