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# EuroIntervention

## PCR LONDON VALVES 2022 EDITION

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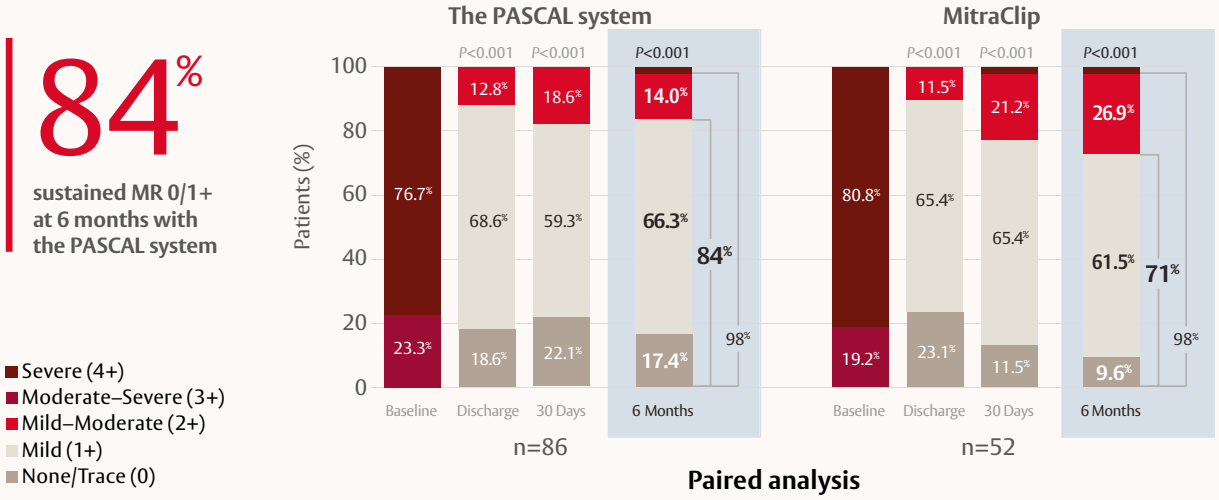


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In early experience, the PASCAL repair system delivered excellent outcomes: low complication rates and robust MR reduction, accompanied by high survival and significant improvements in functional capacity and quality of life at 6 months.


Reference.

1. Lim S, et al. Randomized Comparison of Transcatheter Edge-to-Edge Repair for Degenerative Mitral Regurgitation in Prohibitive Surgical Risk Patients. *JACC Cardiovasc Interv.* 2022 Sep 8;S1936-8798(22)01704-6. doi: 10.1016/j.jcin.2022.09.005. Online ahead of print.


**DMR** = degenerative mitral regurgitation; **TEER** = transcatheter edge-to-edge repair.

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NOVEMBER 2022
Volume 18, Issue 10

IN THIS ISSUE OF EUROINTERVENTION

# The PCR London Valves edition is here! With current debates in valvular disease; long-term risk of unplanned PCI after TAVI; incidence of aortic regurgitation using the ACURATE neo2; Dual ProGlide vs ProGlide and FemoSeal; managing patients with failed mitral prostheses; the BACE device; transcatheter tricuspid valve replacement; and more…

**Davide Capodanno,** *Editor-in-Chief*

The fall meeting season continues with the traditional PCR London Valves. This annual meeting has been reinventing itself year after year without ever losing sight of the ingredients that made it successful to begin with. This year, the Course will do this by showing more cases than ever before.

In the words of the Course Directors, "this year the Main Arena will be filled with wall-to-wall LIVE cases from Copenhagen, London and Toulouse and Virtual LIVE recorded cases from Bern and Mainz. The first LIVE case on Monday will be featuring some 'Wow cases', showing how far we have come in the field in the past 20 years".

In addition, there will be a daily Spotlight session in the Main Arena: Sunday will focus on "transcatheter aortic valve intervention as a mature procedure" with a discussion on the implications of lifelong management of younger and older patients. Monday will be dedicated to transcatheter mitral valve intervention: why it is progressing more

slowly than expected, and what can we do? Tuesday will focus on the boom in and directions of transcatheter tricuspid valve intervention.

PCR London Valves is made up of a series of dedicated practical and livestreamed sessions that include aortic, mitral and tricuspid tracks. New this year, participants will also be able to follow three Simulation Lab Learning Pathways on transcatheter aortic valve implantation (TAVI) as well as simulations on mitral or tricuspid interventions. In step 1, participants will watch experts perform practical demonstrations in the Simulation Lab Learning Room; in step 2, participants will move on to the Hands-on Lab to practice what they have learnt in the Simulation Lab Learning Room; in step 3, participants move on to the Training Village for more device-specific training on what they have just learnt. What a journey!

And, of course, let's not forget the daily late breaking trial sessions (with one co-hosted by EuroIntervention), the interactive case corners, the abstract corner, the sessions dedicated to nurses and allied professionals, the Innovation Hub, the Fellows Course, and so much more. Did I forget anything? Why yes, of course, EuroIntervention. As this issue coincides with PCR London Valves, it is entirely dedicated to valves and structural intervention, so now let me introduce exactly what we have here.

