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The impact of patient-prosthesis mismatch on early and long-term survival after aortic replacement with the Edwards Perimount valve: A propensity score-matched analysis

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Abstract

Background: To investigate the impact of severe patient-prosthesis mismatch (PPM) related to the Edwards Lifesciences Perimount (EP) bioprosthesis in the aortic position on early in-hospital outcomes and long-term survival.

Methods: A total of 5964 consecutive patients underwent aortic valve replacement at the Bristol Heart Institute between 1998 and 2014, 2667 representing the cohort of this study received EP. PPM was defined severe as EOAi < 0.65 cm²/m². To minimize bias, propensity score matching was conducted and two groups A and B (without and with severe PPM) of 320 patients with similar preoperative characteristics were matched. We assessed early in-hospital outcomes including CVA, re-exploration for bleeding, low cardiac output, wound infection, acute renal injury, length of hospital stay, and long-term survival for both groups in unmatched and matched populations.

Results: In the unmatched analysis, 18.3% of patients had severe PPM. Severe PPM was not associated with increased in-hospital mortality (4.5% vs. 2.9%, respectively, \( p = .09 \)) or any other early adverse outcomes except increased length of hospital stay (10.57 ± 8.2 vs. 11.7 ± 9.4, respectively, \( p = .01 \)). Long-term survival differed significantly between groups at 2 and 8 years (91.8% vs. 91.4% and 60.5% vs. 55.7%, respectively, \( p = .02 \)). Matched analysis showed no differences between the groups in early health outcomes and overall survival at 2 and 8 years was also similar (89.7% vs. 91% and 57.3% vs. 58%, group A vs. B, respectively \( p = .9 \)).

Conclusion: Presence of PPM does not seem to affect early in-hospital outcomes or late survival when using EP in patients undergoing aortic valve replacement.

KEYWORDS
patient prosthesis mismatch, valve repair/replacement
INTRODUCTION

In the last two decades, the use of bioprosthesis aortic valve implantation has increased significantly, far exceeding the use of mechanical prostheses.\(^1\,2\)

The Carpentier–Edwards Perimount (EP) bovine pericardial bioprosthesis (Edwards Lifesciences, Irvine, CA) is widely recognized as one of the most commonly used bioprosthetic valves for many years. This valve design was developed to overcome the difficulties observed with previous pericardial prosthetic models with the aim of optimizing the hemodynamic profile with improved durability.\(^2\,3\)

Since its introduction, multiple reports have demonstrated excellent clinical outcomes and durability, especially when implanted in the aortic position.\(^4\)–\(^9\)

One of the most common issues after valve replacement, especially after implantation of a biological prosthesis, is a valve with a reduced effective orifice area compared to the native valve. This condition is referred to as patient–prosthesis mismatch (PPM)\(^10\) and its main hemodynamic consequence consists of an elevated transvalvular gradient through a normal functioning prosthetic valve.\(^11\)

After aortic valve replacement (AVR), PPM can vary in terms of severity according to the effective orifice area (EOA) of the prosthetic valve indexed to the patient’s body surface area (EOAi). In the literature, PPM is described as mild or absent, having no clinical impact, when EOAi > 0.85 cm\(^2\)/m\(^2\); moderate PPM when EOAi is between <0.85 cm\(^2\)/m\(^2\) and >0.65 cm\(^2\)/m\(^2\); and severe when EOAi < 0.65 cm\(^2\)/m\(^2\).\(^2\,3\)

The prevalence of PPM ranges between 20% and 70% for moderate and between 2% and 20%, for severe.\(^12\)

The impact of PPM on short and long-term mortality is still the subject of debate as many studies have reported very conflicting outcomes.\(^12\)–\(^17\)

In this study, we report a single UK center experience with the use of an EP valve implanted in the aortic position. The aim of the study was to investigate the incidence and the clinical impact of severe PPM on early in-hospital outcome and long-term survival in patients undergoing aortic valve replacement with EP valves.

