Relationship Between QT Interval and Outcome in Low-Flow Low-Gradient Aortic Stenosis With Low Left Ventricular Ejection Fraction

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Background—QT interval has been shown to be associated with cardiovascular events. There is no data regarding the association between QT interval and left ventricular (LV) function and prognosis in patients with low LV ejection fraction (LVEF), low-flow, low-gradient aortic stenosis (LF-LG AS). We aimed to examine the relationship between corrected QT interval (QTc) and LV function and outcome in these patients.

Methods and Results—Ninety-three patients (73±10 years; 74% men) with LF-LG AS (mean gradient <40 mm Hg and indexed aortic valve area ≤0.6 cm²/m²) and reduced LVEF (≤40%) were prospectively included in this analysis and 63 of them underwent aortic valve replacement within 3 months following inclusion. Prolonged QTc was defined as QTc >450 ms in men and >470 ms in women. LV global longitudinal strain was measured by speckle tracking and expressed in absolute value (%). QTc correlated with the following: global longitudinal strain (r=−0.40, P=0.005), LVEF (r=−0.27, P=0.02), stroke volume (r=−0.35, P=0.007), and B-type natriuretic peptide (r=−0.45, P=0.0006). During a median follow-up of 2.0 years, 49 patients died. Prolonged QTc was associated with a 2-fold increase in all-cause mortality (hazard ratio=2.05; P=0.01) and cardiovascular mortality (hazard ratio=1.89; P=0.04). In multivariable analysis adjusted for EuroSCORE, aortic valve replacement, previous myocardial infarction, LVEF, and ß-blocker medication, prolonged QTc was independently associated with all-cause mortality (hazard ratio=2.56; P=0.008) and cardiovascular mortality (hazard ratio=2.50; P=0.02).

Conclusions—In patients with LF-LG AS and reduced LVEF, longer QTc interval was associated with worse LV function and increased risk of death. Assessment of QTc may provide a simple and inexpensive tool to enhance risk stratification in LF-LG AS patients.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT 01835028. (J Am Heart Assoc. 2016;5: e003980 doi: 10.1161/JAHA.116.003980)

Key Words: aortic stenosis • B-type natriuretic peptide • Doppler-echocardiography • left ventricular function • low-flow low gradient • outcome • QT interval • risk stratification

Patients with low-flow, low-gradient aortic stenosis (LF-LG AS) and reduced left ventricular ejection fraction (LVEF) have a poor prognosis with conservative therapy and a high operative mortality with aortic valve replacement (AVR).1–7 Risk stratification is essential in these patients to optimize therapeutic management and improve outcomes. Several Doppler echocardiographic parameters have been shown to be helpful for risk stratification and clinical decision making.4,8,9 However, few data are available with regard to the usefulness of electrocardiogram (ECG) risk stratification in these patients.10,11 Previous studies reported that prolonged QT interval is associated with incident cardiovascular events in patients with history or at high risk of coronary artery disease, as well as in apparently healthy subjects12 even though the mechanisms underlying this association remain unclear. We hypothesize that prolonged QT is associated with a more advanced stage of myocardial fibrosis and dysfunction and worse outcome. The aims of this study were to examine (1) the relationship between the QT interval and
echocardiographic parameters and blood biomarkers of left ventricular (LV) function and (2) the impact of prolonged QT interval on mortality in patients with LF-LG AS and low LVEF.

Methods

Study Protocol

For the purpose of this study, we analyzed the data of patients with LF-LG AS (ie, mean gradient <40 mm Hg, indexed aortic valve area [AVAi] ≤0.6 cm²/m²) with reduced LVEF (≤40%) who were prospectively recruited at Quebec Heart and Lung Institute in the context of the True Or Pseudo-severe Aortic Stenosis (TOPAS) observational study (Clinical Trial Registration: https://www.clinicaltrials.gov. Unique identifier: NCT 01835028). Patients were excluded if they presented the following criteria: (1) >mild aortic regurgitation, (2) >mild organic mitral regurgitation, (3) >mild mitral stenosis, and (4) atrial fibrillation/flutter. The study was approved by the Ethics Committee of the Quebec Heart and Lung Institute, and a written informed consent was obtained according to institutional review board approval for the prospective study.

