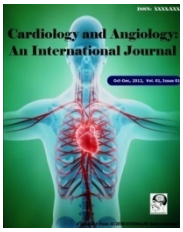

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A Systematic Review and Meta-Analysis of the Incidence of Paravalvular Leak Incidence Post Procedure, Six Months and One-Year Following TAVI

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KEOS, MB and JH designed this study. Authors KEOS and AG performed literature searches and data collection. Author RS performed the statistical analysis. Author KEOS wrote the first draft of the manuscript which was edited by SAE,MB, DS and JH.

Original Research Article

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ABSTRACT

Aims: Paravalvular regurgitation (PVR) post transcatheter aortic valve implantation (TAVI) is associated with poor survival however considerable variability exists between incidences of PVR in current literature. The primary aim of this study was to establish the incidence of PVR post-procedure, at 6-months and 1-year following TAVI. The secondary aims of this study were to review the impact of moderate to severe PVR on mortality and examine strategies employed to reduce PVR.
Methods: PubMed searches included articles detailing paravalvular leak rates post TAVI published between 2002 and 2013. A systematic review and meta-analysis of current literature to identify PVR incidence at three time points was performed using the random effects model of DerSimonian and Laird. A total of 19 studies were identified. For post procedure to 30 days, six months and one year; 7,652, 3,340 and 3,673 patients were included in the analysis of incidence of PVR.
Results: The pooled analysis of PVR incidence was 8.21, 10.2 and 10.98% in each group respectively. Moderate-severe PVR is associated with an increased risk of mortality in all studies reviewed. Management strategies include balloon valvuloplasty,

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transcatheter aortic valve implantation-in-transcatheter aortic valve (TAVI-in-TAV), valve repositioning and the use of occlusion devices.
Conclusion: Moderate-severe PVR occurs in approximately one in ten patients directly following TAVI and does not appear to change significantly in the first year. A number of feasible strategies can be employed to treat PVR. Consideration should be given to the development of early-intervention management algorithms for this patient cohort in order to improve survival post TAVI.

Keywords: TAVI; paravalvular; regurgitation; Cribier Edwards; Medtronic CoreValve; Edwards Sapien.

1. INTRODUCTION

Transcatheter aortic valve implantation has significantly altered the management of severe aortic stenosis in patients for whom surgical aortic valve replacement is not an option, offering improved survival compared with best medical therapy [1]. Since the first TAVI insertion by Alain Cribier in 2002, use of the technique has risen dramatically and increased experience has provided improved insight into the potential drawbacks and future targets for improvement of valve design [2]. The PARTNER (Placement of AoRTicTranscethetER Valve Trial) trial was the first major randomised study performed examining TAVI and while it demonstrated a 20% reduced mortality rate for the TAVI arm versus best medical therapy and non-inferiority compared with surgical aortic valve replacement, it identified a key negative feature associated with TAVI; paravalvular regurgitation (PVR) [1]. The significance of this was highlighted in the two-year PARTNER results, which demonstrated increased mortality associated with even mild PVR [3]. A number of studies report highly variable incidences of moderate to severe PVR post TAVI, a factor demonstrated repeatedly to be an independent predictor of mortality [4-9]. A recent meta-analysis by Athappan*et al* reports pooled overall PVR estimate of 11.7% however there is limited data available estimating PVR at subsequent time points and few studies which follow patients longitudinally [10]. The objective of this meta-analysis is to examine PVR at three time points;postprocedure, 6-months and one year. We also examine the impact of PVR on mortality and the existing management strategies in current practice.

2. MATERIALS AND METHODS

2.1 Study Selection

This review was conducted in accordance with the Prisma guidelines [11]. PubMed was searched by entering the following in the searching algorithm: TAVI and paravalvular and leak OR TAVI and paravalvular 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 10th of February 2013. Studies between 2002 and 2013 were included in the search. Two authors (K.E. O' Sullivan and A. Gough) independently examined the title and abstract of citations, the full texts of potentially eligible trials were obtained and disagreements were resolved by discussion.