MATERIAL AND METHODS

2.1 Patient selection and data collection

We performed a single center retrospective analysis of prospectively collected data of patients undergoing AVR. Data were prospectively collected, validated, and stored by a data management team at our institution, as part of the UK National Institute for Cardiovascular Outcomes Research (NICOR) Registry. The study protocol was in compliance with the local Institutional Clinical Audit Review Board and patient consent was waived.

From January 1998 to December 2014, a total of 5964 consecutive adult patients underwent AVR for Aortic valve disease. Of these, 2667 patients received EP valve for both isolated and combined procedures and they represent the cohort of this study (Table 1).

The baseline data collected includes clinical characteristics, symptom status, and past medical history. (Table 1).

Indications for surgery were based on referral for surgery by a cardiologist, baseline clinical details, echocardiographic results, coronary angiography, and when necessary following case discussion by the Heart Team. Late survival data after discharge were obtained from the UK Office of National Statistics.

2.2 Outcomes measurement

All patients underwent transthoracic echocardiography preoperatively; LV function was assessed by the ejection fraction (LVEF) accordingly to the Simpson rule.

Mean EOA was extracted from previously published data and indexed to patient’s body surface area (EOAi).\(^14\)–\(^18\)

Considering the EOAi < 0.65 cm\(^2\)/m\(^2\) as a cut-off point, patients were divided into two groups: nonsevere PPM (group A) and severe PPM (group B).

Early outcome collected included: in-hospital mortality, cerebrovascular accident (CVA), defined on the basis of a focal or global neurological impairment at a physical examination or at CT scan/ magnetic resonance imaging, postoperative acute kidney injury (AKI) (requiring haemofiltration), low cardiac output (requiring IABP support), postoperative bleeding (requiring surgical re-exploration), deep sternal wound infection (defined as a surgical site-related infection affecting the median sternotomy wound and requiring antibiotics and/or surgical re-exploration) and in-hospital length of stay.

2.3 Statistical analysis

Data are presented as mean ± one standard deviation for continuous variables or as percentages for dichotomous variables. Continuous variables were tested for normality using the Shapiro–Wilk test and then compared between groups with unpaired Student’s t test if not normally distributed or Mann–Whitney U test if not normally distributed. In the case of dichotomous variables, Pearson chi-squared or Fisher’s exact test were used as appropriate. Predictors for outcomes have been tested using a multivariable logistic regression model: a stepwise approach was confirmed by backward and forward selection methods using the Akaike information criterion (AIC). Event-free survival curves were compared between the two groups by Kaplan–Meier methods and subsequently compared with the log-rank test.

To further adjust for patient selection and preoperative characteristics, a propensity score-matched analysis was developed. The group of patients who developed severe PPM matched (1:1) to the group of patients who underwent AVR but did not show severe PPM by all the preoperative variables presented in Table 1. After the propensity score matching, preoperative and postoperative characteristics were compared using paired Student’s t test or paired Wilcoxon test for continuous variables and McNemar (for dichotomous variables) and χ\(^2\) test for ordinal categorical variables.
All tests were two-sided with the alpha level set at .05 for statistical significance. Clinical data were recorded and subsequently tabulated with Microsoft Excel (Microsoft Corp). The statistical analysis was computed using SPSS version 24.

### 3 | RESULTS

#### 3.1 | Whole cohort

Patient characteristics and preoperative variables are summarized in Table 1. In this cohort 489 (18.3%) patients had severe PPM (Table 1). The mean age in the nonsevere group (group A) was 72.2 ± 10.3 vs. 74.3 ± 7.5 years in the severe PPM (group B) (p < .001). Similarly, a significant difference was noted on EuroSCORE I (6.5 ± 2.3 vs. 7 ± 2.3 in the nonsevere and severe PPM, respectively, p < .001). Group B included more females (52.6%) and more patients in class NYHA > II (55.2% vs. 46%). Severe PPM was present more frequently in patients with valve size diameter less than 23 mm. There were no differences between groups in terms of redo surgery, isolated AVR, and critical preoperative state.

