Is valve choice a significant determinant of paravalular leak post-transcatheter aortic valve implantation? A systematic review and meta-analysis

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Abstract

OBJECTIVES: Paravalvular regurgitation (PVR) following transcatheter aortic valve implantation (TAVI) is associated with poor survival. The two main valve delivery systems used to date differ significantly in both structure and deployment technique. The primary objective of this study was to perform a systematic review and meta-analysis of studies identifying PVR in patients post-TAVI using Medtronic CoreValve (MCV) and Edward Sapien (ES) valves in order to identify whether a significant difference exists between valve types. The secondary objective was to identify additional factors predisposing to PVR to provide an overview of the other associated considerations.

METHODS: A systematic review and meta-analysis of the current literature to identify PVR rate in patients with MCV and ES valves was performed. We also sought to examine other factors predisposing to PVR.

RESULTS: A total of 5910 patients were identified from 9 studies. PVR rates for MCV and ES were analysed. MCV was associated with a higher PVR rate of 15.75% [95% confidence interval (CI) 12.48–19.32] compared with ES 3.93% [95% CI 1.05–8.38]. We separately reviewed predisposing factors associated with PVR. A formal comparison of the MCV and ES valve leakage rates by mixed-effects meta-regression with a fixed-effect moderator variable for valve type (MCV or ES) suggested a statistically significant difference in leakage rate between the two valve types (P = 0.0002).

CONCLUSIONS: Unfavourable anatomical and pathological factors as well as valve choice have an impact on rates of PVR. Additionally, certain anatomical features dictate valve choice. A direct comparison of all the predisposing factors at this time is not possible and will require prospective multivariate analysis. There is, however, a significant difference in the PVR rates between valves based on the published observational data available to date. The ES valve associated with a lower incidence of PVR overall; therefore, we conclude that valve choice is indeed a significant determinant of PVR post-TAVI.

Keywords: Aortic valve • Replacement • Heart valve • Transapical • Percutaneous

INTRODUCTION

Paravalvular regurgitation (PVR) of some degree is observed and accepted in the majority of transcatheter aortic valve implantation (TAVI) patients and a recent meta-analysis by Athappan et al. [1]. Both confirmed this association and demonstrated a significant difference in PVR incidence in MCV when compared with Edward Sapien (ES). The management of PVR is not addressed in the current guidelines for management of valvular heart disease; therefore, this issue represents an entirely new, TAVI-specific challenge [2].

Factors such as prosthesis/annulus discongruence, left ventricular outflow tract angle in relation to the aorta (LVOT-AO), valve position and aortic valve calcium can increase the likelihood of developing PVR [3–5]. The primary aim of this study was to perform a systematic review and meta-analysis of studies identifying post-procedural PVR incidence in patients post-TAVI using MCV and ES valves to identify whether any significant difference was notable between valve types. The secondary aim was to identify additional factors predisposing to PVR to allow a discussion of other modifiable and non-modifiable factors warranting consideration.

MATERIALS AND METHODS

Study selection

This review was conducted in accordance with the Prisma guidelines [6]. PubMed was searched by entering the following in the searching algorithm: TAVI and paravalvarular and leak odds ratio (OR) TAVI and paravalvarular and regurgitation OR TAVI and morbidity and leak OR TAVI and morbidity and regurgitation. English was set as a
language restriction. All searches were performed on 10 February 2013. Studies between 2002 and 2013 were included in the search. Two authors (Katie E. O’Sullivan and Aideen Gough) independently examined the title and abstract of citations, the full texts of potentially eligible trials were obtained and disagreements were resolved by discussion.

Inclusion criteria

Studies were included if the following criteria were met: (i) reported data that examined paravalvular leak rates in TAVI post-procedure up to 30 days (ii) reported data on post-TAVI PVR mortality outcomes and (iii) enrolment for TAVI was based on existing and accepted guidelines. We included TAVIs performed both retrogradely and anterogradely and two device types: Medtronic CoreValve (MCV) (Medtronic CV Luxembourg S.a.r.l., Tolochenaz, Switzerland) and Edwards Sapien (Edwards Lifesciences, Santa Ana, CA, USA).

