The Predictive Value of Baseline Pulmonary Hypertension in Early and Long Term Cardiac and All-cause Mortality after Transcatheter Aortic Valve Implantation for Patients with Severe Aortic Valve Stenosis: a Systematic Review and Meta-analysis

DAMIANOS G. KOKKINIDIS, MD

ASSIGNED PROFESSOR/MENTOR:

Dr. GEORGE GIANNAKOULAS, MD, PHD

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Abbreviations

PH: Pulmonary hypertension

AS: Aortic stenosis

PAH: Pulmonary arterial hypertension

WHO: World health organization

HFrEF: Heart failure reduced ejection fraction

LV: Left ventricle

RV: Right ventricle

RHC: Right heart catheterization

PCWP: Pulmonary capillary wedge pressure

AVR: aortic valve replacement

SAVR: Surgical aortic valve replacement

TAVR: Transcatheter aortic valve replacement

CT: Computer tomography

PASP: pulmonary artery systolic pressure

mPAP: mean pulmonary artery pressure

HR: Hazard ratio

OR: Odds ratio

RR: Risk ratio
Chapter 1: Pulmonary Hypertension

Pulmonary hypertension is defined as elevated pressures in the pulmonary artery and is associated with increased mortality. WHO classification for different PH subtypes shows that different subgroups share similarities and differences and they are not always mutually exclusive. It is common in the clinical practice to encounter patients who belong to more than one PH subtypes. WHO Group 1 PH is the pulmonary arterial hypertension (PAH) which can be either idiopathic PAH or secondary to other rare causes including heritable PAH, HIV, congenital heart disease, connective tissue disease and other clinical conditions. WHO Group 2 includes PH secondary to pulmonary venous hypertension (left heart disease). Group 3 is associated with hypoxemia due to lung disease (can be either associated with interstitial lung disease or chronic obstructive pulmonary disease). Group 4 is the chronic thromboembolic form of PH, while Group 5 includes miscellaneous etiologies.
The majority of idiopathic PAH patients are women and their mean age at diagnosis is much younger compared to patients with WHO Group 2 PH. Pulmonary arterial hypertension pathology includes lesions in the level of distal pulmonary arteries such as vasoconstriction, hypertrophy of the media and fibrosis of the intima. Contrary to PH WHO group 1, the other PH groups are much more common and can affect up to 15% of the general population.\textsuperscript{1-3} In WHO Group 2 PH, elevated pressures in pulmonary arteries are secondary to elevation in left heart pressures, including mitral valve stenosis and heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).\textsuperscript{4-6} Moreover, non-Group 1 PH types have a much better prognosis compared to idiopathic PAH. Contrary to the left ventricle (LV) and left heart in general which participates in a high pressure system, the right ventricle is a thin walled cavity that can only withstand low pressures of the pulmonary artery.\textsuperscript{7,8} Thus, the end result of high PH pressures is a dysfunction and finally failure of the right ventricle.

For the diagnosis of high PA pressures, non-invasive imaging (Doppler Echocardiography) and right heart catheterization (RHC) can be used. RHC is the gold standard since it offers more accurate measurements but is an invasive approach.\textsuperscript{7,9-11} Doppler echocardiogram can result in inaccurate measurements not
only secondary to ultrasound related issue but also in patients without tricuspid valve regurgitation and other diseases that can affect the results of the Bernoulli equation, which is used for the Doppler reading (anemia, hypoxemia, red blood cell deformity). Given the limitations of echocardiography for diagnosing PH, expert consensus statements and guidelines use support the use of invasive diagnostic testing to confirm the diagnosis of PH (especially PAH) when possible. RHC criteria for differentiation between PAH and pulmonary venous hypertension include but they are not limited to PCWP < 15 mm Hg.\textsuperscript{12,13} If there is uncertainty about the accuracy of the PCWP, direct measurement of LV end-diastolic pressure should be considered. Because the PH subtype that mainly responds to specific pulmonary vasodilator treatment is PAH, it is generally recommended to perform a diagnostic RHC in the majority of patients before initiating treatment. There are four main classes of pulmonary vasodilators: phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, endothelin receptor antagonists, and prostacyclin analogues, all of them are recommended for PAH. However, it is worth mentioned that in the absence of specific therapies, many patients with the more common forms of PH (non-Group I) are treated with pulmonary vasodilators despite the absence of convincing data.
Chapter 2: Aortic Valve Stenosis

A number of different clinical, genetic and anatomical factors can participate in the pathogenesis of aortic stenosis. Presence of congenital bicuspid valve accounts for a significant percentage of the relatively younger patients who will undergo valve replacement for aortic stenosis. Rheumatic heart disease is rare nowadays in the western world, but this disease remains common in developing countries.\textsuperscript{14,15} The onset of clinical symptomatology is not always associated with the same degree of aortic stenosis; some patients might remain asymptomatic despite having hemodynamically severe disease. Different subtypes of aortic stenosis have also different clinical associations and manifestations. For example, rheumatic aortic disease is usually associated with mitral and tricuspid valve involvement, PH and right heart dysfunction. Aortic stenosis is a disease entity that can dramatically increase the risk for cardiovascular events.\textsuperscript{16,17} Important clinical endpoints in patients with AS are mainly affected by the degree of clinical symptomatology, severity of valve obstruction and the left ventricular response to pressure overload. Aortic valve replacement (surgical or percutaneous) has been shown to increase the survival of patients with severe, symptomatic AS.\textsuperscript{17-20} In order to confirm a diagnosis of severe AS, a transvalvular velocity of at least 4m per second is needed apart from the symptoms.\textsuperscript{21-24}
Apart from symptomatic patients, a timely intervention can also benefit asymptomatic patients who might have a high risk for disease deterioration and HF symptoms in the future. For these patients, measures of disease severity can be proven very useful. AS symptoms include but are not limited to decreased exercise tolerance, dyspnea on exertion, lightheadedness and angina. Syncope and heart failure symptoms will also appear later in the disease course.