Clinical Data

Clinical data included age, sex, height, weight, body surface area, systolic and diastolic blood pressure, New York Heart Association (NYHA) functional class, documented diagnosis of traditional cardiovascular risk factors and comorbidities such as hypertension, diabetes mellitus, dyslipidemia, smoking, and chronic obstructive pulmonary disease, coronary artery disease (history of myocardial infarction or ≥50% coronary artery stenosis on coronary angiography), and logistic EuroSCORE. Medication was recorded at the time of echocardiography.

Electrocardiogram

At the time of the baseline echocardiography examination, a standard 12-lead ECG was obtained with a 10 mm/mV calibration and a speed of 25 mm/s. The QRS interval was measured from the onset of the Q wave, or R wave if no Q wave was visible, to the J point. The diagnosis of intraventricular conduction abnormalities was based on recommendations from the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society for the standardization and interpretation of ECGs. The QT interval was measured from the onset of the QRS to the end of the T wave. The QT interval was corrected for rate using the Bazett formula and prolonged QT interval was defined as QTc >450 ms in men and >470 ms in women. In patients with ventricular paced rhythm, 50 ms was subtracted from the corrected QTc.

Doppler-Echocardiography

All patients underwent a comprehensive transthoracic Doppler-echocardiographic examination using a commercially available ultrasound system (Vivid 7, GE Healthcare or IE33, Philips). All Doppler echocardiographic examinations were performed at rest and at dobutamine stress as previously described. The dobutamine infusion protocol consisted of 8-minute increments of 2.5 to 5 μg/kg per minute up to a maximum dosage of 20 μg/kg per minute. A minimum of 3 consecutive cycles were recorded. Continuous-wave Doppler of the aortic valve velocity spectrum, as well as pulsed-wave Doppler of the LV outflow tract velocity spectrum, were recorded at rest and at each step of the dobutamine protocol. LVEF was measured by the biplane Simpson method. Stroke volume (SV) was measured in the LV outflow tract and was indexed to body surface area (SIV). AS severity was assessed using the projected AVA at a normal transvalvular flow rate (AVAproj) and was calculated with the simplified method: AVAProj=AVArest+(ΔAVA/ΔQ̇)×(250−Q̇rest), where Q̇ is mean transvalvular flow rate. AVArest and Q̇rest are the AVA and Q̇ at rest and ΔAVA and ΔQ̇ are the absolute increases in AVA and Q̇ during dobutamine stress.

LV global longitudinal strain (GLS) was measured by speckle-tracking with dedicated commercial software (2D Cardiac Performance Analysis; TomTec Imaging Systems, Munich, Germany) as previously reported. GLS data were expressed in absolute value ( [%]). GLS was defined as the average of longitudinal strain of the 2-chamber, 3-chamber, and 4-chamber apical views.

Blood Biomarkers

Venous blood samples were drawn at baseline visit from an antecubital vein into EDTA Vacutainer test tubes. Samples were placed immediately on ice and plasma separation was performed at −4°C. Plasma samples were frozen at −80°C until assay. B-type natriuretic peptide (BNP) assay was performed on Architect platform (Abbott Diagnostics) and high-sensitivity troponin T immunoassay was performed on Modular Analytics E170 (Roche Diagnostics).

Statistical Analysis

Continuous data were expressed as mean± SD and were tested for the normality of distribution with the Shapiro–Wilk test. BNP and high-sensitivity troponin T level were not normally distributed and the natural logarithm transformation was applied for normalization. Categorical data were expressed as number and percentage. Patients with...
Table 1. Baseline Clinical and Doppler-Echocardiographic Characteristics of the Study Population According to the QTc Interval