Exclusion criteria

Studies were excluded if any of the following applied: (i) case series containing <100 patients, (ii) studies indexed on PubMed ahead of print on the day of the search, (iii) studies using valves other than MCV (Medtronic CV Luxembourg S.a.r.l.) or ES (Edwards Lifesciences) (iv) studies describing the use of both MCV and ES where individual PVR rates per valve were not described and (v) lack of data detailing PVR or patient characteristics.

Definitions

The literature has a variety of methods whereby paravalvular leak can be classified. For the purposes of this study, clinically significant PVR was defined as moderate/severe or greater or equal to grade 2/4+ regurgitation on echocardiographic examination [2, 3].

Data extraction

Relevant data were collected and included but were not limited to first author, year of publication, journal of publication, study design, number of subjects included, device used, approach used, PVR-associated mortality and follow-up period.

Statistical analysis

Random-effects meta-analysis (with DerSimonian–Laird between-study variance estimation) was performed after transformation of the rates (Freeman–Tukey double arcsine), to combine rates across studies, for each valve type, into a single summary measure. Cronbach’s Q statistic was used to assess heterogeneity of the rates across studies. A formal comparison was performed between MCV and ES PVR incidence by mixed-effects meta-regression with a fixed-effect moderator variable for valve type (CV or ES). Analysis was performed using R version 3.0 (www.r-project.org).

RESULTS

A total of 125 records identified through database searching were reviewed at abstract level. When the exclusion/inclusion criteria were applied, a total of 36 studies examined post-TAVI PVR (Fig. 1). Because of low numbers (n ≤ 100), a further nine studies were excluded. Of the remaining 25 studies, a further six were excluded due to insufficient data. A total of 19 studies were identified that examined post-TAVI PVR in all valve types. A total of four studies examined the ES valve, three the MCV and two studies examined both and reported PVR rate for each individual valve type, these patients were divided into the appropriate category. All data included in this study were observational.

A total of 5910 patients were identified from 9 studies. These were subsequently divided into two valve-specific cohorts for subgroup analyses. A number of studies reported utilized two valve types and where separate PVR rates per valve were expressed these were included in both groups. The studies examined are reported in Table 1.

Between-study heterogeneity was confirmed using Cronbach’s Q statistic for valve-specific analyses (P < 0.00001) and studies were weighted (Table 2). Comparison of the rates for the MCV and ES valves (at the post-procedure and 30-day time point) indicated that the proportion of leakage was higher for the MCV valve, with a rate of 15.8% [95% confidence interval (CI): 12.48, 19.3], than the ES valve, with a rate of 3.9% [95% CI: 1.1%, 8.4%] (Fig. 2).

A formal comparison of the MCV and ES valve leakage rates by mix-effects meta-regression with a fixed-effect moderator variable for valve type (MCV or ES) suggested a statistically significant difference in leakage rate between the two valve types (P = 0.0002). Considerable residual (unexplained) heterogeneity was observed, \( I^2 = 91.9\% \) (P < 0.0001). Additional factors determining PVR were divided into modifiable vs non-modifiable factors. The modifiable factors identified were valve position and size. The non-modifiable factors identified were commissural calcification and LVOT-AO angle; these are reported in Table 3.

DISCUSSION

In summary, our results demonstrate a significantly lower incidence of PVR associated with the ES valve. These findings are supported by the findings of Athappan et al. [1]. However, they are in contrast to those of Chieffo et al. [7] who found no difference between valve types. There are a number of potential reasons for this. While Chieffo et al. performed a propensity-matched comparative study, with 204 patients per group, the numbers were much smaller than those in both the Athappan study and our own. The trend was towards a higher incidence of moderate/severe PVR in the MCV group compared with the ES (1.5 vs 0.5%) although this failed to reach statistical significance, indicating that perhaps with greater numbers this effect might be seen more prominently.