We begin with an intriguing series of debates touching on key topics at PCR London Valves. In the first, **Ignacio J. Amat-Santos and Sara Blasco-Turrión vs Flavio L. Ribichini and Valeria Ferrero** debate the question of whether percutaneous coronary interventions (PCI) of bystander coronary artery lesions should be performed before TAVI. In the second debate, the question of whether you should perform TAVI in patients with moderate aortic stenosis and heart failure is discussed by **Victoria Delgado, Paolo Manca and Michele Senni**. TAVI in younger patients with bicuspid aortic stenosis? Join **Daniel J. Blackman, Noman Ali and Michael A. Borger** for the third debate to see what they think about this question and, in the final debate, **Philippe Généreux and Bernard Iung** argue whether TAVI makes sense in asymptomatic patients with severe aortic stenosis.

The challenge of coronary access after TAVI is at the centre of the first of our clinical articles in which authors **Taishi Okuno, Thomas Pilgrim and colleagues** explore the incidence, characteristics, and predictors of unplanned PCI. They noted that patients with coronary artery disease (CAD) at the time of TAVI were more at risk of unplanned PCI than those patients without acute coronary syndromes and that the number of diseased vessels, male sex, and younger age were independently associated with an increased risk of unplanned PCI. They suggest that an assessment of CAD at the time of TAVI is thus critical in planning the long-term management of these patients.

The use of the first iteration of the ACURATE *neo* in TAVI was associated with a significant incidence of paravalvular aortic regurgitation with an adverse prognostic impact. But what about the new-generation ACURATE *neo2*, what improvements can be seen with this latest device? This is the subject of the next article by **Andrea Scotti, Azeem Latib and colleagues** who looked at the results of patients enrolled in the NEOPRO and NEOPRO2 registries undergoing TAVI with the ACURATE *neo* and *neo2* devices. The ACURATE *neo2* was seen to have lower rates of moderate or severe paravalvular aortic regurgitation, even in the presence of heavy aortic valve calcifications. There was also no increase in the need for pacemaker implantation. Further studies are needed, but this shows clear improvements for the new platform.

**Jonas M.D. Gmeiner, Daniel Braun and colleagues** compare two different percutaneous vascular closure strategies in the next article which looks at a dual ProGlide strategy versus a combination of one ProGlide and one FemoSeal after large-bore arteriotomy for TAVI. Patents treated with the combination strategy had less access-related vascular

complications and bleeding than the dual ProGlide group leading the authors to conclude that a combined suture- and plug-based strategy might be the best approach to take.

What is the best strategy to take in patients with degenerated mitral bioprostheses: valve-in-valve transcatheter mitral valve replacement (ViV-TMVR) or redo surgical mitral valve replacement (redo-SMVR)? This was the question asked by **Salman Zahid, David L. Fischman and colleagues** who used the American Nationwide Readmission Database to evaluate in-hospital and short-term outcomes of ViV-TMVR compared with redo-SMVR. While ViV-TMVR patients were older and had a higher burden of comorbidities, ViV-TMVR still had lower odds of in-hospital mortality, complications, and resource utilisation. In terms of mortality at 30-days and six-months, no difference was observed between the ViV-TMVR and redo-SMVR groups which supports the safety and efficacy of ViV-TMVR when surgery would be too risky.

**Jérémy Bernard, Philippe Pibarot and colleagues** provide us with a research correspondence on the treatment of secondary mitral regurgitation (MR) in patients with heart failure. As we know, this is critical as it represents a marker of increased mortality and rehospitalisation, yet the recommended approach through mitral annuloplasty remains complex and can increase the risk of perioperative complications. Here the authors evaluated the safety and efficacy of a novel technique for managing secondary MR in patients with systolic heart failure, extracardiac annuloplasty using the BACE (Basal Annuloplasty of the Cardia Externally) device. In this pilot study, its use proved to be safe and feasible, reducing secondary MR resulting in positive left ventricular remodelling, and improvement in the patient's quality of life and functional status. Controlled trials are warranted.

The next article, a meta-analysis, takes an "historic" approach studying data from surgical tricuspid valve replacement studies as a basis for evaluating the emerging therapeutic option of transcatheter tricuspid valve replacement (TTVR) for the management of secondary tricuspid regurgitation. Authors **Andrea Scotti, Azeem Latib and colleagues** believe that results from this type of analysis can play a critical role in clinical decision making for tricuspid valve replacement. These data can be seen as representing a benchmark for newer approaches to tricuspid regurgitation and can be useful in judging the durability of emerging bioprosthetic devices.

**Atsushi Sugiura, Marc Ulrich Becher and colleagues** investigate the impact of right ventricular-pulmonary artery (RV-PA) coupling on clinical outcomes in the treatment of tricuspid regurgitation (TR) in patients undergoing mitral transcatheter edge-to-edge repair (TEER). By dividing the tricuspid annular plane systolic excursion (TAPSE) by the pulmonary artery systolic pressure (PASP), they determined a ratio of this coupling. They then show that this ratio affects the outcome of TR in patients undergoing mitral TEER. This offers a new framework for determining the clinical relevance of TR to its severity and concomitant RV-PA coupling ratio.

In the continued evolution of managing severe tricuspid regurgitation, **Emmanuel Teiger, Julien Dreyfus and colleagues** discuss the first-in-human implantation of the new Topaz tricuspid valve for TTVR. With short term clinical improvement in TR, the novel device featured in this research correspondence shows promise for future use of TTVR when TEER is not possible for anatomical reasons.

Finally, do you say "TAVI" or "TAVR"? And if "TAVI", why?

What better moment than in this issue, dedicated to PCR London Valves, to have this fascinating viewpoint by **Philippe E. Gaspard**. Where does the term "TAVI" come from? And how and why might you choose, instead, to "TAVR". Let's begin.