2.2 Inclusion Criteria

Studies were included if the following criteria applied: 1) reported data whether randomized or non-randomised, prospective or retrospective, that examined paravalvular leak rates in patients following TAVI 2) reported data on post-TAVI PVR mortality outcomes, 3) enrollment for TAVI was based on existing and accepted guidelines. We included TAVIs performed via all access points; transfemoral, transapical, transsubclavian and transaortic and included all device types; Medtronic CoreValve (Medtronic CV Luxembourg S.a.r.l., Tolochenaz, Switzerland), Edwards Sapien (Edwards Lifesciences, Santa Ana, California), Cribier Edwards (Edwards Lifesciences, Santa Ana, California) and Edwards Sapient XT (Edwards Lifesciences, Santa Ana, California).

2.3 Exclusion Criteria

Studies were excluded if any of the following applied 1) case series containing less than 100 patients, 2) case reports, 3) studies indexed on PubMed ahead of print on the day of the search, 4) duplicate publication, 5) lack of data detailing PVR or patient characteristics.

2.4 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 as described in previous studies [12,13]. For the purposes of analysis, PVR incidence defined as ‘post procedure’ or ’30-days’ were grouped together to obtain one pooled result.

2.5 Data Extraction

Relevant data was collected and included but was 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.

2.6 Statistical Analysis

Random-effects meta-analysis (DerSimonian-Laird between-study variance estimation) was performed after transformation of the rates (Freeman-Tukey double arcsine), to combine rates across studies, for each time point, into a single summary measure. Cronbach’s Q statistic was used to assess heterogeneity of the rates across studies (all $p<0.0001$). Analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL) and R version 3.0(www.r-project.org).

3. RESULTS AND DISCUSSION

A total of 125 records were 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 post procedure, at 30 days, 6 months or one year (Fig. 1). Because of insufficient data or low numbers (n=<100), a further 9 studies were excluded. Of the remaining 25 studies, a further 6 were excluded due to insufficient data. A total of 19 studies remained, of which 13 examined PVR post procedure, 4 at 30 days, 2 at 6 months and 4 at one year, 4 studies examined PVR at more than one time point and were therefore included more than

once (Table 1). These 19 studies were subsequently divided into three cohorts for subgroupanalysis based on timing of PVR assessment post procedure. Heterogeneity was confirmed using Cronbach's Q statistic at all time points ($p<0.00001$). The immediate postprocedure, and the 30-day rates were combined into one analysis; the estimated pooled rate was 8.21% (95% CI 5.02-12.06) (Fig. 2). At the 6 months, the estimated pooled rate was 10.2% (95% CI: 1.5, 24.9) (Fig. 3). At 1-year, the estimated pooled rate was 10.98% (95% CI: 2.84-23.3) (Fig. 4). Separately, five studies were identified from within the search results evaluating the impact of PVR on mortality. These included studies evaluating the Medtronic Corevalve (MCV), Edward Sapien (ES) and Cribier Edwards (CE) valves with follow-up extending from 6 months to 5 years in one study. All studies identified found clinically significant paravalvular regurgitation to be associated with an increased risk of mortality following TAVI (Table 2).

Management strategies identified were balloon valvuloplasty, transcatheter aortic valve implantation-in-transcatheter aortic valve (TAVI-in-TAV), valve repositioning and the use of occlusion devices [14,15]. No clear guidelines are in existence as to the appropriate patient criteria for intervention or the selection of intervention strategy.

4. DISCUSSION

4.1 Rates of Clinically Significant PVR

All studies used to compare PVR included patients of a similar age and Logistic EUROscores as expected in this patient group (Table 1). We found an overall clinically significant PVR rate of 8.21% post procedure up to 30-days (Fig. 2). This finding is inconsistent with the meta-analysis results of Athappan*et al*, which revealed a PVR incidence of 11.7% (95% CI 9.6-14.1). Possible reasons for this discrepancy are that unlike our study, which selected PVR incidence at specific time points, Athappan et al. report their cumulative figure including studies from post procedure up to 2.5 years. Irrespective, a negative impact on mortality has conclusively demonstrated in this group, the natural history of PVR over time is as yet undetermined by current studies and will require dedicated investigation. Results from the PARTNER trial indicate that no changes in PVR to occur over the first year whilst the two-year results indicate some flux with improvement in 42.6%, no change in 41.0% and deterioration in 16.4% of patients [1,3].