Early outcomes are shown in Table 2. The overall perioperative mortality was 3.2% (85 patients) and did not differ between groups A and B (2.9% vs. 4.5% p = .09). Postoperatively, 151 patients (5.7%)

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**TABLE 1 Preoperative characteristics of patients in unmatched and matched population**

| Unmatched population | Matched population |
|-----------------------|---------------------|
| **Nonsevere PPM group** | **Severe PPM group** | **p value** | **SMD** |
| **A** 2178 (81.4%) | **B** 489 (18.3%) | | |
| **p value** | **SMD** |
| Age (years) | 72.2 ± 10.3 | 74.3 ± 7.5 | <.001 | 0.2 |
| EuroSCORE I | 6.5 ± 2.3 | 7 ± 2.3 | <.001 | 0.2 |
| BMI (kg/m²) | 26.4 ± 4.22 | 30 ± 4.7 | <.001 | 0.2 |
| BSA (m²) | 1.9 ± 0.2 | 2 ± 0.16 | <.001 | 0.8 |
| Women (%) | 711 (32.6) | 257 (52.6) | <.001 | 0.6 |
| Diabetes (%) | 291 (13.4) | 133 (27.2) | <.001 | 0.5 |
| Hypertension (%) | 1341 (61.6) | 356 (72.8) | <.001 | 0.3 |
| Smoking (%) | 138 (6.3) | 21 (4.3) | .09 | 0.2 |
| COPD (%) | 304 (14) | 86 (17.6) | .05 | 0.2 |
| Prev CVA (%) | 222 (10.2) | 64 (13.1) | .06 | 0.2 |
| PVD (%) | 149 (6.8) | 52 (10.6) | .006 | 0.3 |
| Elective (%) | 1570 (72.1) | 344 (70.3) | .4 | 0.2 |
| Redo (%) | 122 (5.6) | 31 (6.3) | .5 | 0.07 |
| LVEF < 50% (%) | 136 (6.2) | 17 (3.5) | .02 | 0.4 |
| NYHA > II (%) | 1002 (46) | 270 (55.2) | <.001 | 0.2 |
| Preop critic st (%) | 16 (0.7) | 1 (0.2) | .7 | 0.4 |
| Isolated valve (%) | 1223 (56.2) | 279 (57.1) | .7 | 0.02 |

| Valve size (%) | | | | |
| 19 | 188 (8.6) | 296 (60.5) | 20 (6.3) | 204 (63.7) |
| 21 | 722 (33.1) | 188 (38.4) | 98 (30.6) | 116 (36.3) |
| 23 | 778 (35.7) | 5 (1) | 138 (43.1) | 0 (0) |
| 25 | 340 (15.6) | 0 (0) | 45 (14.1) | 0 (0) |
| 27 | 124 (5.7) | 0 (0) | 14 (4.4) | 0 (0) |
| 29 | 26 (1.2) | 0 (0) | 5 (1.6) | 0 (0) |

Note: Continuous variables are described as mean and standard deviation. Categorical variables are described as numbers and percentages. Abbreviations: BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; EOAi, effective orifice area indexed; LVEF, Left Ventricular Ejection Function; NYHA, New York Heart Association classification; PPM, patient-prosthesis mismatch; PREOP CRITIC, preoperative critical status; PVD, peripheral vascular disease; SMD, standardized mean difference (reported for the variables included in the propensity score matching process); SMOKING H, smoking history.
required re-exploration for bleeding. A total of 53 patients (2%) had a new CVA, 55 patients (2.1%) developed postoperative AKI requiring haemofiltration, 22 patients (0.8%) required IABP for hemodynamic instability, and 16 patients (0.6%) developed deep sternal wound infection.

The overall length of stay was 10.8 ± 8.4 days and was significantly higher in the severe PPM group (10.57 ± 8.2 group A vs 11.7 ± 9.4 group B, \( p = .01 \)).

The overall survival after AVR was significantly different between the groups (91.8% vs. 91.4%, 87% vs. 82.6%, 81.1% vs. 78%, 60.5% vs. 55.7%, respectively, group A vs Group B \( p = .02 \)) (Figure 1).

The univariate Cox model (Table 3) did identify severe PPM as an independent predictor of increased long-term mortality \( (p = .02) \). Similarly; age \( (p < .001) \), diabetes \( (p = .002) \), COPD \( (p = .01) \), EuroSCORE I \( (p < .001) \), poor left ventricle (LV) function \( (p < .001) \), redo surgery \( (p < .001) \), nonelective surgery \( (p < .001) \), and PVD (HR, 1.8; CI, 1.4–2.3, \( p < .001 \)) were all associated with increased hazard of mortality.