The issue is a complex one and there are multiple factors to consider. We considered the issue of selection bias and examined the methodology of each study included for meta-analysis. No study stipulated indications for choosing one valve type over another. However, certain anatomical characteristics can prompt the use of one valve type over another; for example, low ostial implantation and heavy ostial calcification are more amenable to self-expanding prostheses [8]. Also, there is evidence to suggest a...
difference in PVR based on access type. Although this is yet to be assessed by a randomized controlled trial, transapical TAVI appears to be associated with a lower incidence of PVR according to both the France 2 investigators and the UK TAVI registry [9, 10]. There are a number of key structural and design differences between the MCV and ES valves that could explain the differences seen between valve types. Additionally, a number of dedicated studies examine the factors other than valve choice per se that predispose to PVR post-TAVI (Table 3).

A further consideration is the means by which PVR is assessed. There is a lack of consensus in the literature regarding the classification of PVR post-TAVI. At present, definitions are applied on a study-by-study basis, which must be addressed to allow adequate comparisons among future studies [2, 3]. For the purposes of discussion, these can be divided into modifiable and non-modifiable. Modifiable factors identified were valve position and size. Non-modifiable factors identified were commissural calcification and LVOT-AO angle.

**Modifiable factors predisposing to PVR**

**Design differences between MCV and ES.** We must first consider that each valve differs significantly in structure and deployment technique (Table 4, Figs 3 and 4).
Valve and stent structure. The ES valve is a tricuspid bovine pericardial xenograft mounted in a balloon-expandable, low-profile stainless steel stent crimped onto a balloon catheter prior to the procedure. The MCV is a tricuspid porcine pericardial xenograft mounted on a self-expanding nitinol frame.

The MCV stent is composed of nitinol, a metal alloy of nickel and titanium that exhibits hysteresis, dependence not only on its current environment but also on its past environment. Nitinol stents are said to exert a gentle chronic outward force in a fashion more physiological than balloon-expandable stents. The material is strongly temperature-dependent and exhibits a characteristic stress/strain curve at body temperature [11]. The mechanical properties of nitinol and stainless steel differ significantly. Young's modulus is a measure of the stiffness of an elastic material and this is considerably higher in stainless steel than in nitinol (28 vs 12 Msi). However, the tensile strength of nitinol is higher (276 vs 80 ksi) [12]. It is feasible, therefore, to argue that while nitinol stents may exhibit greater ability to withstand stress and manipulation than stainless steel, it lacks the stiffness required to withstand the compressive force of the hard and calcified native valve.

Table 2: Meta-analysis of incidence of moderate/severe PVR with MCV vs ES

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamburino et al.</td>
<td>0.2097</td>
<td>[0.1793; 0.2427]</td>
<td>22.21</td>
</tr>
<tr>
<td>Gotzmann et al.</td>
<td>0.1414</td>
<td>[0.0961; 0.1979]</td>
<td>16.53</td>
</tr>
<tr>
<td>Nuis et al.</td>
<td>0.1262</td>
<td>[0.0848; 0.1782]</td>
<td>16.99</td>
</tr>
<tr>
<td>Gilard et al.</td>
<td>0.1323</td>
<td>[0.1123; 0.1544]</td>
<td>23.47</td>
</tr>
<tr>
<td>Moat et al.</td>
<td>0.1748</td>
<td>[0.1409; 0.2130]</td>
<td>20.79</td>
</tr>
<tr>
<td>ES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilard et al.</td>
<td>0.0826</td>
<td>[0.0712; 0.0952]</td>
<td>17.95</td>
</tr>
<tr>
<td>Bagur et al.</td>
<td>0.0000</td>
<td>[0.0000; 0.0362]</td>
<td>15.05</td>
</tr>
<tr>
<td>Leon et al.</td>
<td>0.1173</td>
<td>[0.0741; 0.1737]</td>
<td>16.27</td>
</tr>
<tr>
<td>Unbehauen et al.</td>
<td>0.0056</td>
<td>[0.0007; 0.0200]</td>
<td>17.14</td>
</tr>
<tr>
<td>Drews et al.</td>
<td>0.0108</td>
<td>[0.0013; 0.0383]</td>
<td>16.33</td>
</tr>
<tr>
<td>Moat et al.</td>
<td>0.0951</td>
<td>[0.0685; 0.1277]</td>
<td>17.26</td>
</tr>
</tbody>
</table>