For patients whose physical examination and symptomatology is suspicious for AS, echocardiography can help with the diagnosis. For patients with an estimate life expectancy > 1 year, AVR should be considered as this procedure is likely to improve patients’ symptoms and stop disease progression. The exact timing of the intervention can be important in the disease process and should be based on many different factors, including age, comorbidities, presence of concomitant coronary artery disease, heart failure, echocardiographic findings, procedural costs etc. This is where the heart team (heart surgeon, interventional cardiologists, imaging cardiologists, general cardiologists, anesthesiologists, primary care providers) comes to play an important role in order to choose the best option for the patient.

If an intervention is needed, options include surgical (SAVR) and transcatheter aortic valve replacement (TAVR). SAVR is used for the majority of patients without excessive comorbidities that make them being inoperable. SAVR can be performed with two different valves (mechanical or bioprosthetic). In general mechanical valves
have an improved long-term durability and are preferred for patients who do not have contraindications to Vitamin K antagonists. Bioprosthetic valves can be used in elderly patients who may have contraindications to anticoagulation and have relatively limited prognosis. For the last 10 years, TAVR is utilized more and more in patients with AS and the indications are constantly expanded.

Chapter 3: Transcatheter aortic valve replacement

AVR is an intervention that has been proven to prolong the survival of patients with severe AS. Often these patients have contraindications for SAVR, and TAVR is an alternative option. TAVR should be the intervention of choice for patients with severe symptomatic AS who have a prohibited risk of surgery but an expected survival more than 12 months. TAVR is also an excellent alternative to SAVR in patients with a high (but not prohibited) risk for surgery. Many ongoing trials are expected to expand TAVR applications to a larger pool of patients in the future. Two different valves for TAVR are currently approved by the U.S Food and Drug Administration (FDA): Edwards Sapien system and the CoreValve. When the Edwards Sapien aortic valve, which is self-expanding valve was tested in the Partner A and B trial and was found to be non-inferior compared to the surgical replacement in mortality (short or long term) and superior to medical therapy for
inoperable patients. Comparisons also between the CoreValve system (balloon expandable) and the surgical approach have resulted in similar outcomes in severe AS patients who are inoperable.\textsuperscript{27} No mortality difference was found between the two valves systems, but the balloon expandable valve system was found to be associated with lower aortic valve regurgitation risk and lower incidence of valve embolization, need for new pacemaker implantation and the need for new valve implantation (valve in valve). Pre-TAVR routine work-up includes CT scan, RHC and left heart catheterization.\textsuperscript{28-30} With the technological advancements in the field, it is likely that more and more AS will be selected for TAVR in the future, but given the high cost of the procedure, physicians should maintain a high threshold in patient selection.
Abstract

Background: Transcatheter aortic valve implantation (TAVI) is a safe and effective alternative to surgical aortic valve replacement (SAVR) for the treatment of severe aortic valve stenosis (AS). The impact of concomitant baseline elevated pulmonary artery pressures in these patients on outcomes after TAVI has not been established yet, since different studies used different definitions of pulmonary hypertension (PH).

Objective: To reach to conclusions for the impact of PH on early and late cardiac and all-cause mortality.

Methods: We performed a meta-analysis of studies comparing patients with elevated pulmonary artery pressures (defined as pulmonary hypertension) versus patients without elevated pulmonary artery pressures. We first performed stratified analyses based on the different PH cut-off values utilized by the included studies and subsequently pooled the studies together irrespectively of their cut-off
values. We used a random effects model for the meta-analysis and assessed heterogeneity with I-square.

Results: In total 22 studies were included in this systematic review. Our results show that PH is associated with increased 30-day cardiac mortality, late cardiac mortality and late all-cause mortality. The association between baseline PH and 30-day all-cause mortality remains unclear. The PH cut-off value that was most likely to predict cardiac and all-cause mortality was pulmonary artery systolic pressure of 60mmHg.

Conclusion: This systematic review and meta-analysis points out the importance of baseline PH in predicting mortality outcomes after TAVI. Additional studies are needed to clarify the association between elevated baseline pulmonary artery pressures and outcomes after TAVI.
INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been proven to be an effective and safe alternative to surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis (AS) with comorbidities and a high surgical risk.\textsuperscript{27,31,32} PH prevalence ranges from 20\% to 71\% across different TAVI series, indicating the existing heterogeneity in PH definition.\textsuperscript{33} Pulmonary hypertension (PH) has been reported by some studies to be an independent risk factor for cardiovascular and overall mortality after TAVI, in addition to its established association with worse outcomes post-surgical aortic valve replacement (SAVR).\textsuperscript{34-38} Moreover, given the higher perioperative risk of PH patients, the benefits of valve replacement in these patients merit discussion. In addition, there is an absence of a clear PH cut-off point that could predict which patients should not undergo TAVI or have a higher risk for post-TAVI mortality and morbidity. PH (defined as pulmonary artery systolic pressure (PASP) > 60 mm Hg) is included in the EuroSCORE criteria but not in the Society of Thoracic Surgeons score.\textsuperscript{39} Due to the heterogeneity in PH definitions used by different studies (elevated PASP or elevated mean pulmonary artery pressure) and despite the plethora of studies reporting on the association of
baseline PH/elevated pulmonary artery pressures with post-TAVI mortality, there is not a clear consensus on the values that affect the mortality after TAVI. Thus, our aim in this study is to systematically review the literature and qualitatively and quantitatively synthesize the literature on the association of baseline PH and early and late cardiovascular and overall mortality.