The 5-year outcomes following successful TAVI by Toggweileret al. specifically followed changes in PVR over time noting at least moderate PVR rates of 5.7%, 1.2%, 0%, 0% and 0% of patients at 1 to 5 years respectively [6]. This is currently the only study with longitudinal follow-up PVR patients up to 5-years post procedure however it fails to address the specific reasons for the decline in incidence. Further studies are required to fully clarify the contribution of mortality versus improvement in PVR to the decrease in significant PVR over time, as existing data would suggest that there an inherent degree of complexity and individual patient variability not explained by one theory alone [1,3,6].

Table 1. Studies reporting paravalvular leak rates post procedure, 30 days, 6 months and one year post TAVI

Author	Journal	Year	Patients	Valve	Male n (%)	Age	Logistic EUROSCORE	Significant PVR n (%)
D'Onofrio et al (19)	J Thorac and CardiovascSurg	2012	468	ES, SXT	190 (40)	82±4	26±14.4	3 (0.6)
Tamburino et al (8)	Circulation	2011	663	MCV	292 (44)	81±7.3	23±13.7	139 (20.9)
Gotzmann et al (5)	Am J Cardiol	2012	198	MCV	93 (47)	80±6	22±16	28 (13.8)
Nuis et al (20)	Am J Cardiol	2012	211	MCV	107 (50)	80±8	13.8±8.2	24 (12)
Vasa-Nicotera et al (4)	JACC CardiovascInterv	2012	122	ES, MCV	65 (53.3)	81.7±6.8	22.4±13	20 (16.4)
Nombela-Franco et al (21)	JACC CardiovascInterv	2012	211	ES, SXT	86 (40.8)	79±8	24.9±15.2	59 (27.9)
Bagur et al (9)	JACC Cardiovasc Imaging	2011	100	ES, SXT	41 (41)	79±9	25.8±17.6	0
Masson et al (22)	Catheter cardiovascinterv	2010	136	CE, ES	69 (50.7)	85.1±6.9	29±12.5	11 (8.08)
Unbehaun et al (23)	J Am CollCardiol	2012	358	ES	120 (34)	79.5±8.3	38.2±20.7	2 (0.6)
Drews et al (24)	An ThoracSurg	2013	186	ES	64 (34.4)	81±8	63±16	2 (1.07)
Fraccaro et al (25)	Circ CardiovascInterv	2012	384	ES, MCV, SXT	185 (48)	80±7	24±15.6	16 (4.1)
Panico et al*(26)	Minerva Cardioangiol	2012	118	ES, MCV	55 (46.6)	82.5±5.87	25.8±15.4	24 (20.4)
Haensig et al (27)	Eur J CardiothoracSurg	2012	120	ES	30 (25)	82.6±6.2	30.1±15.5	4 (3.33)
Gilard et al*(28)	N Engl J Med	May 2012	3195	MCV, ES	1630 (51)	82.7±7.2	21.9. ±14.3	316 (9.89)
Moat et al (29)	J Am CollCardiol	2011	870	MCV, ES	456 (52.4)	81.9±7.1	18.5±9.4	118 (13.6)
D'Errigo et al (30)	Int J Cardiol	2012	133	MCV, SXT	83 (62.4)	79±7.4	8.8±9.5	8 (6.01)
Leon et al*(1)	N Engl J Med	2010	179	ES	82 (45.8)	83.1±8.6	26.4±17.2	21 (11.8)
Gotzmann et al (7)	Am Heart J	2011	145	MCV	NS	79.1±6.4	21±16.2	25 (17.2)
Gilard et al*(28)	N Engl J Med	2012	3195	MCV, ES	1630 (51)	82.7±7.2	21.9. ±14.3	316 (9.89)
Ussia et al (31)	Eur Heart J	2012	181	MCV	80 (44.2)	80.9±6.1	24±13.5	32 (17.7)
Gilard et al*(28)	N Engl J Med	2012	3195	MCV, ES	1630 (51)	82.7±7.2	21.9. ±14.3	316 (9.89)
Leon et al*(1)	N Engl J Med	2010	179	ES	82 (45.8)	83.1±8.6	26.4±17.2	21 (11.8)
Panico et al*(26)	Minerva Cardioangiol	2012	118	ES, MCV	55 (46.6)	82.5±5.87	25.8±15.4	24 (20.4)