Table 4: Differences between MCV and ES

<table>
<thead>
<tr>
<th>Valve features</th>
<th>ES</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue type</td>
<td>Bovine pericardium</td>
<td>Porcine pericardium</td>
</tr>
<tr>
<td>Valve sizes</td>
<td>23 mm, 26 mm</td>
<td>26 mm, 29 mm, 31 mm</td>
</tr>
<tr>
<td>Stent height</td>
<td>14.3–16.1 mm</td>
<td>52–55 mm</td>
</tr>
<tr>
<td>Frame</td>
<td>Stainless steel</td>
<td>Nitinol frame</td>
</tr>
<tr>
<td>Annulus range</td>
<td>18–25 mm</td>
<td>18–29 mm</td>
</tr>
<tr>
<td>Approach</td>
<td>Transfemoral, transapical</td>
<td>Transfemoral, subclavian and direct aortic</td>
</tr>
<tr>
<td>Deployment</td>
<td>Circular valve deployment via balloon inflation</td>
<td>Self-expanding frame</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>6 months</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>

Stent length. The MCV height ranges from 52 to 55 mm, whereas the ES valve is 14.3–16.1 mm in height. Acute angulation between the LVOT and aorta is likely to create paravalvular leak; Sherif et al. [4] determined it to be the strongest predictor of significant aortic regurgitation associated with the MCV, hypothesizing that the incidence was likely due to the more acute angle affecting the ability of the valve to obtain a radial seal sufficient to completely obliterate the paravalvular space. If the device with which you traverse this angulation is almost four times the length, as is the discrepancy seen with the longer MCV, it is likely that there will be more of a tendency to form paravalvular leak. Krsmanovic et al. [13] illustrate this through the use of computer modelling. They

Figure 2: Meta-analysis comparing PVR per valve type.
<table>
<thead>
<tr>
<th>Author</th>
<th>Factor</th>
<th>Patients</th>
<th>Valve</th>
<th>Modality</th>
<th>Measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modifiable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detaint et al.</td>
<td>Prosthesis/valve discongruence</td>
<td>74</td>
<td>ES</td>
<td>TOE</td>
<td>Cover index: 100 × (prosthesis diameter - TOE annulus diameter)/prosthesis diameter</td>
<td>Low cover index an independent predictor of AR ≥ 2</td>
</tr>
<tr>
<td>Santos et al.</td>
<td>Mismatch index</td>
<td>33</td>
<td>ES</td>
<td>Annulus area</td>
<td>Mismatch index: annulus area - prosthesis area</td>
<td>Mismatch index an independent predictor of significant PVR</td>
</tr>
<tr>
<td>Takagi et al.</td>
<td>Valve position</td>
<td>79</td>
<td>MCV</td>
<td>Angiography</td>
<td>Prosthesis position</td>
<td>MCVs placed too low are an independent predictor of clinically significant PVR on multivariate analysis</td>
</tr>
<tr>
<td>Sherif et al.</td>
<td>Valve position</td>
<td>50</td>
<td>MCV</td>
<td>Angiography</td>
<td>Prosthesis position</td>
<td>PVR with MCV is minimized with a prosthesis depth of 10 mm</td>
</tr>
<tr>
<td><strong>Non-modifiable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koos et al.</td>
<td>Aortic valve calcification</td>
<td>57</td>
<td>ES</td>
<td>ECG-gated CT</td>
<td>Agatston score (based on area and peak Hounsfield units in aortic valve calcium)</td>
<td>Agatston score &gt;3000 sensitivity of 86%, specificity of 80% for PVR ≥ 3</td>
</tr>
<tr>
<td>Sherif et al.</td>
<td>LVOT-AO angle Device depth relative to the non-coronary cusp</td>
<td>50</td>
<td>MCV</td>
<td>Aortography</td>
<td>Angle of the LVOT-AO angle</td>
<td>If 2 × LVOT-AO angle + (depth to NCC - 10)² ≥ 50 significant PVR predicted with sensitivity of 85%, specificity of 87%</td>
</tr>
<tr>
<td>Gripari et al.</td>
<td>Commissural calcification, annulus area pre-TAVI, prosthesis diameter</td>
<td>135</td>
<td>ES</td>
<td>TOE</td>
<td>Aortic valve cusp calcification scored 1-4, Area cover index: (1-annulus area/prosthesis nominal area)</td>
<td>Calcification of the commissure between RCC and NCC, area cover index pre-TAVI independent predictor of significant PVR</td>
</tr>
<tr>
<td>Haensig et al.</td>
<td>Aortic valve calcification</td>
<td>120</td>
<td>ES</td>
<td>ECG-gated CT</td>
<td>Agatston score &gt;3000</td>
<td></td>
</tr>
</tbody>
</table>