**METHODS**

This review protocol has been registered in the PROSPERO International Prospective Register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017059929). This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Medline, Scopus and Cochrane databases were reviewed for prospective or retrospective studies published until April 10, 2017 reporting comparative outcomes for early and late cardiovascular or overall mortality after TAVI for patients with baseline PH vs. patients without PH.

**Study Selection and Data Extraction**

Three different databases were searched (Medline, Scopus and Embase). The
keywords used were the following: tavi, transcatheter aortic valve, percutaneous aortic valve, transcutaneous aortic valve, tavr, transcather aortic valve replacement, transcatheter aortic valve implantation, pulmonary hypertension. A manual search of the references of the included papers was also performed in order to identify additional relevant papers. Two reviewers (DGK, CAP) independently assessed the eligibility of the included studies. A third reviewer (EKO) was involved in order consensus to be reached when necessary. In order a study to be eligible for this review it had to fulfill the following inclusion criteria: i) original research studies published in any language and conducted in patients with severe aortic stenosis who undergo TAVI; ii) studies presenting comparative mortality (cardiac or overall) outcomes between patients with PH and without PH. For PH we used the definitions utilized by the different included studies, with PH defined as mean pulmonary artery (PA) pressure 25 mm Hg or greater. When this definition was absent, we enrolled in the PH group, patients with PASP higher than 40. When we encountered studies that described the same or overlapping series of patients with the same outcomes and endpoints, only one of the studies was included for every endpoint. However, when two studies had included common patients/were conducted in the same centers but reported outcomes in a different way (PH definitions, endpoints, hazard ratios or relative risks/odds ratios), they were both included in our systematic review but were never pooled together in order to avoid
counting patients twice in the meta-analysis. The detailed flow diagram is presented in Figure 1.

Two reviewers (DGK, CAT) independently extracted the data and discrepancies were resolved by the involvement of a third reviewer (EKO).

**Outcomes**

This study had 4 different outcomes: i) 30-day cardiac mortality; ii) 30-day all-cause mortality; iii) late (>6-month) cardiac mortality; iv) late (>6-month) all-cause mortality. Cardiovascular mortality instead of cardiac mortality was used when studies reported only cardiovascular mortality.

**Data Analysis**

The meta-analysis for all outcomes was performed with two different ways: i) across studies reporting outcomes with hazard ratios (HRs); ii) with relative risks (RRs)/odds ratios (ORs) across studies that originally reported outcomes with absolute or relative frequencies of patients who had an event (cardiac or all-cause death) in the PH and non-PH group. The authors of the original studies were contacted for additional data as needed. When the original studies reported only relative frequencies of the events, the absolute events numbers in each arm were calculated. The included studies separately for ORs and HRs were combined.
according to their cut-off values for PH definition initially and were next pooled independently of their PH definition. For studies that reported comparisons for two different PH potential definitions (i.e PASP=40 mmHg and PASP=60 mmHg), we used the highest value for the pooled meta-analysis. Studies with potentially duplicated populations were not included in the pooled analysis, so that every population/center would be counted once. A random effects model was selected a priori because the included studies had heterogeneous study design and baseline patients characteristics.\textsuperscript{41} A forest plot was used to illustrate the individual study findings and the random effects meta-analysis results. The I-square statistic ($I^2$) was used to assess for heterogeneity among the studies. Values $<25\%$ indicated low, 25\% to 70\% indicated moderate, and $>70\%$ indicated severe heterogeneity.\textsuperscript{42} Contoured enhanced funnel plots were used to visually assess for publication bias and the Egger's test to quantitatively assess it.\textsuperscript{43} Continuous variables are presented as mean values $\pm$ SD. Categorical variables are presented as absolute and relative frequencies. The estimated incidence rates were expressed as percent and 95\% confidence interval (CI). The results were regarded as statistically significant at a two-sided $p <0.05$. We used STATA 14.1 (StataCorp, College Station, Texas) as the statistical software for all analyses.
Results