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## VIEWPOINT



## DEBATES



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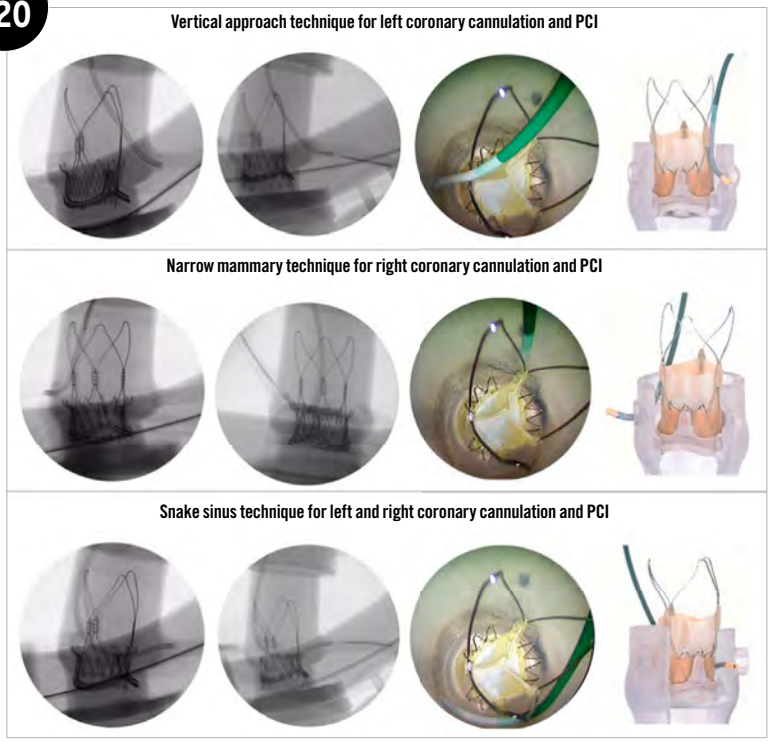


*Image taken from the following paper printed in this issue:*
*Coronary access techniques following ACURATE neo2 implantation in surgical bioprosthesis*
*A.A. Khokhar, F. Ponticelli, A. Zlahoda-Huzior, P. Zakrzewski, G. Mikhail, D.Dudek, F. Giannini*
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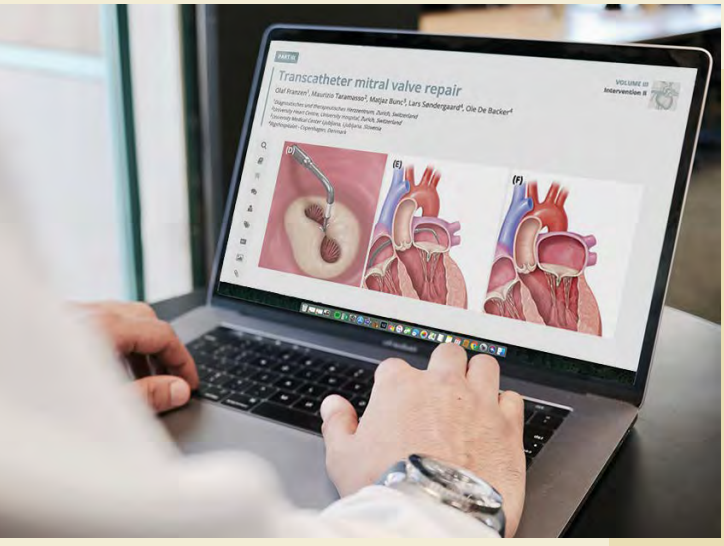


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# In search of the origin of the acronym TAVI

**Philippe E. Gaspard***, MD

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The term TAVI is currently part of familiar language. But who invented this acronym? Let's go back to the beginning of catheter-based interventions **(Figure 1)**.

## Where does the term "TAVI" come from?

In 1979, Andreas Grüntzig presented the results of non-operative dilatation of coronary artery stenosis. He used the acronym PTCA which incorporated the words employed by his famous predecessors, in chronological order: "percutaneous" (Seldinger), "transluminal" (Dotter), "coronary" (Judkins) and "angioplasty" (Zeitler).

In 1992, Henning Andersen reported his results with a new expandable aortic valve in closed-chest pigs, using the terms "implantation", "artificial heart valve" and "transluminal"[1]. He was inspired by Julio Palmaz, whom he heard at a conference in Scottsdale, Arizona, USA in 1989. By an amazing coincidence, Julio had the idea of a balloon-expandable stent whilst attending a conference by Andreas Grüntzig in New Orleans, Louisiana, USA, eleven years earlier, in 1978. But Henning Andersen was mistaken when he said that Charles Dotter had conducted a lecture on angioplasty in Frankfurt, Germany in 1964 which had been attended by Andreas Grüntzig. That particular year, Charles Dotter had been in Portland, Oregon, USA, and Andreas Grüntzig was obtaining his medical degree from the University of Heidelberg, Germany. In fact, the lecture referred to by Andersen was given by Eberhard Zeitler – who contributed to the development of Dotter's method in Europe – 5 years later, in 1969, just before Andreas arrived in Zurich, Switzerland.

In 2000, Philipp Bonhoeffer reported the first-in-man (FIM) stent implantation combined with a valve replacement in a right ventricle to pulmonary artery prosthetic conduit with valve dysfunction[2]. He used the terms "replacement", "valve" and "percutaneous". The terms "percutaneous" and "transluminal" were used by Andreas Grüntzig in 1979.