*ES Edward Sapien, MCV Medtronic CoreValve, SXT Sapien XT, ECHO echocardiography, PP post procedure, NS not specified, * included at more than one time point.*

Table 2. The impact of paravalvular regurgitation on mortality and treatment response

Author	Patients	Follow-up	Valve	Impact of significant PVR	
Tambourino et al (8)	663	1 year	MCV	Increased risk of mortality at one year	HR 3.79, 95% CI 1.57 to 9.10, p 0.003
Gotzmann et al (7)	145	6 months	MCV	1. Independent predictor of all-cause mortality	OR 4.26 95% CI 1.58 to 11.44, p 0.004
				2. Independent predictor of poor treatment response	OR10.1, 95% CI 3.2 to 31.93, p <0.001
VasaNicotera et al (4)	122	1 year	MCV ES	1. On univariate analysis, associated with mortality	HR 4.2, 95% CI 2.1 to 8.6, p<0.001
				2. AR* index <25 predicts 1-year mortality, sensitivity 73%, specificity 66%	
Gotzmann et al (5)	198	1 year	MCV	1. All-cause mortality significantly increased	HR 4.89 95% CI 2.79 to 8.55, p<0.001
				2. Cardiovascular mortality significantly increased	HR 7.9 95% CI 3.94 to 15.8, p<0.001
Toggweiler et al (6)	88	5 years	CE ES	Risk of death significantly increased at 5 years with moderate PVR	HR 2.98, 95% CI 1.44 to 6.17

*MCV Medtronic CoreValve, ES Edward Sapien, CE Cribier Edwards *AR index: ([DBP-LVEDP]/SBP)x100*

4.2 Impact of Paravalvular Regurgitation Following TAVI on Mortality and Response to Treatment

Risk factors for developing PVR are multiple and include valve undersizing, malposition, acute angulation between the left ventricular outflow tract and aorta and finally heavy aortic valve calcification. All studies examining PVR-associated mortality have identified moderate-severe PVR as an independent risk factor for mortality at time points ranging from 6 months to 5-years [4-8]. Meta-analysis of five studies by Athappanet al. report an unfavourable outcome in patients with moderate-severe PVR with a HR of 2.27 (95% CI 1.84-2.81, p=0.001)[10]. In 2011, Tambourinoet al. were the first to identify post procedural PVR ≥2 as an independent predictor of late mortality between 30 days and 1 year (HR 3.79) in a multicentre study of early and late mortality predictors in 663 patients undergoing TAVI with CoreValve (Table 2) [8]. Subsequent to this, Gotzmann*et al* published the results of a 145 patient study, again using CoreValve, where moderate to severe PVR was identified as an independent predictor of all-cause mortality at 6 months (OR 4.26, p=0.004) and an independent predictor of poor treatment response (OR 10.1, p=<0.001) [7]. These findings are in line with the Tambourino study but furthermore identify the poorer treatment response of those with moderate to severe PVR as an additional consideration.