Study Selection Process and Studies Characteristics

In total 956 studies were screened and 28 full-text articles were reviewed for eligibility. A PRISMA flow diagram with the selection process is shown in the Data Supplement (Supplementary Figure 1). There were six studies that despite meeting the initial inclusion criteria, were excluded from the analysis since they included potentially duplicated populations without reporting different cut-off values or different outcomes/endpoints. Finally, 22 studies were included in our meta-analysis. In total, 16 of the included studies were conducted in Europe. The mean age of the included studies ranged from 78±6 to 85±7 years, while the percentage of female patients ranged from 34.1% to 65.2%. The total number of enrolled patients in the individual studies ranged from 122 to 3195. Fifteen out of 22 studies reported the diagnostic method they used for PH. Transthoracic echocardiogram was used by 10 studies, right heart catheterization by three studies, while a combination of the two strategies by two studies. All the patients in this meta-analysis had severe baseline AS. The most commonly used valves were Edwards Sapien and Sapien XT, and Medtronic’s CoreValve. Transfemoral, transapical and the subclavian approach were used in almost all of the included cases. Details on baseline clinical and procedural characteristics of the included studies are presented in Table 1 and in the Supplementary Table 2. The
assessment of the risk of bias of the included studies is presented in detail in the Data Supplement (Supplementary Table 1), while the overall risk of bias for each included study is presented at Table 1. The results of the Egger's test and visual inspection of the contour funnel plots did not show publication bias in the included studies. A quantitative synthesis was performed for 4 different clinical outcomes (30-day cardiac mortality, 30-day all-cause mortality, late cardiac mortality, late all-cause mortality) with two different methods (HRs and ORs) for each outcome. Across the different cut-offs for all the outcomes, MPAP=25 and PASP=60 were more strongly associated with worse survival (Table 2).

30-day cardiac mortality

Cardiac mortality after 30-days as an outcome was used in total by six studies (one with HR and five with RRs). In the pooled analysis, PH independently of the cut-off value used was associated with 30-day cardiac mortality (pooled RR [pRR]: 1.41; 95% CI: 1.04 - 1.92, without important heterogeneity, $I^2$=28%). The pRRs for different PH cut-offs used by the studies are presented in Table 2. Only one study used HR for 30-day cardiac mortality, thus we did not proceed with a HR meta-analysis for this outcome.46

30-day all-cause mortality
All-cause mortality after 30-days as an outcome was reported in total by 16 studies (three reported HRs only, 11 RRs only and two both RRs and HRs). The pooled HR among five studies was 0.95; 95% CI: 0.33 – 1.56, with significant heterogeneity ($I^2=79.2$, Figure 2), while the pooled RR among 13 studies was 1.77 (1.39 – 2.24), with moderate heterogeneity ($I^2=47.8\%$, Figure 3). Table 2 presents the subgroup analyses for the different PH cut-offs.

**Late cardiac mortality**

Late cardiac mortality as an outcome was used in total by six studies. The pooled HR among the three studies was 1.3; 95% CI: 1.3 – 2.3; $I^2=0$ (Figure 4), while the pooled RR was 1.48; 95% CI: 1.25 – 1.76; $I^2=20.3$ (Figure 5). Thus, baseline PH was associated with increased late cardiac mortality in both of our pooled analyses.

**Late all-cause mortality**

Late all-cause mortality as an outcome was used in total by 15 studies. Baseline PH was associated with late all-cause mortality in both the HR meta-analysis (12 studies, HR: 1.56; 95% CI: 1.13 – 1.98; $I^2=79.7$, Figure 6) and in the meta-analysis of RRs (12 studies, RR: 1.66; 95% CI: 1.35 – 2.03; $I^2=79.8$, Figure 7).
Discussion

This study was a meta-analysis of 22 studies and pooled individual studies’ results for 4 different outcomes. Our results show that: i) baseline PH is associated with 30-day cardiac mortality; ii) baseline PH association with 30-day all-cause mortality remains unclear; iii) baseline PH is associated with late cardiac mortality; iv) baseline PH is associated with late all-cause mortality.

Our results support the findings of several studies that have previously reported a prognostic value of baseline PH in patients with severe AS who undergo a TAVI procedure. A previous well-conducted meta-analysis on this topic by Tang et al. also showed the impact of baseline PH in post-TAVI mortality. Our team has already pointed out the methodological remarks of this study and believes that by providing a meta-analytic approach for both HRs and RRs separately, with different meta-analyses for all the cut-off values used by the individual studies we were able to further validate and expand their findings. Similarly to TAVI, SAVR studies for patients with severe AS have shown an association of PH with increased risk of post-operative mortality. Interestingly however, PASP values take more time to normalize after SAVR compared to TAVI.
Despite the number of studies that have explored the association of PH with outcomes post-TAVI, the choice of the optimal cut-off point for the definition of PH as a risk factor in the pre-operative evaluation of these patients remains unclear. Currently, the only established score that takes pre-TAVI PH values into account is the euroSCORE (PASP assessed by echocardiography = 60 mmHg). In our analysis, we calculated pooled estimates for hazard and risk ratios for different cut-offs (PASP=60mmHg, PASP=50mmHg, PASP=40mmHg, MPAP=25mmHg). Across these different cut-offs, MPAP=25mmHg and PASP=60mmHg were more strongly associated with mortality risk. Our results thus confirm that the use of 60mmHg as a cut-off for PH definition at the euroSCORE is correct and justified, while MPAP=25 could be a reasonable alternative. However, it has to be emphasized that accurate mPAP measurements can be only made with RHC.