| Demographics and physical exam | Whole Cohort (n=93) | Normal QTc (n=56) | Prolonged QTc (n=37) | P Value |
|-------------------------------|---------------------|------------------|---------------------|--------|
| Age, y                        | 73.3±9.9            | 72.3±10.8        | 74.8±8.4            | 0.24   |
| Male sex, n (%)               | 69 (74)             | 41 (73)          | 28 (75)             | 0.80   |
| Body mass index, kg/m²        | 27.2±5.7            | 27.6±5.0         | 26.6±6.6            | 0.39   |
| Body surface area, m²         | 1.82±0.23           | 1.83±0.23        | 1.80±0.23           | 0.59   |
| Heart rate, bpm               | 71±14               | 69±15            | 74±12               | 0.12   |
| Systolic blood pressure, mm Hg| 123±17              | 123±17           | 123±18              | 0.94   |
| Diastolic blood pressure, mm Hg| 71±11               | 69±11            | 72±11               | 0.19   |
| NYHA functional class ≥III, n (%) | 49 (53)           | 28 (50)          | 21 (57)             | 0.50   |
| Risk factors and concomitant diseases | | | | |
| Hypertension, n (%)           | 60 (65)             | 39 (70)          | 21 (57)             | 0.18   |
| Diabetes mellitus, n (%)      | 22 (24)             | 13 (23)          | 9 (24)              | 0.90   |
| Dyslipidemia, n (%)           | 72 (77)             | 45 (80)          | 27 (73)             | 0.40   |
| Smoking, n (%)                | 60 (65)             | 37 (66)          | 23 (62)             | 0.93   |
| Coronary artery disease, n (%)| 78 (84)             | 49 (88)          | 29 (78)             | 0.15   |
| Coronary artery bypass graft, n (%) | 30 (32)       | 20 (36)          | 10 (27)             | 0.38   |
| Previous myocardial infarction, n (%) | 53 (57)          | 37 (66)          | 16 (43)             | 0.04   |
| COPD, n (%)                   | 64 (69)             | 37 (66)          | 27 (73)             | 0.48   |
| Renal failure, n (%)          | 25 (27)             | 12 (21)          | 13 (35)             | 0.14   |
| History of atrial arrhythmia, n (%) | 44 (47)          | 27 (48)          | 17 (46)             | 0.83   |
| Logistic EuroSCORE, %         | 18.2±11.2           | 17.9±12.2        | 18.5±9.6            | 0.80   |
| Medication                    |                     |                  |                     |        |
| β-Blockers, n (%)             | 55 (59)             | 38 (68)          | 17 (43)             | 0.02   |
| ACEI/ARB, n (%)               | 51 (55)             | 33 (59)          | 18 (49)             | 0.30   |
| Diuretics, n (%)              | 67 (72)             | 42 (75)          | 25 (68)             | 0.50   |
| Statins, n (%)                | 68 (73)             | 45 (80)          | 23 (62)             | 0.07   |
| Amiodarone, n (%)             | 21 (23)             | 12 (21)          | 9 (24)              | 0.67   |
| Type of treatment             |                     |                  |                     |        |
| AVR, n (%)                    | 63 (68)             | 38 (68)          | 25 (68)             | 1.0    |
| Surgical AVR, n (%)*          | 45 (48)             | 27 (48)          | 18 (48)             | 1.0    |
| Concomitant CABG, n (%)†       | 26 (58)             | 15 (56)          | 11 (61)             | 0.71   |
| Electrocardiogram             |                     |                  |                     |        |
| Heart rate, bpm               | 73±13               | 71±13            | 77±13               | 0.02   |
| QRS, ms                       | 122±34              | 111±29           | 137±40              | 0.0006 |
| LBBB, n (%)                   | 20 (21)             | 7 (13)           | 13 (35)             | 0.01   |
| RBBB, n (%)                   | 9 (10)              | 6 (11)           | 3 (8)               | 1.0    |
| QT interval, ms               | 406±48              | 385±50           | 438±45              | <0.0001|
| QTc, ms                       | 435±34              | 405±39           | 480±23              | —      |
| Intracardiac device           |                     |                  |                     |        |
| Pacemaker, n (%)              | 17 (18)             | 9 (16)           | 8 (21)              | 0.50   |
| Defibrillator, n (%)          | 0                   | 0                | 0                   | —      |
| CRT, n (%)                    | 0                   | 0                | 0                   | —      |

DOI: 10.1161/JAHA.116.003980
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Results

Patient Characteristics

Patient characteristics are shown in Table 1. Among the 93 patients included in this study (mean age: 73±10 years; 74%, n=69 males), 49 (53%) were in NYHA functional class≥ III. Baseline AVA was 0.83±0.24 cm², mean gradient: 23±9 mm Hg, AVAproj: 1.09±0.22 cm², LVEF: 31±9%, and rest GLS: |10.1|±3.1%. Sixty-three patients (68%) underwent AVR within 3 months of enrollment and the remaining patients (n=30, 32%) were treated conservatively. Forty-five patients underwent surgical AVR (26 with concomitant coronary artery bypass graft surgery) and 18 underwent transcatheter AVR. The therapeutic decision (AVR or conservative management) was left to the discretion of the treating physicians.