However, the multiple Cox regression analysis showed that age (HR, 1.1; CI, 1.0–1.2, \( p < .001 \)), EuroSCORE I (HR, 1.1; CI, 1.0–1.2, \( p < .001 \)), NYHA > II (HR, 1.3; CI, 1.2–1.4, \( p < .001 \)), and peripheral vascular disease (PVD) \( (p = .006) \) were independent predictors of long-term mortality. Interestingly, the presence of severe PPM did not impact long-term mortality \( (p = .1; \text{Table 3}) \).

### 3.2 Propensity matched analysis

After propensity score matching, the overall number of patients was reduced to 320 patients with non-severe PPM (group Am) and 320 patients with severe PPM (group Bm), with similar preoperative characteristics (Table 1). The early postoperative outcome of the matched analysis is shown in Table 2. In-hospital mortality was similar between the groups (2.2% group Am vs. 3.8% group Bm, \( p = .3 \)). There were no differences in the incidence of CVA (2.5% group Am vs. 2.2% group Bm, \( p = .1 \)), postoperative AKI (2.4% group Am vs. 2.7% group Bm, \( p = .8 \)), deep sternal wound infection (0.3% Group Am vs 0.3% Group Bm, \( p = 1 \)), and length of stay in hospital (11.8 ± 10.1 days group Am vs. 11.8 ± 10.1 days group Am, \( p = .6 \)).

Overall survival at 2 and 8 years was also similar (89.7% vs. 91% and 57.3% vs. 58%, group Am vs. group Bm \( p = .9 \); Figure 2).

### 4 DISCUSSION

During the last two decades, a generational change in aortic valve prosthesis implantation has been observed with biological prostheses implanted progressively more often than mechanical ones.\(^1\) Freedom from anticoagulation, better outcome in redo surgery and, furthermore, the increased performance of the new

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**TABLE 2** In-hospital outcomes after AVR in unmatched and matched population

|                | Overall 2667 | Nonsevere PPM 2178 (81.4%) | Severe PPM 489 (18.3%) | \( p \) value |
|----------------|-------------|-----------------------------|------------------------|--------------|
| In-hospital mortality | 85 (3.2%)  | 63 (2.9%)               | 22 (4.5%)              | 0.09         |
| IABP            | 22 (0.8%)   | 16 (0.7%)               | 6 (1.2%)               | 0.3          |
| New CVA         | 53 (2%)     | 42 (1.9%)               | 11 (2.2%)              | 0.6          |
| Length of stay (days) | 10.8 ± 8.4 | 10.57 ± 8.2              | 11.7 ± 9.4             | 0.01         |
| Re-exploration for bleeding | 151 (5.7%) | 104 (4.8%)              | 33 (6.7%)              | 0.07         |
| AKI requiring renal replacement therapy | 55 (2.1%) | 42 (1.6%)               | 13 (2.7%)              | 0.3          |
| Deep wound infection | 16 (0.6%)  | 12 (0.6%)               | 4 (0.8%)               | 0.5          |

|                | Overall 320 | Nonsevere PPM 320 (group Am) | Severe PPM 320 (group Bm) | \( p \) value |
|----------------|-------------|-----------------------------|------------------------|--------------|
| In-hospital mortality | 19 (3%)    | 7 (2.2%)                   | 12 (3.8%)              | 0.3          |
| IABP            | 5 (0.8%)    | 1 (0.3%)                   | 4 (1.3%)               | 0.4          |
| New CVA         | 15 (2.3%)   | 8 (2.5%)                   | 7 (2.2%)               | 1            |
| Length of stay | 11.8 ± 10.1 | 11.4 ± 9.2                 | 11.8 ± 10.1            | 0.6          |
| Re-exploration for bleeding | 35 (5.5%)  | 11 (3.4%)                  | 24 (7.5%)              | 0.04         |
| AKI requiring renal replacement therapy | 14 (2.2%) | 8 (2.5%)                   | 6 (1.9%)               | 0.8          |
| Deep wound infection | 4 (0.6%)   | 2 (0.3%)                   | 2 (0.3%)               | 1            |