Another important point to make is that postcapillary PH (mean pulmonary artery systolic pressure ≥25 mmHg and left ventricular end-diastolic pressure >15 mmHg both assessed by right heart catheterization) has proved to be benign with regards to post-TAVI outcomes, compared to precapillary (mean pulmonary artery systolic pressure ≥25 mmHg and left ventricular end-diastolic pressure ≤15 mmHg) or combined and pre- and postcapillary PH (mean pulmonary artery systolic pressure ≥25 mmHg and left ventricular end-diastolic pressure >15 mmHg and pulmonary artery diastolic pressure gradient ≥7 mmHg) in the study by O'Sullivan et al.46
Postcapillary PH is always associated with left heart disease.\textsuperscript{67} As expected, this group of patients was the one that showed the highest improvement after TAVI, since the improvement of their valvular problem with the procedure improved their left heart function and subsequently their PH which was induced by backward transmission of high left-sided filling pressures. On the other hand, patients with precapillary PH with possible fixed intrinsic changes to the pulmonary vasculature did not have an improvement in PASP or right ventricular function after the intervention. Interestingly however, patients with combined PH showed an improvement in their PASPs after TAVI, suggesting that the changes in this group are not irreversible. While it is not clear whether these differences are in fact due to a different underlying PH etiology,\textsuperscript{68} they could have an impact on patient selection before TAVI. Being able to predict the subgroup of PH patients with the highest improvement in their PASP values after TAVI is also useful because patients who have lower PASPs after TAVI tend to have a better prognosis compared to patients who continue to have elevated PASP.\textsuperscript{52,60} Furthermore, chronic obstructive pulmonary disease is a common comorbidity among patients with post-capillary PH.\textsuperscript{69} Previous studies have shown that patients with chronic obstructive pulmonary disease have indeed increased mortality rates after TAVI, but despite these limitations TAVI remains an important therapeutic option in this patient group.\textsuperscript{70} The worse outcomes observed in patients with baseline PH highlight the need for
further research and development of novel therapies that will aim at decreasing PASP in addition to TAVI for AS. Indeed, given the well-established association of post-TAVI PASP values maintenance with worse survival post-TAVI, the necessity of adjunctive medical therapy to decrease PASP values needs to be addressed in future studies.

Study Limitations

This was a meta-analysis of real-world studies, thus, our results should be interpreted in the context of the observational research and its limitations. Moreover, some of the included observational studies had a retrospective design, further increasing the risk of bias, while in many studies the evaluation of PH predictive role in patients with aortic stenosis undergoing TAVI was not the primary study purpose. Different diagnostic methods and PH cut-off values were used among the included studies, introducing heterogeneity. Some of the sensitivity analyses for the different cut-off values were based on a small number of studies. Unreported confounding factors for which we were unable to adjust for may affect the generalizability of our results.
Conclusions