In 2002, Alain Cribier reported the FIM non-operative treatment of calcific aortic stenosis[3], using the terms "percutaneous" and "transcatheter implantation of an aortic valve". The term "transcatheter" was originally used for therapeutic arterial embolisations in the early 1970s and for the first time in the field of cardiology in 1976, when William Rashkind related his experience with transcatheter closure of atrial and ventricular septal defects in experimental animals. This word was adopted in 1989 for the TCT (Transcatheter Cardiovascular Therapeutics) meeting launched by Kenneth Kent, Martin Leon, Augusto Pichard and Lowell Satler. Alain initially used the acronym PHV (percutaneous heart valve).

In 2006, the transapical approach induced a radical shift, and Samuel Lichtenstein thereafter spoke of transapical transcatheter aortic valve implantation. In 2007, the acronym TAP-AVI for "transapical aortic valve implantation" was proposed by Thomas Walther[4]. The term "percutaneous" disappears in favour of "transcatheter". Alain Cribier also transformed the acronym PHV to THV (transcatheter heart valve).

In 2008, a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI), concerning transcatheter valve implantation for patients with aortic stenosis, was published in 3 journals under the leadership of Alec Vahanian. The position statement was published in the European Heart Journal in June, in the European Journal of Cardio-Thoracic Surgery in July and in EuroIntervention in August[5]. The acronym TAVI for "transcatheter aortic valve implantation" appeared for the first time in these joint publications. It was in fact a revival

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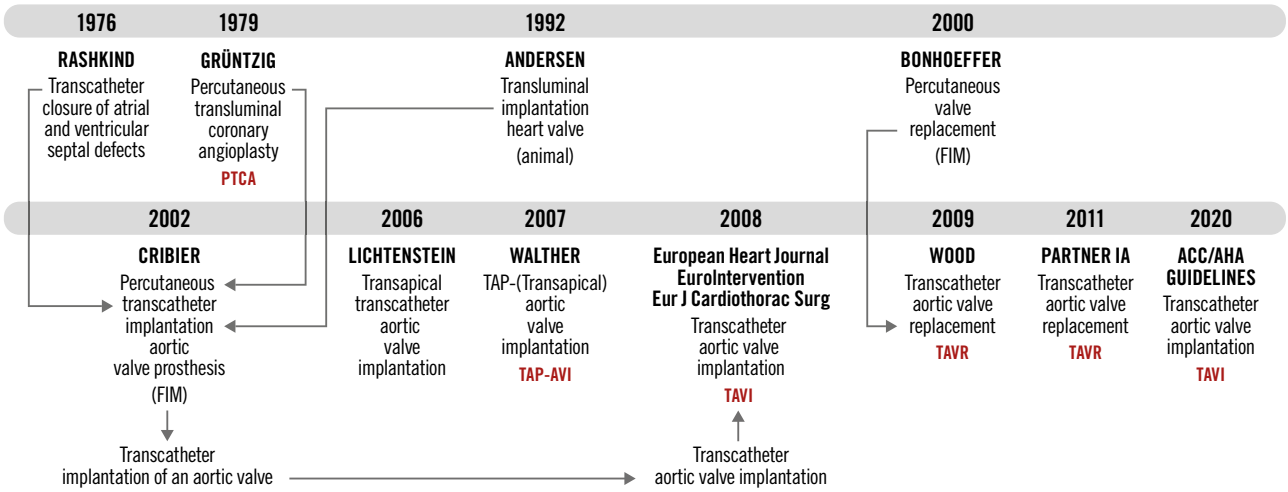


**Figure 1.** *The history of the acronym TAVI. FIM: first-in-man*

of the terms initially used by Alain Cribier in 2002, removing the term "percutaneous" and changing the expression "implantation of an aortic valve" to "aortic valve implantation", which is more consistent with the English language. In fact, TAVI sounds better than TIAV…and, coincidentally, TAVI in French, phonetically, means "your life"… Without knowing it, Alain Cribier was indirectly but likely responsible for the origin of the acronym TAVI.

But the story doesn't end here…

## TAVI or TAVR ? How to choose?

In 2007, the term TAVR appeared with the CoreValve TAVR ReValving clinical trial, whereby Rüdiger Lange related the first successful transapical aortic valve implantation with the CoreValve Revalving System (Medtronic). The following year, Hendrik Ruge reported the first successful aortic valve implantation with the CoreValve Revalving System via right subclavian artery access. In this case, the transapical delivery system was not available at the time of surgery. In both these cases, the letter T stood for "transapical".

In 2009, the acronym TAVR for "transcatheter aortic valve replacement" appeared for the first time[6]. Transcatheter included both surgical and percutaneous approaches.

In 2010, Martin Leon still used the acronym TAVI in The Placement of AoRtic TraNscathetER Valves (PARTNER IB) Trial using the Edwards SAPIEN heart-valve system (Edwards Lifesciences): Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery.

In 2011, however, the term "replacement" was used in preference to "implantation" in the PARTNER IA trial: Transcatheter versus Surgical Aortic-Valve Replacement in High-risk Patients. The main reason for this was to get easier U.S. Food and Drug Administration (FDA) approval. Furthermore, reimbursement for TAVI required a similar code to surgery: transcatheter AVR may well be compared with surgical AVR. TAVR was subsequently used in the PARTNER 2 Trial (Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients) and the PARTNER 3 Trial (Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients).

Finally, in an effort to homogenise the acronyms, in the latest 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease, the acronym TAVI has been reintroduced in place of TAVR[7]. The right choice?