Vasa-Nicotera*et al* performed a study of 122 Medtronic CoreValve and Edwards-Sapien valve patients to evaluate the performance of the aortic regurgitation (AR) index as a new haemodynamic parameter in an independent TAVI cohort and validate its application [4]. Using echocardiography, angiography and peri-procedural measurement of the dimensionless AR index ([diastolic blood pressure-left ventricular end-diastolic pressure]/systolic blood pressure) x 100, they found that patients with an AR index <25 had a significantly increased 1-year mortality rate than those with an AR index >25 (42.3% vs. 14.3%, p<0.001) [4]. This confirmed the validity of the AR index in this small cohort, providing prognostic information that was complimentary to the severity of PVR however the event count gathered was not sufficient to support multivariate analysis therefore further studies are required to fully validate it's prognostic value.

Gotzmannet al. subsequently published a study describing the long-term outcome of patients with moderate to severe PVR after TAVI with CoreValve[5]. The 202-patient cohort was divided into groups depending on the presence of moderate to severe PVR, which was found to be the strongest independent risk factor of all-cause-mortality (HR 4.89, 95% CI 2.78-8.56, p<0.001) and the strongest independent risk factor of cardiovascular mortality within (HR 7.9, 95% CI 3.95-15.81, p<0.001) and after 30 days (HR 9.44, 95% CI 4.193-21.27, p<0.001). The 5-year results of an 88-patient cohort who underwent TAVI with the Cribier Edwards or Edwards Sapien valves demonstrate that PVR is at least moderate in 5.7%, 1.2%, 1.2%, 0%, 0% and 0% of patients at years 1-5 respectively and at least moderate PVR post TAVI was associated with an increased risk of death (HR 2.98, 95% CI 1.44-6.17) confirming the adverse prognostic value of moderate to severe PVR in TAVI patients [6].

4.3 Management of PVR Following TAVI

The first indicator of moderate to severe PVR post insertion is an unexpectedly low aortic diastolic pressure. Rising ventricular filling pressure may lead to ventricular dysfunction, myocardial ischaemia and shock. Confirmation is obtained using aortography or more accurately with transoesophageal echocardiography [16]. Four key management options

currently exist which address PVR depending on the aetiological factor responsible; balloon valvuloplasty, TAVI-in TAV, valve repositioning and the use of occlusion devices.

Ussia*et al* identified 18 of 110 patients post Medtronic CoreValve TAVI with early implant failure, defined as sub-optimal positioning, prosthesis under-expansion resulting in PVR with haemodynamic instability and intraprocedural prosthesis embolisation[15]. The commonest cause identified was prosthesis under-expansion resulting in moderate to severe PVR (44.4%). Prosthesis deployment too low or too high resulting in severe PVR occurred in 22.5% and 5.5% of patients respectively. The group demonstrates that in the case of valve under-expansion it is possible to successfully treat with post implant balloon dilation under rapid pacing which results in reduced PVR. In the case of a valve positioned too high, they used the Core Revalving System (CRS) to allow the valve be aligned with the aortic annulus. In the case of a valve being too low a goose neck catheter engaging one of the loops of the implanted valve can gently pull the device towards the ascending aorta [15].

Martinez et al. studied a cohort of 100 patients, of which 27 were identified as having haemodynamically significant PVR requiring additional interventions during or after the index procedure [17]. They performed repeat ballooning on 19 patients, 7 TAVI-in-TAV procedures and 6 transcatheter device closure procedures. Procedural success rate was 90.6% and mortality rates were reported as 7.4%, 18.5% and 22% at 30-days, 3 months and 6 months respectively [17]. They report one particularly complicated case requiring 4 procedures; TAVI insertion, balloon post insertion, attempted use of a Vascular plug II to close a PVR jet adjacent to the left coronary cusp which ultimately required closure with a VSD occlude device 176 days post index procedure. This would indicate that while initial attempts to treat PVR may not yield success, subsequent interventions can be attempted with ultimate success obtained. Another case presented underwent valve-in valve during the index procedure and presented with worsening PVR around the left and non-coronary cusps underwent successful closure with a Vascular II plug via retrograde transfemoral approach 42 days after the index procedure [17].