Abbreviations: AKI, acute kidney injury; AVR, aortic valve replacement; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; PPM, patient prosthesis mismatch.
generation of tissue valve played an important role in this trend.\textsuperscript{1,19}

Patient-prosthesis mismatch may be a controversial issue in patients undergoing aortic valve replacement. Several studies describing the impact of moderate and severe PPM after valve replacement have been published without producing a consensus. This may be potentially a consequence of a number of confounding factors: heterogeneous cohorts of patients examined, comparison between different models of the valve, dissimilarity in surgical strategies, and/or methodological approaches.\textsuperscript{20}

The concept of PPM was initially described in the late seventies by Rahimtoola et al who stated that mismatch can be considered to be present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve.\textsuperscript{10}

Subsequently, after aortic valve replacement, it is well defined that an indexed EOA ≤0.85 cm\(^2\)/m\(^2\) is generally the threshold to define PPM. Values between 0.65 and 0.85 cm\(^2\)/m\(^2\) have been classified as moderate PPM and those <0.65 cm\(^2\)/m\(^2\) as severe PPM.\textsuperscript{14}

The effects of PPM on short and long-term outcomes continue to be a matter of debate, a recent study by Blais et al.\textsuperscript{13} suggested that one of the strongest independent predictors of mortality after AVR was the presence of postoperative PPM. Similarly, Pibarot et al.\textsuperscript{21} in a subanalysis from the PARTNER trial cohort showed that severe PPM was an independent predictor of 2-year mortality in the surgical AVR cohort. Hong et al.\textsuperscript{22} analyzed data from patients who underwent isolated AVR and showed that early survival was not significantly affected by PPM, however, in the group with severe PPM the overall survival as well as the cardiac-related-death-free survival were significantly reduced at 12 years.\textsuperscript{20}

Interestingly, other studies report no significant differences in outcome ascribed to the presence of postoperative PPM. A recent study by Swinkels et al.\textsuperscript{23} in a cohort of 673 consecutive patients, compared 510 patients with no PPM to 163 patients with PPM demonstrated that, after aortic valve implantation, the presence of PPM was not an independent predictor of decreased long-term survival. Similarly, Tully et al.\textsuperscript{24} showed that moderate and severe PPM were, overall, unrelated to in-hospital morbidity or mortality. In the same study, however, discrete mortality risk was attributable to the group of patients with moderate and severe PPM in association with older age, left ventricular dysfunction, NYHA class III, or the need for concomitant coronary artery bypass grafting.

Moreover, Kato et al.\textsuperscript{25} after a follow-up of ten years after surgery, found there was no significant difference between patients with mismatch and those without mismatch in terms of overall survival, actuarial freedom from cardiac-related death, and freedom from any valve-related mortality or morbidity. In addition, using multivariate analysis, PPM was not a predictor of late cardiac-related death or all deaths. Furthermore, echocardiographic examination showed that left ventricular wall thickness and left ventricular mass significantly decreased postoperatively in both groups.

In this study, we evaluated the postoperative rate of PPM based on EOA\(_i\) using previously published data\textsuperscript{14–18} and a single type of valve (EP).
The findings of our unmatched analysis are in keeping with previous reports published showing that the presence of EOAi < 0.65 cm²/m² in patient receiving EP bioprosthesis is only affecting the in-hospital length of stay (p = .01) but was not associated with any other differences in in-hospital outcomes. Long-term survival demonstrated that the presence of EOAi < 0.65 cm²/m² is associated with reduced long-term survival (p = .018) which was supported by the univariate, not the multivariate Cox regression.

To further appreciate the impact of PPM based on EOAi < 0.65 cm²/m² and taking into account any heterogeneity that might bias the results, a propensity-matched analysis was undertaken to better equalize the characteristics between the groups. Considering the adjusted data it was remarkable to note that the results were in contrast to the one shown by the whole population, in fact, it has clearly demonstrated that the presence of severe PPM (EOAi < 0.65 cm²/m²) after EP implantation affects neither the short nor the long-term survival.