## Conflict of interest statement

The author has no conflicts of interest to declare.

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# PCI of bystander coronary artery lesions should be performed before TAVI: pros and cons

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## Pros: PCI pre-TAVI, better safe than sorry

**Ignacio J. Amat-Santos, MD, PhD; Sara Blasco-Turrión, MD**

In stable patients, percutaneous coronary intervention (PCI) of severe lesions in the proximal coronary arteries before transcatheter aortic valve implantation (TAVI) has been the empirical approach for patients with severe aortic stenosis who are deemed candidates for percutaneous treatment. Despite the lack of evidence for this order at the dawning of TAVI, some reasons that are still valid supported such an approach. First, it was intuitively considered that if the coronary ostia were below the upper part of the prosthesis' stent frame, coronary access would be difficult. This was demonstrated to be true over the following years with several authors reporting a prolonged time for cannulation (from a median of 0/10" to 50/30" for left and right coronary arteries, respectively), or its impossibility (0.4 to 17% according to the device) in a non-negligible number of cases[1]. Secondly, the mortality rate for ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) cases following TAVI (~1/3 at 30 days) was higher than in alternative settings or in the general population, and this was in relationship to a low rate of utilising an invasive approach (<1/3) likely due to anticipated challenging coronary cannulations[2].

Recent research has tried to provide new technical guidelines for coronary cannulation following TAVI[3]. However, the need for these bench test analyses is a consequence of the increased difficulty of post-TAVI coronary interventions which suggest that it is unreasonable to postpone the revascularisation that needs to be performed. And that is the other key question: does it really need to be done? For decades, coronary bypass grafts have been performed at the same time as surgical aortic valve replacements (SAVR) to avoid pump failure once the intervention was finished. Although complications with TAVI have decreased to a minimum, they still exist, and annular rupture, cardiac tamponade, or severe ventricular arrhythmias are likely to lead to worse outcomes due to extended ischaemia and pump failure if severe coronary disease remains untreated at this point. The TransCatheter Valve and Vessels Trial (ClinicalTrials.gov: NCT03424941) is aiming to explore the differences between SAVR and coronary bypass versus TAVI and fractional flow reserve (FFR)-guided PCI; in this nuance – incorporating physiology-guided PCI – we might find

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the key to this unresolved clinical question. Of course, coronary revascularisation makes sense before TAVI, but since ischaemia tests are not free from risk in the presence of severe aortic stenosis, we might be overtreating our patients. Conversely, the use of fractional flow reserve (FFR) or resting indices (such as quantitative flow ratio [QFR]) have been thoroughly investigated and demonstrated to be safe in patients with aortic stenosis[4]. Therefore, a more precise revascularisation performed before TAVI might be the key to better outcomes while also minimising the risk of restenosis in the future.

All in all, reducing the need for coronary re-access after TAVI is, from every point of view, crucial for the life-long management of patients harbouring a TAVI device; let us focus our efforts there.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

## Cons: PCI first provides no long-term benefit

**Flavio Ribichini, MD; Valeria Ferrero, MD**

Patients with severe aortic stenosis (AS) often seek help for symptoms that are related to valve disease. Angina is the least common and, even when it does occur, coronary flow can appear normal.

It is the valve, however, that endangers the patient's survival, and it is this fact that should always drive the reasoning and therapeutic approach, especially considering that complex PCI in a patient scheduled for TAVI may be riskier (and more difficult) than the valve replacement itself. Therefore, before treating the coronary artery disease (CAD) occasionally found during the TAVI workup, one should bear in mind the following: first, performing TAVI before or after PCI yields comparable intraprocedural and in-hospital adverse events. This suggests that the presence of "high-risk" lesions with a large ischaemic burden (i.e., left main or 3-vessel disease) by no means compromises the TAVI procedure when coronary lesions are treated after TAVI, regardless of the valve type[5]. Second, performing PCI before TAVI increases the risk of stroke, bleeding and kidney injury compared to PCI performed after TAVI (ideally done as a combined procedure)[5-7]. Clinical outcomes indicate that the PCI-first strategy provides no long-term benefit[5-7].

PCI is performed before TAVI because of the as yet unproven, but still widespread, concern about safety related to the acute ischaemic risk of leaving significant coronary stenosis untreated during valve implantation. There is also a misleading indication in the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgeons (ESC/EACTS) Guidelines which recommends treatment of significant CAD before TAVI (IIa)[8], as well as concerns related to coronary access after TAVI particularly among professionals with no TAVI experience. The need for low-volume centres to maintain a certain caseload is also a consideration.

PCI after TAVI may be better, and ideally should be performed in the same session. There is no need for a pre-TAVI hospital admission dedicated to the diagnosis and treatment of CAD. This helps avoids unnecessary hospital care, the repeated administration of contrast media (and renal toxicity), and repeat vascular access. TAVI performed after PCI implies the use of a dual antiplatelet therapy, a strategy that has been proven to be unfavourable. Additionally, the removal of the aortic valve obstruction before PCI permits a more accurate diagnosis of the ischaemic potential of a given angiographic lesion by physiologic assessment, especially in asymptomatic patients.

TAVI promptly releases the left ventricular pressure overload, with immediate improvement of the cardiac contractility and hence the cardiac output. Procedures that include large ischaemic burdens, complex bifurcations, chronic total occlusions or that require debulking techniques are therefore better tolerated in case of hypotension and complications. This haemodynamic effect may have particular importance for organs with low ischaemic thresholds such as the brain and kidneys, which may be already hypoperfused in severe AS. This implies that any kind of cardiovascular intervention in the setting of hypoperfusion may increase the chances of haemodynamic, renal or cerebral ischaemic sufferance.

