Residual aortic regurgitation (AR) is a major complication after transcatheter aortic valve implantation (TAVI). Although the echocardiographic assessment of post-TAVI AR remains challenging, cardiac magnetic resonance (CMR) allows direct quantification of AR. The aim of this study was to review the level of agreement between 2-dimensional transthoracic echocardiography (2D TTE) and CMR on grading the severity of AR after TAVI, and determine the accuracy of TTE in detecting moderate or severe AR. Electronic databases were searched in order to identify studies comparing 2D TTE to CMR for post-TAVI AR assessment. Kappa coefficient was used to determine the level of agreement between the 2 imaging modalities. CMR was used as the reference standard in order to assess the diagnostic accuracy of 2D TTE. Seven studies were included in this systematic review. Six studies reported a low correlation between 2D TTE and CMR (kappa coefficient ranging from \(-0.02\) to \(0.41\)), whereas one study showed good agreement with a kappa coefficient of \(0.72\). Given the heterogeneity in the included studies the diagnostic accuracy of TTE was evaluated by estimating the hierarchical summary receiver operator characteristic curve. The area under the curve for detection of moderate or severe AR with TTE was \(0.83\) (95% confidence interval \(0.79\) to \(0.86\)). In conclusion, despite the reported significant disconcordance between TTE and CMR grading of AR, TTE has sufficient ability to discriminate moderate or severe AR from mild or none AR after TAVI in the clinical setting. CMR should be considered when TTE results are equivocal.

Transcatheter aortic valve implantation (TAVI) has evolved into an indispensable therapeutic option for patients with severe aortic stenosis, who cannot undergo, or who is considered at high risk for surgical aortic valve replacement.\(^1\)\(^2\) Despite the marked improvements in prosthetic valve design and procedural techniques, aortic regurgitation (AR)—mainly secondary to paravalvular leak (PVL)—remains a major postprocedural complication. Significant post-TAVI AR (moderate or severe) is independently associated with higher mortality rates.\(^3\)\(^4\)

Two-dimensional transthoracic echocardiography (2D TTE) is the most commonly used imaging modality for AR assessment following TAVI.\(^5\) Several echocardiographic parameters have been proposed for the quantification of AR severity post-TAVI.\(^6\)\(^7\) However most of these indices are primarily used to assess native AR and may be less accurate for the assessment of eccentric PVL jets due to the acoustic shadowing from the valve stent, notwithstanding other limitations of echocardiography (e.g., poor acoustic windows, operator-dependency).\(^8\) By contrast to echocardiography, cardiac magnetic resonance (CMR) confers more accurate and reproducible quantitative measurements of AR severity using phase-contrast velocity mapping.\(^9\)\(^{12}\) With this study, we aim to (1) review the degree of concordance between CMR and TTE for post-TAVI AR assessment, and (2) determine the ability of 2D TTE to detect identify moderate or severe AR.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses.\(^1\)\(^3\) A study was considered to be eligible for this review, if the following inclusion criteria were fulfilled: (1) primary research comparing 2D TTE to CMR for post-TAVI AR assessment, irrespective of the imaging parameters assessed;
(2) studies reporting kappa coefficient or data that could be used for its calculation to determine the agreement between TTE and CMR on grading of AR severity, (3) studies published in any language until April 6, 2018. The electronic databases Medline (PubMed) EMBASE and Cochrane CENTRAL Library were searched for relevant studies. We searched electronic databases using a search algorithm, composed of the following medical subject headings: (1) CMR OR “cardiac magnetic resonance” and (2) TAVI OR “transcatheter aortic valve implantation” OR TAVR OR “transcatheter aortic valve replacement”. The results of these 2 independent searching themes were combined using the Boolean operator “AND.”

Two independent reviewers (CAP, AKJ) assessed the eligibility of the potentially included studies according to the prespecified inclusion and exclusion criteria. An article was deemed to be eligible, if both reviewers agreed. A third reviewer (EO) was involved when needed in order consensus to be reached. Data extraction was performed independently by 2 reviewers (CAP, DGK) based on prespecified forms with epidemiological and clinical information.