TOE: transoesophageal echocardiography; AR: aortic regurgitation; LVOT: left ventricular outflow tract; AO: aorta; MCV: Medtronic CoreValve; ES: Edward Sapien; RCC: right coronary cusp; NCC: non-coronary cusp; ECG: electrocardiography; CT: computed tomography.
Figure 3: The ES valve is a tricuspid bovine pericardial xenograft mounted in a balloon-expandable, low profile stainless steel stent crimped onto a balloon catheter prior to the procedure. Stent height ranges from 14.3 to 16.1 mm.

Figure 4: The MCV is a tricuspid porcine pericardial xenograft mounted on a self-expanding nitinol frame. Stent height ranges from 52 to 55 mm.
demonstrate that maximal displacement force (DF) is achieved at peak systolic flow and that the orientation of the DF vector is perpendicular to the greater curvature of the aorta with upward and sideways components. This model is arguably directly applicable to the ‘bend’ seen between the LVOT and aorta crossed during TAVI and illustrates that the lower aspect of the MCV would be susceptible to more perpendicular radial DF, thereby creating a potential area of laxity in apposition at the opposite aspect of the valve or the inner aspect of the curving LVOT-AO. Further echocardiographic studies will be required to dissect the exact nature and location of regurgitant jets to establish whether this principle applies to TAVI in clinical practice. Additionally, the most accurate imaging modality for determining angulation of the LVOT-AO is yet to be established. All studies we reviewed used preprocedural echocardiography (transthoracic ± transoesophageal). Sherif et al. [4] also performed a preoperative ventriculography in 30° right anterior oblique and 50° left anterior oblique projections, together with coronary angiography to compare with post-TAVI aortography in assessing severity of PVR. Furthermore, the ventriculography was used to assess the LVOT axis during preparation for the procedure. Further studies are, therefore, required to first determine the parameters warranting an alternate delivery approach and secondly to assess the most accurate modality for its assessment.

Deployment technique. The ES valve has a delivery system significantly different from that of the MCV; it is positioned by a balloon aortic valvuloplasty catheter, and then deployed by a volume-based inflation balloon. In addition to the mode of deployment, the physiological conditions under which the valves are deployed differ significantly. The ES valve is deployed by balloon dilatation under conditions of rapid ventricular pacing. A number of issues arise at this juncture; considering the mainstay of treatment of PVR is prosthesis post-dilatation after deployment, it is feasible that this method of valve deployment confers greater stent-aorta apposition from the offset, thus reducing PVR post-procedure [14]. Additionally, it is possible that the chronic, slow outward force exerted by the MCV in traversing the rigid stenosed and heavily calcified aortic valve in a patient with severe aortic stenosis is not as effective as the ES valve in preventing PVR. This possibility is supported by the findings of Takagi et al. [15], who demonstrated post-dilatation with a MCV-specific significantly reduced the severity of PVR in those with clinically significant levels.