Patients’ Characteristics According to QTc Interval

We divided the cohort into 2 groups according to a previously published cut point value of abnormally prolonged QTc interval.14 Patients with prolonged QTc had similar demographics and clinical data compared to those with normal QTc, except for a history of myocardial infarction and use of β-blocker medication that were significantly more frequent in patients with normal QTc (P=0.04 and 0.02, respectively; Table 1). Regarding Doppler-echocardiographic data, patients with prolonged QTc had smaller SVi (27±6 versus 30±6 mL/m²; P=0.03) and lower GLS (|9.0|±3.0% versus |10.8|±3.2%; P=0.05) compared to those with normal QTc. The baseline

Table 1. Continued

| Doppler-echocardiographic data | Whole Cohort (n=93) | Normal QTc (n=56) | Prolonged QTc (n=37) | P Value |
|--------------------------------|---------------------|-------------------|----------------------|---------|
| Dimensions and systolic function |                     |                   |                      |         |
| LV end-diastolic diameter, mm | 57±8                | 57±8              | 57±8                 | 1.0     |
| LV end-systolic diameter, mm | 46±9                | 45±9              | 48±9                 | 0.17    |
| LV stroke volume, mL          | 54±13               | 56±13             | 50±13                | 0.03    |
| LV stroke volume index, mL/m² | 29±6                | 30±6              | 27±6                 | 0.03    |
| LV ejection fraction, %       | 31±9                | 33±9              | 28±9                 | 0.03    |
| Global longitudinal strain, % (n=50) | 10.1±3.1           | 10.8±3.2          | 9.0±3.0              | 0.05    |
| Aortic stenosis severity      |                     |                   |                      |         |
| Mean gradient, mm Hg          | 23±9                | 22±8              | 24±9                 | 0.18    |
| Mean peak gradient, mm Hg     | 27±11               | 26±10             | 29±11                | 0.33    |
| Aortic valve area, cm²         | 0.83±0.24           | 0.87±0.24         | 0.76±0.23            | 0.02    |
| Peak aortic valve area, cm²   | 1.06±0.24           | 1.10±0.22         | 0.99±0.28            | 0.09    |
| Projected aortic valve area, cm² | 1.09±0.22          | 1.11±0.20         | 1.05±0.24            | 0.27    |
| Projected aortic valve area index, cm²/m² | 0.60±0.15 | 0.61±0.14 | 0.58±0.16 | 0.55 |

Values are mean±SD or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVR, aortic valve replacement; bpm, beats per minute; CAGB, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; RBBB, right bundle branch block; LV, left ventricle; NYHA, New York Heart Association; QTc, corrected QT interval.

*Subset of patients who underwent AVR (n=63).

†Subset of patients who underwent surgical AVR (n=45).
rest AVA was smaller in patients with prolonged QTc. However, the AVA<sub>proj</sub> and indexed AVA<sub>proj</sub> as well as mean peak gradient measured during dobutamine stress were similar, therefore confirming that the AS severity was similar in both groups (Table 1).

**Correlation Between QTc and Parameters of LV Function and Blood Biomarkers**

Table 2 shows the results of the correlations between QT<sub>c</sub> and the echocardiographic parameters and blood biomarkers of LV function. There was a significant and inverse correlation between QT<sub>c</sub> and the echocardiographic parameters of LV systolic function. GLS showed the most significant correlation with QT<sub>c</sub> (r=−0.40; P=0.005; Figure 1A) followed by stroke volume (r=−0.35; P=0.007). Regarding blood biomarkers, BNP and high-sensitivity troponin T were significantly associated with QT<sub>c</sub> (r=0.45; P=0.0006 and r=0.31; P=0.03, respectively; Table 2 and Figure 1B). Correlations between QRS width and parameters of LV function and biomarkers are shown in Table 3. There was only a modest correlation between QRS width and QTc duration (r=0.40; P=0.0001).