As previously demonstrated by some studies these results suggest that within balanced groups the same risk factors had a similar impact on early and long-term mortality independently from the presence of moderate PPM. In that study, the classification of PPM has been extracted from previously published reference values followed by echocardiographic validation.

The question of PPM remains a matter of debate as there are many unanswered questions that need to be prudently addressed before reaching any solid conclusions that impact surgical practices.

Most of the data available are based on tables provided by manufacturers which often report the best evaluation of the EOA; moreover, data are usually presented only as mean, while standard deviation is known to be a significant parameter to take into account. Since the determination of the EOA can substantially differ when investigated in-vivo, the EACTS-STS-AATS Valve Labeling Task Force has been advocating the regulation and standardization of the information provided in the valve prosthesis charts.

Furthermore, the specifics of the PPM assessment that should be conducted in vivo need to account for the optimal time frame, the need and the rate of repeated examinations, and the findings required to reach a conclusive result.

Lastly, it is still under debate whether BSA is the most accurate parameter to investigate the surface area in the context of PPM assessment, as lean mass has also been suggested as a potentially effective alternative.

Our study has many limitations and the results should be interpreted carefully as we showed that PPM based on EOAi is not associated with the increased adverse outcome; however, as argued above this may not be the correct method to look at PPM.

The EOAi assessment was extracted following previous publications and not based on echocardiography. Nonetheless, even though the majority of studies in the literature have broadly described the evaluation of PPM based on the calculation by echocardiogram and Doppler of the continuity equation across the LVOT, the accuracy of this assessment has been questioned for several reasons, such as anatomical and methodological factors.

Additionally, this was a retrospective single-center analysis on prospectively collected data in a limited cohort. The allocation of patients to the study group was by surgeon expertise, and this might have led to undetected difference in risk profile between groups. The study included a patient cohort treated over a long-time period, hence with possible confounding factors due to changes in clinical practice over time.

Finally, the evaluation of long-term outcomes after surgery was limited to all-cause mortality as no data were available on structural valve deterioration or the need for re-do surgery.

We conclude that the presence of EOAi < 0.65 cm²/m² based on published valve areas measurement in patients undergoing AVR using EP valves does not affect early or late outcomes.

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**Table 3**: Univariate and multivariate Cox regression for long-term survival

| Univariate Cox | HR CI p value |
|----------------|--------------|
| Age            | 1.1 1-1.1 <.001 |
| DM             | 1.4 1.1-1.7 .002 |
| Women          | 1.1 0.9-1.3 .1 |
| EuroSCORE I    | 1.2 1.1-1.2 <.001 |
| Severe PPM     | 1.2 1-1.5 .02 |
| Poor LV        | 2 1.6-2.7 <.001 |
| Urgent         | 1.3 1.1-1.7 <.001 |
| Redo surgery   | 1.6 1.2-2.2 <.001 |
| PVD            | 1.8 1.4-2.3 <.001 |
| Critical pre-op| 1.5 0.7-3 .3 |
| NYHA > II      | 1 1.4-1.9 <.001 |

| Multivariate Cox | HR CI p value |
|------------------|--------------|
| Urgent           | 1 0.9-1.5 .5 |
| Age              | 1.1 1-1.1 <.001 |
| DM               | 1.2 0.9-1.5 .05 |
| PVD              | 1.5 1.1-1.2 .006 |
| Redo surgery     | 1.2 0.9-1.2 .3 |
| COPD             | 1.1 0.9-1.2 .2 |
| Severe PPM       | 1.2 0.95-1.4 .1 |
| Poor LV          | 1.3 0.9-1.7 .1 |
| EuroSCORE I      | 1.1 1-1.1 <.001 |
| NYHA > II        | 1.3 1.1-1.5 .009 |

Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; NYHA, New York Heart Association classification; PPM, patient prosthesis mismatch; PVD, peripheral vascular disease.
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The authors declare that there are no conflict of interests.

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All authors contributed to the design, data analysis, writing,
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version.

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DATA AVAILABILITY STATEMENT
Data related to this publication can be made available upon rea-
sonable request to the authors.

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