In addition to the aforementioned study, there are a number of case reports and case series of valve-in valve deployment to treat severe PVR post TAVI. Ussia*et al* describe a case of severe PVR post TAVI ballooned unsuccessfully post procedure which was managed with repeat TAVI resulting in a reduction of PVR from 4+ to 1+ however patient follow up was only reported as far as six months and while PVR remained +1 at this stage [14].Guerioset al. performed valve-in-valve deployment for 6 patients with mild residual PVR in 5 and moderate in 1 [18]. Of their series, they performed retrieval of the initial aortic valve to the ascending aorta prior to re-implantation of a new valve therefore this was not an issue for that 4-patient group. The remaining two patients who did have true TAVI-in TAV had a mean indexed effective valve area of 0.97+/- 0.17cm^2 /m^2 and therefore no prosthesis-patient mismatch, however this is a concern associated with the technique.

Whilst TAVI-in TAV may be required, as an emergency or elective procedure to overcome PVR in addition to structural valve dysfunction, little is known about the longer-term consequences associated. Optimum management is dependent on the aetiology of PVR. For patients in whom malposition is the issue, this can be addressed as described above however; it appears that balloon valvuloplasty post insertion is likely to form the mainstay of PVR management going forward. Specific management algorithms will likely be required to determine PVR severity warranting intervention and guide the choice of management appropriately.

4.4 Factors Influencing PVR

These are easily divided into non-modifiable; such as the angle between the left ventricular outflow tract and the aorta and aortic valve calcification, and modifiable factors such as valve choice, prosthesis-annulus discongruence and valve position. A recently published meta-analysis has demonstrated a significantly higher incidence of PVR associated with the Medtronic CoreValve in comparison to the Edwards Sapien valve making valve choice an important determinant [19].Under what anatomical circumstances this comes into play mostly remains unknown. Avoidance of PVR is therefore multifactorial. However, accurate valve sizing, positioning and appropriate valve choice appear to be the key factors in its avoidance. A high index of suspicion for its presence should be maintained as increasingly, it appears that prompt management as outlined above is superior to leaving PVR untreated.

4.5 Study Limitations

The studies examined in our meta-analysis were pooled results inclusive of all valve types and was limited to one-year post procedure, information regarding the outcome of these patients beyond this will be valuable. Additionally, the primary end point of many studies included was not PVR. There were a number of methods whereby different authors classified PVR, which has the potential to reduce the accuracy of our results. Despite these limitations, patient numbers included in our meta-analysis are large and our results highlight the need for ongoing evaluation of the natural history of moderate-severe PVR post TAVI.