Valve position. Correct valve positioning depends on the valve type in use. All of the reported studies examining this to date are MCV-specific. Aortography identifying the number of CoreValve struts below the level of the annulus has been utilized as a method of determining it with optimum implantation depth defined as a strut number between at least 1 and <3 at the level of the annulus [15]. In a device-specific study, Takagi et al. [15] examined predictors of PVR in a group of 79 patients undergoing MCV TAVI with an overall incidence of PVR ≥2 in 54.4% (n = 43), determining low CoreValve implantation to be an independent predictor (OR 3.67, 95% CI 1.01–13.35, P = 0.049). Forming part of their predictive model of PVR, Sherif et al. [4] determined that the chance of PVR occurring is minimized when the depth delivery, measured as the distance from the native aortic annular margin on the side of the non-coronary and left coronary cusps to the most proximal edge on the corresponding side of the deployed stent-frame, is ~10 mm.

Prosthesis/annulus discongruence. Naturally, valve sizing is also a critical determinant and a balance between oversizing and annular rupture must be reached without undersizing with its resultant PVR. Instinctually, greater degrees of oversizing are associated with lower rates of PVR and the lowest rate is associated with oversizing >25% [16]. This must be considered alongside the negative aspects of severe oversizing: the need for post-procedural pacemaker insertion and annular rupture such that the appropriate balance must be reached when valve sizing is being performed [16, 17]. A further complicating consideration is that the shape of the annulus in many cases is in fact ovoid. Detaint et al. [3] utilized echocardiographic examinations performed on 74 patients who underwent TAVI with a balloon-expandable device. The cohort with PVR post-procedure was 93% (n = 69) and following multivariate analysis, the authors determined low cover index (a measure of annulus-device congruence determined by the formula 100× (prosthesis diameter-transoesophageal echocardiography (TOE) annulus diameter)/prosthesis diameter) to be an independent predictor of PVR ≥2 (OR: 1.22, P = 0.02). These findings suggest that a certain degree of prosthesis over sizing may be required to overcome this. Confirming this hypothesis, Santos et al. [18] defined a ‘mismatch index’ expressed as: (annulus area-prosthesis area) using 3D TOE planimetry to calculate the annulus area. As with the previous study, they only studied one valve type (ES), finding ‘mismatch index’ to be the only independent predictor of significant PVR (OR 10.614, 95% CI 1.04–17.21, P = 0.04) and comparison of three dimensional and two dimensional TOE determined the former to be more accurate in predicting the appearance of significant PVR.

Non-modifiable factors predisposing to PVR

There are two key anatomical factors predisposing to PVR: the angulation of the aorta relative to the LVOT and the degree of calcification present in the native aortic valve.

Angle between LVOT-AO. Sherif et al. [4] performed a study to determine predictors of PVR, using the MCV. Of the 50-patient cohort, 13 developed grade II PVR and 7 developed grade III PVR. Determining the former to be more accurate in predicting the occurrence of significant PVR with Agatston scores >3000. All patients developing grade 3 PVR showed extremely calcified aortic valves on DSCT (P = 0.03) [5]. These findings relate to a study by Gripari et al. [20] who concluded that calcification of the commissure between the right coronary and non-coronary cusps...
was an independent predictor of significant PVR after TAVI (OR 2.66, 95% CI, P = 0.001). Area cover index was an independent predictor also (OR 0.95, 95% CI, P = 0.006).

**Study limitations**

There were a number of limitations presented by the way in which study data were reported. No randomized controlled trials have been performed and, therefore, data reported are of an observational nature. It was also not possible to determine the most important PVR determinant due to the lack of statistically comparable data. This, however, would be of great interest in the future.

**CONCLUSION**

MCV is associated with significantly higher rates of PVR compared with ES, a finding identified by a number of studies as an independent predictor of mortality [21–25]. Two key anatomical, non-modifiable factors impact on the likelihood of PVR: aortic valve calcification and LVOT-AO angle. While they are non-modifiable, their impact on the valve type is different and valve type dependent. There are two other valve-related, modifiable factors that determine the incidence of PVR: prosthesis-annulus discongruence and valve position. Determination of the most important determinant of PVR will require prospective, multivariate analysis and is beyond the scope of this article. It is, however, reasonable to conclude that valve choice is a significant determinant of PVR post-TAVI.

**Conflict of interest:** none declared.

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