This systematic review and meta-analysis points out to the value of baseline PH in predicting post-TAVI cardiac and all-cause mortality. Our results show that PASP=60mmHg and mean pulmonary arterial pressure=25mmHg were the most capable of predicting the mortality compared to PASP=40mmHg. Clinicians should carefully evaluate patients before deciding on further therapeutic options. Even if PH by itself is not capable of adequately stratify patients, considering the importance and the prognostic value of baseline PH, future AS/TAVI scores should include its assessment in their scoring system.
Table 1: Characteristics of the Included Studies
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Total N (PH vs. no PH)</th>
<th>PH cut-off values</th>
<th>PH Dx</th>
<th>Values</th>
<th>Access route</th>
<th>COPD</th>
<th>Severe MR</th>
<th>Logistic euroSCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindman 2015</td>
<td>USA</td>
<td>2180 (1395 vs. 785)</td>
<td>MPAP = 25, MPAP = 35</td>
<td>RHC</td>
<td>SAPIEN</td>
<td>TF (59%), TA (41%)</td>
<td>46.2%</td>
<td>21.8%</td>
<td>NA</td>
</tr>
<tr>
<td>Lucon 2014</td>
<td>France</td>
<td>2435 (1590 vs. 845)</td>
<td>SPAP = 40, SPAP = 60</td>
<td>TTE</td>
<td>SAPIEN, CoreValve (32.5%)</td>
<td>TF, TA, TSC</td>
<td>22.9%</td>
<td>2.1%</td>
<td>15.6% (10.0–23.9)/ 28.3% (20.3–40.7)</td>
</tr>
<tr>
<td>O’Sullivan 2015</td>
<td>Switzerland</td>
<td>433 (325 vs. 108)</td>
<td>MPAP = 25</td>
<td>RHC</td>
<td>CoreValve, SAPIEN (54.1%), Symetis (1.9%)</td>
<td>TF (80.6%), TA (18%), TSC (1.4%)</td>
<td>17.6%</td>
<td>NA</td>
<td>15.4% (10.0–25)/ 29% (17.3–43.9)</td>
</tr>
<tr>
<td>Testa 2016</td>
<td>Italy</td>
<td>990 (644 vs. 346)</td>
<td>SPAP = 40, SPAP = 60</td>
<td>TTE</td>
<td>NA</td>
<td>TF (90.4%), TSC (9.6%)</td>
<td>23.3%</td>
<td>2.6%</td>
<td>12.8% (4%)/26.2% (4%)</td>
</tr>
<tr>
<td>Rodes-Cabau 2010</td>
<td>Canada</td>
<td>339 (84 vs. 255)</td>
<td>SPAP = 60</td>
<td>RHC/TTE</td>
<td>SAPIEN</td>
<td>TF (49.6%), TA (50.7%)</td>
<td>29.5%</td>
<td>8%</td>
<td>NA</td>
</tr>
<tr>
<td>Barbash 2015</td>
<td>USA</td>
<td>415 (243 vs. 172)</td>
<td>SPAP = 50</td>
<td>TTE</td>
<td>SAPIEN (66.7%), SAPIEN XT (17.3%), CoreValve (13.7%)</td>
<td>TF (75.4%), TA (23.6%)</td>
<td>29.7%</td>
<td>11.6%</td>
<td>30% (24%)</td>
</tr>
<tr>
<td>Bishu 2014</td>
<td>USA</td>
<td>251 (171 vs. 80)</td>
<td>SPAP = 36, SPAP = 48</td>
<td>TTE</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Souza 2016</td>
<td>Brazil</td>
<td>136 (33 vs. 103)</td>
<td>SPAP = 60</td>
<td>NA</td>
<td>CoreValve (97%), SAPIEN (3%)</td>
<td>TF (94.9%), TSC (4.4%), TAVo (0.8%)</td>
<td>9.6%</td>
<td>68.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Schewel 2014</td>
<td>Germany</td>
<td>439 (231 vs. 208)</td>
<td>MPAP = 25</td>
<td>RHC</td>
<td>CoreValve (58.3%), SAPIEN (41.7%)</td>
<td>TF (81.4%), TA (10.9%), TSC (7.2%), TAVo (0.4%)</td>
<td>15.7%</td>
<td>51%</td>
<td>24% (17%)</td>
</tr>
<tr>
<td>Medvedofsky 2015</td>
<td>Israel</td>
<td>122 (49 vs. 73)</td>
<td>SPAP = 50</td>
<td>TTE</td>
<td>CoreValve (80.3%), SAPIEN (19.7%)</td>
<td>TF</td>
<td>NA</td>
<td>30.5%</td>
<td>PH: 33% (13%)/ No PH: 26% (15%)</td>
</tr>
<tr>
<td>Sinning 2014</td>
<td>Germany, UK</td>
<td>353 (251 vs. 102)</td>
<td>SPAP = 30, SPAP = 60</td>
<td>TTE</td>
<td>CoreValve (89%), SAPIEN (11%)</td>
<td>TF (96%), TSC (4%)</td>
<td>31.6%</td>
<td>NA</td>
<td>26.6% (16.5%)</td>
</tr>
<tr>
<td>Lindsay 2015</td>
<td>UK</td>
<td>279 (49 vs. 230)</td>
<td>SPAP = 60</td>
<td>NA</td>
<td>CoreValve, SAPIEN</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zahn 2013</td>
<td>Germany</td>
<td>1318 (865 vs. 453)</td>
<td>SPAP = 60</td>
<td>NA</td>
<td>CoreValve (81.6%), SAPIEN (17.9%)</td>
<td>TF (88%), TA (8.6%), TSC (2.7%), TAVo (0.8%)</td>
<td>28.1%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>D’Ascenzo 2014 Derivation Cohort</td>
<td>Italy</td>
<td>1069 (221 vs. 848)</td>
<td>SPAP = 50</td>
<td>NA</td>
<td>SAPIEN (41.5%), CoreValve (41.1%)</td>
<td>TF (64.9%), TA (23.5%), TSC (11.7%)</td>
<td>26.9%</td>
<td>NA</td>
<td>18.3% (14.1%)/ 19.3% (2%)</td>
</tr>
<tr>
<td>D’Ascenzo 2014 Validation Cohort</td>
<td>Italy</td>
<td>177 (35 vs. 142)</td>
<td>SPAP = 50</td>
<td>NA</td>
<td>SAPIEN (52.5%), CoreValve (44.1%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>D’Ascenzo 2015</td>
<td>Italy, Netherlands</td>
<td>674 (319 vs. 355)</td>
<td>SPAP = 40</td>
<td>TTE</td>
<td>SAPIEN (35%), CoreValve (31.9%)</td>
<td>TF (71.5%), TA (16.9%), TSC (11.3%)</td>
<td>32.3%</td>
<td>NA</td>
<td>PH: 18.5% (19%), No PH: 17.2% (13.1%)</td>
</tr>
<tr>
<td>Halkin 2016</td>
<td>Israel</td>
<td>1291 (142 vs. 1149)</td>
<td>SPAP = 60</td>
<td>NA</td>
<td>CoreValve (67.3%), SAPIEN (30.1%)</td>
<td>TF (87.4%), TA (7.6%)</td>
<td>18.8%</td>
<td>15.5%</td>
<td>17.6% (11.9%)/ 28.8% (19%)</td>
</tr>
<tr>
<td>Muñoz-García 2013</td>
<td>Spain, Portugal, IberoAmerica</td>
<td>1218 (229 vs. 989)</td>
<td>SPAP = 60</td>
<td>TTE</td>
<td>CoreValve</td>
<td>TF (94.7%), TSC (5.3%)</td>
<td>26.5%</td>
<td>18.5%</td>
<td>17.8% (13%)</td>
</tr>
<tr>
<td>Faruta 2015</td>
<td>France</td>
<td>3195 (295 vs. 2900)</td>
<td>SPAP = 60</td>
<td>TTE</td>
<td>SAPIEN (66.4%), CoreValve (32.7%)</td>
<td>TF, TA, TSC</td>
<td>24.7%</td>
<td>NA</td>
<td>21.8% (14.3%)</td>
</tr>
<tr>
<td>Seiffert 2014</td>
<td>Germany</td>
<td>1052 (273 vs. 779)</td>
<td>NA</td>
<td>NA</td>
<td>SAPIEN, SAPIEN XT, CoreValve, ACURATE TA, Jena Valve</td>
<td>NA</td>
<td>28.8%</td>
<td>NA</td>
<td>20.4% (12.7–31.7)/ 25.8% (15.8–40.6)</td>
</tr>
<tr>
<td>Koifman 2016</td>
<td>USA</td>
<td>648 (99 vs. 549)</td>
<td>SPAP = 60</td>
<td>NA</td>
<td>CoreValve, SAPIEN, SAPIEN XT, Portico</td>
<td>TF (79.7%), TA (20.3%)</td>
<td>32.6%</td>
<td>9.9%</td>
<td>NA</td>
</tr>
<tr>
<td>Tamburino 2011</td>
<td>Italy</td>
<td>663 (76 vs. 587)</td>
<td>SPAP = 60</td>
<td>TTE</td>
<td>CoreValve</td>
<td>TF (90.3%), TA (9.7%)</td>
<td>21.3%</td>
<td>6.3%</td>
<td>23% (13.7%)</td>
</tr>
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</table>
Table 2. Results of the meta-analyses for different PH cut-off values and outcomes stratified by HRs and RRs