Our reasoning is in line with previous indirect observations[6,7] and does not align with the current guideline recommendations. These recommendations are not evidence-based and are in clear conflict with the findings of the ISCHEMIA trial which are well fitted to stable and/or asymptomatic presentations of CAD that emerge from TAVI workup angiographies.

Last, but not least… is the possibility of monitoring severe adverse clinical events related to PCI occurring in patients undergoing TAVI, while events occurring in patients who undergo "preventive revascularisation" before TAVI, mostly in non-TAVI centres, are likely ignored. Therefore, there is a concrete risk that major adverse events of preventive PCI in lower-volume centres were largely under-reported, unpublished, and not censored.

To synthesise, a TAVI-first strategy in many patients offers advantages in terms of resource optimisation, better management of antithrombotic therapy, reliable coronary functional evaluation, more stable haemodynamics with better organ perfusion without jeopardising procedural success, and, in particular, allows adequate monitoring of clinical outcomes compared to procedures performed before TAVI without dedicated quality and safety controls[9].

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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# TAVI in moderate aortic stenosis and heart failure: pros and cons

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## Pros: trials that challenge the guidelines

**Victoria Delgado, MD, PhD**

Current international guidelines recommend aortic valve replacement (AVR) in severe aortic stenosis (AS) if it is causing symptoms or left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <50%). However, several registries have shown that performing AVR when symptoms or reduced LVEF occur is associated with poor outcomes. Staging algorithms that consider the extent of structural and/or functional alterations associated with AS help to refine the risk stratification of patients with severe AS[1]. Accordingly, the question that then arises is whether performing AVR in asymptomatic patients with severe AS and no clear structural and functional abnormalities in response to the pressure overload would lead to better survival as compared to a watchful waiting strategy. This hypothesis was tested in 2 recent randomised trials that included patients with critical AS and patients with severe AS and a negative exercise test, respectively[2,3]; however, both trials had a limited number of patients. The mean age of the patients was around 65 years old and the proportion of bicuspid aortic valve anatomy was more than 50% in one of the trials: characteristics that do not resemble those of the patients currently treated with transcatheter aortic valve implantation (TAVI). In addition, recruitment of patients was performed almost entirely in a single centre in one of the trials[2], while in the other trial, the heart valve clinics did not confirm symptomatic status nor utilise the watchful waiting strategy[3]. The ongoing Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis (EARLY TAVR; ClinicalTrials.gov: NCT03042104) trial, which aimed to recruit more than 1,000 asymptomatic patients with severe AS, will shed more light onto the survival benefits of early intervention.

Meanwhile, large registries have shown that patients with moderate AS have worse clinical outcomes as compared to patients with less severe forms of AS[4]. Independent of the presence of reduced LVEF, diastolic left ventricular systolic dysfunction and other comorbidities, moderate AS is associated with a 5-year mortality rate of 56%[4]. A recent systematic review of 12,134 patients with moderate AS, who were followed up for a median of almost 4 years, showed pooled rates per 100 person-years of 9.0 events for all-cause death, 4.9 for cardiac death, 3.9 for heart failure and

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1.1 for sudden death[5]. In addition, the presence of symptoms or left ventricular systolic dysfunction were associated with a significant impact on the overall estimate of all-cause death[5]. These findings lead to the hypothesis that AVR would be beneficial in patients with moderate AS, particularly in those with symptoms and/or left ventricular dysfunction.

Currently, surgical AVR should be considered in patients undergoing surgical coronary artery revascularisation or surgery of the aortic root and ascending aorta. However, the low complication rates of TAVI and the lower in-hospital mortality rates of TAVI as compared to surgical AVR in patients with low, intermediate and high operative risk begs the question of whether TAVI could be a valuable option for patients with moderate AS. In particular, among patients with moderate AS and reduced LVEF or heart failure symptoms and in whom there is no indication for coronary revascularisation or surgery of the aortic root and ascending aorta, TAVI could alleviate the pressure overload of the failing left ventricle and improve symptoms as well as left ventricular remodelling. To answer this question, 3 ongoing randomised trials will provide more information. The Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure (TAVR UNLOAD; ClinicalTrials.gov: NCT02661451) trial is aiming to recruit 300 patients with heart failure and moderate AS who will be randomised to TAVI using a balloon-expandable bioprosthesis versus guideline-directed heart failure therapy. The results are expected in 2023. The PROGRESS Trial: Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR (ClinicalTrials.gov: NCT04889872) will randomise 750 patients with moderate AS and symptoms or cardiac damage to TAVI with a balloon-expandable bioprosthesis versus medical therapy, while the Evolut EXPAND TAVR II Pivotal Trial (ClinicalTrials.gov: NCT05149755) will randomise 650 patients with symptomatic moderate AS to TAVI versus clinical surveillance under medical therapy. Besides knowing the potential survival benefit of TAVI in patients with moderate AS, it will certainly be interesting to see if TAVI is associated with a regression of the haemodynamic consequences of the increased pressure overload. This hypothesis will be challenged by the risk of pacemaker implantation and the presence of more than mild paravalvular regurgitation associated with TAVI. While the concept of performing TAVI in moderate AS seems reasonable from the pathophysiological point of view, the results of these trials will help to demonstrate this.