**Association Between QT<sub>c</sub> and Mortality**

During a median follow-up of 2.0 years (interquartile range: 0.6–3.8), 49 (53%) patients died and 25 deaths occurred in the group of patients treated conservatively. Deaths were from cardiac cause in 44 (90%) patients. Overall, the 2-year survival was 75±6% in patients with normal QT<sub>c</sub> compared to 58±9% in patients with prolonged QT<sub>c</sub> (P=0.01; Figure 2A).

| Table 2. Correlation Between QT<sub>c</sub> Interval and Parameters of LV Function and AS Severity |
|---------------------------------|-------|----------|
| Variable                       | R     | P Value  |
| Aortic valve area               | −0.35 | 0.0005   |
| Peak stress aortic valve area   | −0.18 | 0.17     |
| Projected aortic valve area     | −0.10 | 0.40     |
| Mean gradient                   | 0.12  | 0.15     |
| Peak stress mean gradient       | 0.06  | 0.64     |
| Global longitudinal strain, %  | −0.40 | 0.005    |
| LV stroke volume                | −0.35 | 0.007    |
| LV stroke volume index          | −0.32 | 0.002    |
| LV ejection fraction            | −0.27 | 0.02     |
| Log BNP (n=55)                  | 0.45  | 0.0006   |
| Log hsTnT (n=50)                | 0.31  | 0.03     |

AS indicates aortic stenosis; hsTnT, high sensitivity troponin; Log-BNP, logarithmic transformation of B-type natriuretic peptide; LV, left ventricular.

The results were similar in the subset of patients without left bundle branch block (n=73) and those with QRS <120 ms (n=60) (all P<0.05). There was no significant interaction (P=0.36) between QT<sub>c</sub> and the type of treatment (AVR versus conservative). The individual associations between the ECG variables and all-cause mortality are shown in Table 4.

In multivariable Cox analysis adjusted for type of treatment (AVR versus conservative), EuroSCORE, previous myocardial infarction, LVEF, and β-blocker medication, prolonged QT<sub>c</sub> was independently associated with all-cause mortality (hazard ratio [HR]=2.56; 95% CI: 1.28–5.11; P=0.008; Table 5, Model #1). Prolonged QT<sub>c</sub> remained independently associated with all-cause mortality with adjustment for SVi instead of LVEF (HR=2.16; 95% CI: 1.11–4.11; P=0.02; Table 5, Model #2).

**Figure 1.** Correlation between corrected QT interval and left ventricular global longitudinal strain and B-type natriuretic peptide. (A) The correlation between corrected QT interval and left ventricular global longitudinal strain. (B) The correlation between corrected QT interval and B-type natriuretic peptide. The solid line represents the regression line; QT<sub>c</sub>, corrected QT interval; GLS, global left ventricular longitudinal strain; BNP, B-type natriuretic peptide.
The results were similar after adjustment for presence of left bundle branch block (HR=2.45; 95% CI: 1.25–4.77; \( P=0.009 \); Table 5, Model #3) or QRS duration (HR=2.59, 95% CI: 1.12–5.78; \( P=0.02 \); Table 5, Model #4). Presence of pacemaker was not associated with mortality in univariable (\( P=0.71 \)) or multivariable analysis (\( P=0.29 \)). Amiodarone medication may influence QTc. However, amiodarone was not associated with increased or decreased risk of mortality (\( P=0.80 \)) and after adjustment for this medication, QTc remained associated with mortality (HR=2.29, 95% CI: 1.21–4.37; \( P=0.01 \)).

Functional capacity, projected AVA, and LVEF at peak dobutamine stress have been shown to be associated with increased risk of mortality in patients with LF-LG AS.\(^4\) Prolonged QTc remained associated with mortality when adding NHYA functional class (HR=2.62; 95% CI: 1.34–5.09; \( P=0.005 \)), projected AVA (HR=4.55; 95% CI: 1.90–10.86; \( P=0.0007 \)), or peak stress LVEF (HR=3.00; 95% CI: 1.15–7.80; \( P=0.02 \)) to the variables included in Model #1. Results were similar after adjustment for renal failure (HR=2.45, 95% CI: 1.26–4.74; \( P=0.007 \)).