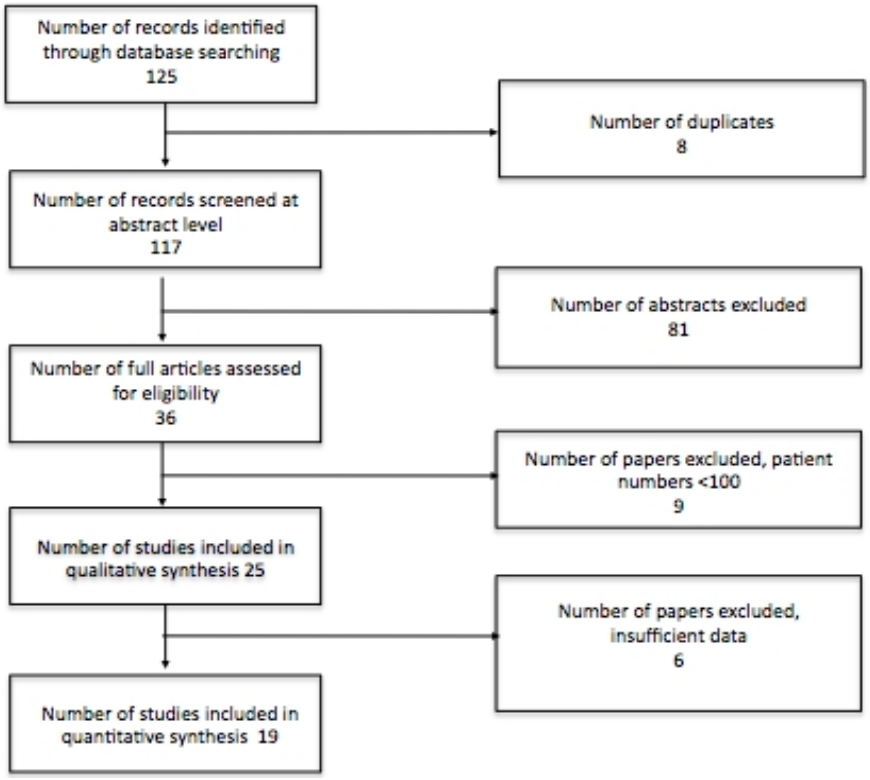

Fig. 1. Prisma diagram illustrating study selection

Post-procedure and 30 day

Study	Proportion	95% confidence interval	Weight
D Onofrio et al.	0.0064	[0.0013; 0.0186]	6.12
Tamburino et al.	0.2097	[0.1793; 0.2427]	6.18
Gotzmann et al.	0.1414	[0.0961; 0.1979]	5.87
Nuis et al.	0.1137	[0.0743; 0.1645]	5.90
Vasa-Nicotera et al.	0.1639	[0.1031; 0.2418]	5.62
Nombela-Franco et al.	0.2796	[0.2202; 0.3454]	5.90
Bagur et al.	0.0000	[0.0000; 0.0362]	5.49
Masson et al.	0.0809	[0.0411; 0.1401]	5.69
Unbehaun et al.	0.0056	[0.0007; 0.0200]	6.07
Drews et al.	0.0108	[0.0013; 0.0383]	5.85
Fraccaro et al.	0.0417	[0.0240; 0.0668]	6.08
Panico et al.	0.2034	[0.1349; 0.2873]	5.60
Haensig et al.	0.0333	[0.0092; 0.0831]	5.61
Gilard et al.	0.0989	[0.0888; 0.1098]	6.29
Moat et al.	0.1356	[0.1136; 0.1602]	6.21
D Errigo et al.	0.0602	[0.0263; 0.1151]	5.68
Leon et al.	0.1173	[0.0741; 0.1737]	5.83

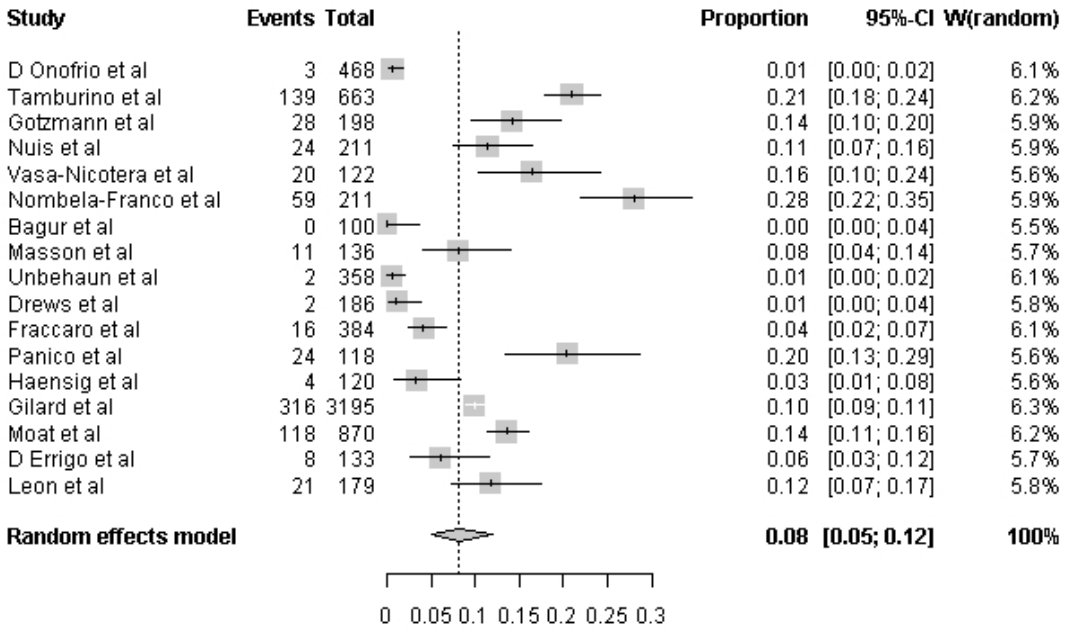

Fig. 2. Studies included in the analysis of PVR incidence post-procedure and at 30-days with Forest plot representing meta-analysis of studies included