## Conflict of interest statement

V. Delgado received speaker fees from Abbott Vascular, Edwards Lifesciences, Medtronic, GE Healthcare, Philips, and Novartis; and consulting fees from Edwards Lifesciences, and Novo Nordisk (heart failure).

## Cons: TAVI, a role to be explored

Michele Senni, MD, PhD; Paolo Manca, MD

The prevalence of both AS and heart failure (HF) increases exponentially with advancing age, leading to a frequent coexistence of the 2 conditions in the elderly. Consistent data are available about the prognostic role of severe AS in HF patients, and the benefit of TAVI for this condition has been demonstrated[6]. Conversely, data on patients with moderate AS and HF are scarce and derived from small observational studies[7-10]. Furthermore, the possible role of TAVI in this population is almost unexplored[7].

In a cohort of 262 patients affected by heart failure with reduced ejection fraction (HFrEF) who were matched with a corresponding group without AS, moderate AS was shown to be a strong independent predictor of HF hospitalisation and mortality (hazard ratio [HR] 2.34)[7]. In the same study, 44 patients with baseline moderate AS required AVR during follow-up. In this subgroup, TAVI, but not surgical AVR was associated with survival benefit; however, TAVI was performed in only 15 patients. Furthermore, patients who underwent AVR had worse baseline characteristics compared to the other cohorts and could not be adequately matched. Lastly, HF treatment was not optimal and did not include new HF therapies such as angiotensin-neprylisin inhibitors and sodium-glucose cotransporter 2 inhibitors. Another recent study, which enrolled 952 patients affected by moderate AS who were matched with a comparable population without AS, found similar results, showing a significantly higher risk of mortality in moderate AS patients, regardless of left ventricular ejection fraction[8]. However, HF prevalence in this study was low (<10%), and patients who underwent AVR were excluded. Moreover, some baseline differences between the 2 groups still remained after matching, leaving doubts regarding the possible independent prognostic role of moderate AS.

In contraposition, a previous report which included 107 patients with low-flow low-gradient AS and HFrEF demonstrated a significantly lower risk of death in patients affected by moderate AS compared to those with severe AS (HR 0.53)[9]. Also, a group of 28 HFrEF patients with moderate AS was adequately matched with 28 HFrEF patients without AS and no difference in the 5-year survival rate was documented.

Lastly, in a recently published series of 1,974 patients affected by moderate AS, who were divided into 4 groups based on flow-gradient patterns, only paradoxical low-flow low-gradient and classical low-flow low-gradient moderate AS emerged as independent predictors of mortality, while concordant moderate AS and normal-flow AS did not[5]. Interestingly, patients with these patterns were also significantly older and had a higher prevalence of comorbidities.

Taking all these data together, the independent prognostic role of moderate AS in HF remains unclear, with some conflicting results in the literature. The number of patients enrolled in these reports was usually low, and the possible beneficial role of TAVI was only reported in a very small sample size, clearly limiting the conclusions for this population. It should instead be emphasised

EuroIntervention 2022;18:787-789

that optimal medical treatment was generally underrepresented and it must be implemented in future studies. Additionally, the prompt treatment of comorbidities, which are usually seen in these patients, is fundamental as they could independently act as casual factors for the ventricular-valvular afterload observed in AS patients. Finally, whether moderate AS may have a different impact in patients with HFrEF or HF with preserved ejection fraction (HFpEF) is still controversial **(Figure 1)**.

Two randomised clinical trials in 2 different clinical settings are currently ongoing. The TAVR UNLOAD (ClinicalTrials.gov: NCT02661451) trial will randomise 300 patients with moderate AS and LVEF <50% to TAVI versus optimal HF treatment, and the PROGRESS Trial (ClinicalTrials.gov: NCT04889872) will randomise 750 adults older than 65 with moderate AS to TAVI versus clinical surveillance, irrespective of the presence of HF. The results of these 2 studies will probably shed light on this complex topic.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

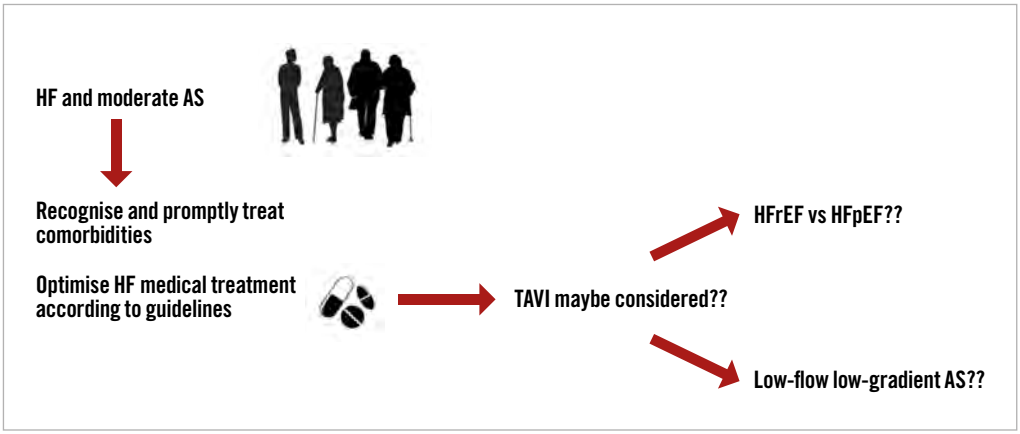


**Figure 1.** *Possible flowchart of the treatment of patients with heart failure and moderate aortic stenosis. AS: aortic stenosis; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; TAVI: transcatheter aortic valve implantation*

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# TAVI in younger patients with bicuspid aortic stenosis: pros and cons

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## Pros: safety and efficacy of TAVI in BAV

**Daniel J. Blackman, MD, MRCP; Noman Ali, PhD, MRCP**

There are a number of specific considerations when performing transcatheter aortic valve implantation (TAVI) in younger patients because of the need to consider lifetime management when life expectancy is measured in decades. We address each in turn, outlining how bicuspid anatomy may be advantageous for lifetime management, and describe the growing evidence supporting the safety and efficacy of TAVI in bicuspid aortic valves (BAV).