Prolonged QTc was also associated with cardiovascular mortality (Figure 2B) in univariable analysis (HR=1.89; 95% CI: 1.01–3.47; \( P=0.04 \)) and in multivariable Cox analysis (HR=2.50; 95% CI: 1.19–5.19; \( P=0.02 \)) after further adjustment for the same variables as in Model #1 in Table 5.

### Discussion

The main findings of the present study are that in patients with LF-LG AS and low LVEF: (1) QTc is associated with worse LV systolic function and higher plasma levels of BNP; and (2) prolonged QTc is independently associated with 2-fold increased risk in all-cause and cardiovascular mortality.

Previous studies reported that QRS width was associated with worse outcomes in patients with AS.\(^{11,19} \) In the present study, QRS width was not found to be significantly associated with mortality (\( P=0.5 \)). Furthermore, QTc remained independently associated with mortality after further adjustment for QRS width.

In a recent study by Beinart et al, prolonged QT interval has been shown to be associated with incident cardiovascular diseases and death in the general population.\(^{12} \) Yet, the underlying mechanisms related to the higher mortality observed in patients with prolonged QT interval remain unclear. In this study by Beinart et al that included a cohort of middle-aged participants free of cardiovascular diseases (CVD) at baseline, the authors suggested that LV abnormalities such as LV hypertrophy, which has been shown to be positively associated with high sympathetic tone and longer QT interval, may explain, at least in part, this association.\(^2 \) In
our study, there was no significant association between LV mass measured by echocardiography and QTc. Nevertheless, the results of the present study showed an association between LV systolic function and the QT interval and suggest that the effect of QT interval on outcomes may be in part mediated by the worse LV function. Longer QTc was associated with lower GLS, lower LVEF, lower SV, and higher BNP (Table 2 and Figure 1) and reduced survival. All these factors have been shown to be associated with worse outcomes in patients with cardiovascular diseases.4,7,18,20–22 Yet, the QT interval remained independently associated with mortality even after adjustment for parameters of LV systolic function. These findings suggest that other mechanisms beyond impairment of LV function are also responsible for the higher mortality risk in patients with prolonged QT. Myocardial fibrosis may contribute to the alteration of conduction within the myocardium and thus to prolongation of QT interval. Myocardial fibrosis may provide a substrate for potentially fatal LV arrhythmias and is a strong predictor of adverse events in patients with AS and those with hypertrophic cardiomyopathy.23–26 Hence, prolonged QT might provide a surrogate marker of LV structural abnormalities and extent of myocardial fibrosis and therefore of increased risk of adverse events in patients with LF-LG AS and low LVEF. The QTc is a low-cost and reproducible measure that can easily be obtained from a routine ECG. This simple parameter might be useful for risk stratification in patients with LF-LG AS. However, further studies are needed to confirm the potential value of QTc as a surrogate marker of LV fibrosis and associated cardiac events.

### Study Limitations

The population size may have limited our ability to detect significant associations with some other risk factors and to perform a more comprehensive adjustment in multivariable analysis. Some multivariable models were overfitted. Further studies are needed to confirm the results of the present study. The interaction of other medications commonly used in the elderly (antibiotics, antidepressants, antipsychotics, and so on) with QT interval and outcome was not performed in this analysis due to lack of data in a substantial number of patients or to the very small number of patients with such medications (eg, n=2 with antibiotics) at the time of ECG.

### Conclusions

In patients with LF-LG AS and reduced LVEF, longer corrected QT interval is associated with worse LV systolic function and with increased risk of mortality. The QTc is simple, rapid, and inexpensive to obtain in practice and may be useful for prognostication and therapeutic decision making in patients with low LVEF, LF-LG AS. Further studies are needed to confirm these results in other AS populations and to better understand the mechanisms underlying the association between QTc and mortality.

### Sources of Funding

This work was supported by a grant (FDN-143225, MOP# 126072, MOP# 57445) from the Canadian Institutes of Health Research Ottawa, Canada. Dahou was supported by a fellowship grant from L’Agence de la santé et des services sociaux de la Capitale Nationale, Québec, Canada. Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research.
Disclosures

None.

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