Baseline characteristics of the patient population were presented as mean values ± standard deviation (SD) for continuous variables or absolute and relative frequencies for categorical variables. The level of agreement between CMR and TTE was reported using the Cohen’s kappa statistic with corresponding 95% confidence interval (CI).

When kappa coefficient and 95% CI were not directly available, they were calculated using appropriate formulas. The level of agreement was considered to be: poor if $k < 0.20$, fair if $k = 0.21$ to $0.40$, moderate if $k = 0.41$ to $0.60$, good if $k = 0.61$ to $0.80$, almost perfect if $k = 0.81$ to 1.0. Given that kappa coefficient is affected by the distribution of the outcome of interest, prevalence index was calculated. When conflict between kappa and percent agreement was detected because of prevalence or bias effect, prevalence-adjusted-bias-adjusted-kappa was calculated.

Greater than mild residual AR has been proven to be the turning point toward increased mortality. Therefore, we assessed the diagnostic accuracy of 2D TTE in detecting moderate/severe AR after TAVI. For this purpose, CMR was used as the reference standard. Given the significant heterogeneity in the parameters assessed for AR classification across the included studies, the overall diagnostic performance of TTE was evaluated by estimating the hierarchical summary receiver operator characteristic curve, without interpreting summary sensitivity and specificity, which are clinically meaningless in this case. Publication bias was not assessed given the low number of the included studies (<10). All analyses were performed with Stata 13.0 (Stata-Corp, College Station, Texas).

Results

A total of 424 studies were screened and 9 full-text articles were assessed for eligibility. Seven studies met the inclusion criteria and were finally included in our systematic review. A detailed flow diagram is shown in Figure 1. As expected, patients had a high surgical risk profile and suffered from moderate-to-severe symptoms of heart failure. Details on baseline characteristics of the included studies are shown in Table 1. AR assessment was performed at various time intervals ranging from 5 to 180 days postoperatively. Different imaging parameters, recommended by either American Society Echocardiography or VARC-2, were adopted by each study for the assessment of AR severity with TTE. Finally, different cut-off values of regurgitant fraction, measured by CMR, were used as reference standards for grading the severity of post-TAVI AR (Table 2).

The Cohen’s kappa coefficient ranged from $-0.02$ to 0.72. Poor and fair agreement were indicated by 3 and 2 studies, respectively, whereas moderate and good agreement were each indicated by one study. Data on the diagnostic performance of TTE for the detection of moderate-to-severe post-TAVI AR are presented in Table 3.

Three of the included studies in the systematic review were excluded from statistical analysis. Two of them did not provide data for the sensitivity and specificity of TTE whereas the other one used TTE as the reference standard for AR classification. Using the remaining 4 studies in our hierarchical summary receiver operating characteristic analysis, the area under the curve (AUC) for detecting moderate or severe with TTE was 0.83 (95% CI 0.79 to 0.86; Figure 2).

Discussion

This is the first systematic review and meta-analysis of studies reporting on the level of agreement between CMR and 2D TTE for grading AR severity after TAVI. The major findings of our study are the following: (1) 2D TTE generally correlates poorly with CMR for AR assessment post-TAVI, with wide variation in the level of agreement (kappa coefficient ranging from $-0.02$ to 0.72); (2) despite the significant discordance between the 2 imaging modalities over all grades of AR, 2D TTE has a good ability to discriminate moderate or severe from mild or no AR (AUC 0.83).

The poor and variable correlation between the 2 imaging modalities is most likely due to the limited quantitative accuracy of echocardiography compared with the direct quantification of AR offered by CMR. Despite the numerous studies that have explored the importance of residual AR after TAVI, a unanimous grading system of validated echocardiographic parameters remains challenging. In an attempt to achieve uniformity in the assessment of postprocedural AR, VARC-2 proposed a multiparametric and multivindow approach, which classified AR severity into 3 categories (mild, moderate, and severe) according to semiquantitative and qualitative indices. Recently, Pibarot et al proposed a multimodality approach based mainly on echocardiography and secondarily on complementary imaging methods (cineangiography, invasive hemodynamic assessment, and CMR), with a recommendation for a 5-class scheme (mild, mild to moderate, moderate, moderate to severe, and severe). Although this approach may improve the accuracy of AR grading providing a better classification of debatable jets, it has inherent limitations. First, the recommended echocardiographic parameters in both approaches are based on experts’ consensus without being validated in well-conducted, real-world registries. Moreover, a recent study, which analyzed more than 1,000 echocardiographic
data from 5 TAVI registries, demonstrated that the combination of the VARC-2 parameters was feasible in only half of the cases.