<table>
<thead>
<tr>
<th></th>
<th>Early cardiac</th>
<th>Early overall</th>
<th>Late cardiac</th>
<th>Late overall</th>
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</thead>
<tbody>
<tr>
<td>Nijenhuis 2016</td>
<td>Netherlands</td>
<td>227* (113 vs. 114)</td>
<td>MPAP =25</td>
<td>cath/ TTE</td>
</tr>
<tr>
<td><strong>Poole d HIG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR/RR</td>
<td>HR</td>
<td>RR</td>
<td>I², %</td>
<td>HR/RR</td>
</tr>
<tr>
<td>Poole d HIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.41</td>
<td>44, 47</td>
<td>0.74-1.5</td>
<td>1.0-1.9</td>
</tr>
<tr>
<td>RR</td>
<td>1.05</td>
<td>45,47</td>
<td>0</td>
<td>0.74-1.5</td>
</tr>
<tr>
<td>PASP 60</td>
<td>HR</td>
<td>1.45</td>
<td>48,5</td>
<td>0.4-2.5</td>
</tr>
<tr>
<td>PASP 50</td>
<td>HR</td>
<td>1.33</td>
<td>45,61</td>
<td>0.78-2.3</td>
</tr>
<tr>
<td>PASP 40</td>
<td>HR</td>
<td>1.47</td>
<td>44,46, 51</td>
<td>1.2-1.8</td>
</tr>
<tr>
<td>RR</td>
<td>1.76\footnote{44,46,55}</td>
<td>1.2-2.5</td>
<td>0</td>
<td>2\footnote{44,46,51,55}</td>
</tr>
<tr>
<td>1st Author</td>
<td>Period</td>
<td>Study design</td>
<td>Late mortality definition</td>
<td>Aortic valve area (cm²/m²)</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>--------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Lindman 2015</td>
<td>NA</td>
<td>Registry from PARTNER I</td>
<td>1y</td>
<td>NA</td>
</tr>
<tr>
<td>Lucon 2014</td>
<td>1/2010-10/2011</td>
<td>prospective</td>
<td>1y</td>
<td>0.62/0.7</td>
</tr>
<tr>
<td>O’Sullivan 2015</td>
<td>8/2007-12/2012</td>
<td>prospective</td>
<td>1y</td>
<td>0.54 (0.2)/0.65 (0.2)</td>
</tr>
<tr>
<td>Testa 2016</td>
<td>6/2009-4/2013</td>
<td>prospective</td>
<td>1y</td>
<td>NA</td>
</tr>
<tr>
<td>Rodes-Cabau 2010</td>
<td>1/2005-6/2009</td>
<td>prospective</td>
<td>8m(3-14)*</td>
<td>0.63 (0.17)</td>
</tr>
<tr>
<td>Barbash 2015</td>
<td>2007 - 2013</td>
<td>retrospective</td>
<td>1y</td>
<td>0.65 (0.1)</td>
</tr>
<tr>
<td>Bishu 2014</td>
<td>11/2008-6/2013</td>
<td>prospective</td>
<td>11m(4.5-22)*</td>
<td>NA</td>
</tr>
<tr>
<td>Souza 2016</td>
<td>7/2009 - 2/2015</td>
<td>prospective</td>
<td>1y</td>
<td>0.67 (0.17)</td>
</tr>
<tr>
<td>Schewel 2014</td>
<td>7/2009-9/2012</td>
<td>prospective</td>
<td>1y</td>
<td>NA</td>
</tr>
<tr>
<td>Medvedofsky 2015</td>
<td>2009 -2011</td>
<td>prospective</td>
<td>2y</td>
<td>PH:0.63/0.13 No PH:0.72/0.17</td>
</tr>
<tr>
<td>Sinning 2014</td>
<td>1/ 2007-12/2011</td>
<td>prospective</td>
<td>2y</td>
<td>0.68 (0.17)</td>
</tr>
<tr>
<td>Lindsay 2015</td>
<td>2007 - 2011</td>
<td>prospective</td>
<td>3y</td>
<td>0.71 (0.34)/0.74 (0.36)</td>
</tr>
<tr>
<td>Zahn 2013</td>
<td>1/2009-6/2010</td>
<td>retrospective</td>
<td>1y</td>
<td>0.68</td>
</tr>
<tr>
<td>Study</td>
<td>Dates</td>
<td>Study Design</td>
<td>Follow-up</td>
<td>PH</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-----------</td>
<td>----</td>
</tr>
<tr>
<td>D’Ascenzo 2014</td>
<td>1/2007 - 12/2012</td>
<td>Retrospective</td>
<td>1y</td>
<td>NA</td>
</tr>
<tr>
<td>D’Ascenzo 2015</td>
<td>1/2007 - 12/2013</td>
<td>Retrospective</td>
<td>16m*</td>
<td>PH:0.64(0.19)</td>
</tr>
<tr>
<td>Halkin 2016</td>
<td>2008 - 2014</td>
<td>Retrospective</td>
<td>NA</td>
<td>0.66 (0.16) / 0.70 (0.21)</td>
</tr>
<tr>
<td>Muñoz-García 2013</td>
<td>7/2007 - 5/2012</td>
<td>Retrospective</td>
<td>8m*</td>
<td>0.62 (0.18)</td>
</tr>
<tr>
<td>Faruta 2015</td>
<td>NA</td>
<td>Retrospective</td>
<td>5.1m*</td>
<td>0.67 (0.02) / 0.68 (0.02)</td>
</tr>
<tr>
<td>Seiffert 2014</td>
<td>NA</td>
<td>Retrospective</td>
<td>1y</td>
<td>NA</td>
</tr>
<tr>
<td>Koifman 2016</td>
<td>5/2007 - 7/2014</td>
<td>Prospective</td>
<td>1y</td>
<td>0.65 (0.12) / 0.67 (0.13)</td>
</tr>
<tr>
<td>Tamburino 2011</td>
<td>6/2007 - 12/2009</td>
<td>Prospective</td>
<td>19m ±6**</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>Nijenhuis 2016</td>
<td>6/2007 - 12/2015</td>
<td>Prospective</td>
<td>2y</td>
<td>0.40 (0.17) / 0.43 (0.16)</td>
</tr>
</tbody>
</table>