Study	Proportion	95% confidence interval	Weight
Gilard et al.	0.0520	[0.0445; 0.0602]	52.03
Gotzmann et al.	0.1724	[0.1148; 0.2439]	47.97

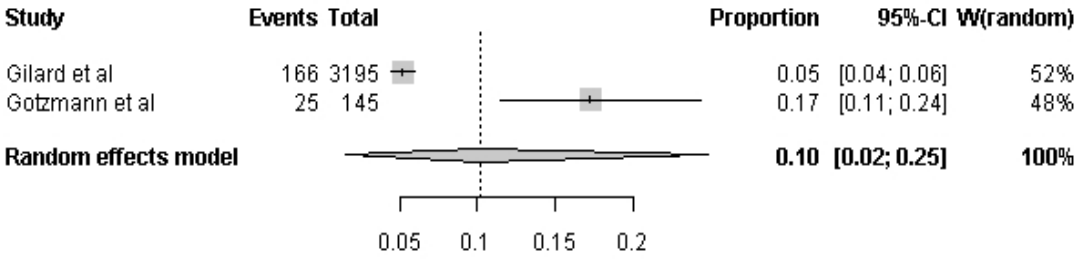

Fig. 3. Meta-analysis of PVR incidence at 6 months

Study	Proportion	95% confidence interval	Weight
Ussia et al	0.1768	[0.1242; 0.2403]	24.86
Gilard et al	0.0263	[0.0210; 0.0324]	26.05
Leon et al	0.1061	[0.0651; 0.1608]	24.85
Panico et al	0.1780	[0.1137; 0.2591]	24.24

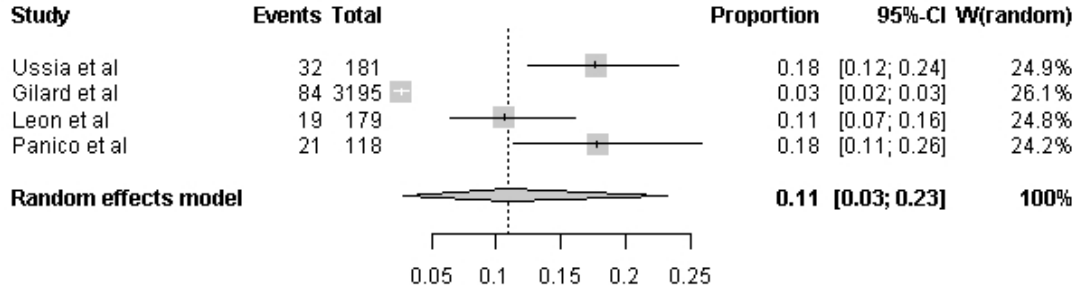

Fig. 4. Meta-analysis of PVR at 1 year

4. CONCLUSION

PVR occurs post TAVI in 8.21, 10.2 and 10.98% of patients post procedure to 30-days, at 6 months and one year respectively. All studies performed to date demonstrate an increased risk of mortality with moderate to severe PVR. This would suggest that post procedure intervention could improve survival in this patient cohort. A number of management strategies can be employed to improve PVR, depending on aetiology, however specific algorithms are required to guide physicians in identifying patients for whom intervention is appropriate.

CONSENT

Consent is not required.

ETHICAL APPROVAL

Ethical approval is not required.

ACKNOWLEDGEMENTS

The authors have no disclosures to make.

COMPETING INTERESTS

The authors declare that no competing interest exists.

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