In contrast, CMR appears to be an attractive alternative, which fills the gaps of echocardiography. Phase-contrast velocity mapping allows precise and objective measurements of AR severity by measuring forward and backward blood volume through the aortic valve, enabling the calculation of regurgitant volume, and fraction. Considering the pathophysiological changes and the subsequent concentric hypertrophy that occurs in patients with pre-existing severe aortic stenosis, regurgitant fraction may be more accurate than regurgitant volume for assessing the severity of AR. Compared with TTE, CMR provides much lower interobserver (120.3% ± 62.3% vs 1.7% ± 1.1%) and intraobserver variabilities (75.2% ± 55.9% vs 1.9% ± 1.9%) for quantification of AR fraction after TAVI, suggesting that the highly accurate and reproducible CMR not only improves the quantification of post-TAVI AR, but also exhibits a significant prognostic role in this patient population. Ribeiro et al demonstrated that higher regurgitant fraction, as determined by CMR post-TAVI, was independently associated with increased all-cause mortality and the combined end point of mortality and rehospitalization for heart failure (hazard ratios 1.18, 95% CI 1.08 to 1.30 and 1.19, 95% CI 1.15 to 1.23, for each 5% increase in regurgitant fraction (RF) respectively). Interestingly, a cut-off value of 30% was the best predictor of poor clinical outcomes (AUC 0.678 for 2-year mortality and AUC 0.679 for the combined end point of mortality and rehospitalization for heart failure). The superiority of CMR in predicting adverse events in patients who developed post-TAVI AR was also confirmed by the study of Hartlage et al. Greater than mild AR, as determined by a CMR value higher than 20%, was associated with a higher incidence of the combined end point (all-cause mortality, heart failure hospitalization, recurrent heart failure symptoms necessitating repeat invasive therapy at 1-year follow-up), while the stratification of AR by echocardiography did not show significant predictive value.

Limited data exist on the level of agreement between CMR and other imaging modalities for the quantification of post-TAVR AR severity. Altiok et al reported a modest-to-moderate agreement between 3D TTE and CMR with a kappa coefficient of 0.446. Similarly, Frick et al showed a moderate correlation between angiographic analysis of AR severity and CMR derived regurgitant fraction (r = 0.42, p < 0.01). Although these results suggest a slightly better agreement compared to 2D TTE, the level of agreement is at best moderate. Further research is needed to
explore the accuracy of these methods and establish them in the diagnostic algorithm of AR grading.

Our study has some limitations. First, this was a systematic review of real-world studies, and therefore carries the inherent limitations of observational research. Importantly, there was a significant heterogeneity in the design of included studies. More specifically, different echocardiographic parameters and cut-off values of CMR derived regurgitant fraction were used to assess AR severity, whereas the assessment was performed at different time intervals after the TAVI procedure.

Our systematic review demonstrated that TTE measures of AR correlate poorly with CMR post-TAVI across all grades of AR. However, TTE has a good ability to discriminate mild from moderate or severe AR. Therefore, we recommend TTE for the initial evaluation of AR severity in all patients post TAVI, whereas CMR should follow only when TTE results are equivocal or difficult to obtain. Further prospective studies are needed to identify the optimal diagnostic approach associated with improved outcomes for patients who develop post-TAVI AR.
Table 3
Diagnostic performance of TTE for the detection of moderate/severe post-TAVI AR

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<td>Sensitivity</td>
<td>46%</td>
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<td>19%</td>
<td>75%</td>
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<tr>
<td>Specificity</td>
<td>93%</td>
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AR = aortic regurgitation; TAVI = transcatheter aortic valve implantation; TTE = transthoracic echocardiography.

Disclosures
The authors have no conflicts of interest to disclose.

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