Supplementary Table I
Figure 1. PRISMA Flow Diagram of the Included Studies
Figure 2. Early (<30 days) overall mortality. The results were reported as Hazard Ratios by the individual studies. There was no difference between patients with and without pulmonary hypertension (pHR: 0.95; 95% CI: 0.33 - 1.56)
Figure 3. Early (<30 days) overall mortality. The results were reported as Risk Ratios by the individual studies. Patients with pulmonary hypertension were more likely to die (pRR: 1.77; 95% CI: 1.39 – 2.24).
Figure 4. Late cardiac mortality. The results were reported as Hazard Ratios by the individual studies. Patients with pulmonary hypertension were more likely to die (pHR: 1.80; 95% CI: 1.30 – 2.30).
Figure 5. Late cardiac mortality. The results were reported as Risk Ratios by the individual studies. Patients with pulmonary hypertension were more likely to die (pRR: 1.48; 95% CI: 1.25 – 1.76).
Figure 6. Late overall mortality. The results were reported as Hazard Ratios by the individual studies. Patients with pulmonary hypertension were more likely to die (pHR: 1.56; 95% CI: 1.13 – 1.98).
Figure 7. Late overall mortality. The results were reported as Risk Ratios by the individual studies. Patients with pulmonary hypertension were more likely to die (pHR: 1.66; 95% CI: 1.35 – 2.03).

<table>
<thead>
<tr>
<th>STUDY</th>
<th>RR (95% CI)</th>
<th>WEIGHT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindman 2015 (MPAP=35)</td>
<td>1.21 (1.02, 1.44)</td>
<td>10.65</td>
</tr>
<tr>
<td>Lucon 2014 (SPAP=60)</td>
<td>1.10 (0.91, 1.35)</td>
<td>10.39</td>
</tr>
<tr>
<td>O'Sullivan 2015 (MPAP=25)</td>
<td>1.90 (1.04, 3.48)</td>
<td>5.68</td>
</tr>
<tr>
<td>Testa 2016 (SPAP=60)</td>
<td>1.45 (1.10, 1.90)</td>
<td>9.54</td>
</tr>
<tr>
<td>Roders Cabau 2010 (SPAP=60)</td>
<td>1.91 (1.29, 2.84)</td>
<td>8.01</td>
</tr>
<tr>
<td>Souza 2016 (SPAP=60)</td>
<td>2.08 (0.93, 4.65)</td>
<td>4.06</td>
</tr>
<tr>
<td>Schewel 2014 (MPAP=25)</td>
<td>1.68 (1.11, 2.53)</td>
<td>7.80</td>
</tr>
<tr>
<td>Sinning 2014 (SPAP=60)</td>
<td>4.52 (3.00, 6.81)</td>
<td>7.82</td>
</tr>
<tr>
<td>Zahn 2013</td>
<td>1.13 (0.90, 1.41)</td>
<td>10.09</td>
</tr>
<tr>
<td>Munoz-Garcia 2013 (SPAP=60)</td>
<td>1.78 (1.23, 2.57)</td>
<td>8.32</td>
</tr>
<tr>
<td>Tamburino 2011 (SPAP=60)</td>
<td>1.82 (1.22, 2.72)</td>
<td>7.93</td>
</tr>
<tr>
<td>Nijenhuis 2016 (MPAP=25)</td>
<td>1.76 (1.36, 2.28)</td>
<td>9.71</td>
</tr>
<tr>
<td>Overall (I-squared = 79.8%, p = 0.000)</td>
<td>1.66 (1.35, 2.03)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
References


68. Bishu K. Letter by Bishu Regarding Article,“Effect of Pulmonary Hypertension Hemodynamic Presentation on Clinical Outcomes in Patients With Severe Symptomatic Aortic Valve Stenosis Undergoing Transcatheter Aortic Valve Implantation: Insights From the New Proposed Pulmonary Hypertension Classification”. *Circulation: Cardiovascular Interventions* 2015;8:e003047.