Valve durability: Valve durability remains the most important factor when considering TAVI in younger patients. A principal determinant of durability is the size of the implanted transcatheter heart valve (THV), with larger effective orifice areas being associated with lower rates of structural valve deterioration (SVD)[1]. Patients with BAV tend to have larger annular dimensions than those with tricuspid anatomy[2], allowing for implantation of larger THV, which should translate to better valve durability.

Redo TAVI: Whilst improved durability of the index THV can delay the onset of haemodynamically significant SVD, the ability to safely perform subsequent valve-in-valve interventions is critically important. The key factor determining the feasibility of redo TAVI is the risk of coronary obstruction from the "neoskirt" created by the displaced THV leaflets, either through direct ostial occlusion or sinus sequestration. Patients with BAV have larger aortic dimensions, sinuses of Valsalva (SOV) and sinotubular junction (STJ)[2], which reduce the risk of coronary obstruction with TAV-in-TAV, making revalving feasible in the majority of patients.

Coronary access post-TAVI: Preserving coronary access is a key consideration in younger patients where the probability of coronary artery disease requiring intervention over a lifetime is increased. The principal reason for challenging coronary access post-TAVI is the close proximity of the THV frame to the walls of the aorta at the STJ and coronary ostia. Larger aortic root dimensions in BAV patients, including the diameter and height of the SOV and STJ, mean that coronary access either above or alongside the THV frame should be more easily achieved. Coronary access is likely to be even more challenging after redo TAVI due to the creation of the "neoskirt". Again, larger STJ and SOV dimensions mean that coronary catheterisation can be more readily achieved.

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Permanent pacemaker implantation: The long-term negative consequences of permanent pacemaker implantation (PPM) post-TAVI are undoubtedly greater in patients with a longer life-expectancy, including adverse remodelling with reduced LV systolic function, greater requirement for generator changes and lead revision, and increased risk of pacemaker-related complications. Minimising interaction with the left ventricular outflow tract (LVOT) is key to reducing the risk of conduction disturbance. Current guidelines support higher implantation of THV in bicuspid anatomy[3], using the leaflets and raphe for anchoring and sealing, hence minimising LVOT interaction, which should translate to a lower risk of PPM.

Evidence for TAVI in bicuspid anatomy: There is growing evidence demonstrating favourable outcomes following TAVI in younger BAV patients. PARTNER 3 and the Evolut Low Risk Trial adopted parallel registries which included BAV patients with low surgical risk treated with TAVI. Using propensity score matching, these patients were compared to those with tricuspid anatomy from the main trials[4,5]. The PARTNER 3 Bicuspid Registry found no difference in the composite primary endpoint of all-cause mortality, stroke and cardiovascular-related rehospitalisation at 1 year[4], whilst the Evolut Low Risk Trial substudy demonstrated no difference in all-cause mortality or disabling stroke at 1 year[5]. Both studies also showed no difference in haemodynamic echocardiographic parameters at 1 year.

While longer-term outcome studies would be welcomed, contemporary data with current-generation THV demonstrate that outcomes of TAVI among younger low-surgical risk patients with BAV are similar to those with tricuspid valves. Furthermore, the specific anatomical characteristics of BAV appear favourable in addressing critical lifetime management factors in younger patients undergoing TAVI.

## Conflict of interest statement

D.J. Blackman is a consultant & proctor for Medtronic; and a consultant for Abbott Vascular, Boston Scientific, and Edwards Lifesciences. N. Ali has received speaker fees from Medtronic.

## Cons: negative implications of BAV for TAVI

**Michael A. Borger, MD, PhD**

Surgical aortic valve replacement (SAVR) is the current gold standard for young patients with BAV disease and will remain that way for the foreseeable future. SAVR is recommended in aortic stenosis (AS) patients younger than 75 years of age in the current European valvular guidelines[6], and one of the principal reasons behind this recommendation is that a large proportion of young AS patients have BAV pathology. BAV morphology has important short- and long-term negative implications for TAVI, but negligible impact on SAVR.

BAV is associated with higher rates of several important complications post-TAVI when compared to patients with tricuspid aortic valve (TAV) stenosis, including paravalvular leak (PVL), pacemaker implantation, conversion to surgery and lack of procedural success[7]. Results for SAVR, by contrast, are largely independent of valve morphology. BAV status has never emerged as a risk factor in any SAVR risk scoring system (e.g., Society of Thoracic Surgeons [STS], EuroSCORE) and has rarely been a focus of surgical studies. However, Celik et al from Rotterdam recently compared results of BAV versus TAV in SAVR ± coronary bypass grafting patients (n=3,145) operated on between 1987 and 2016[8]. These investigators found significantly better survival in BAV patients, even after propensity- and age-matching. Twenty-year survival of BAV patients was 40%, as compared to only 18% for TAV patients[8].

These marked differences between SAVR and TAVI in BAV patients may be explained, in large part, by severe valve calcification and a non-spherical annular shape which are much more common in BAV than TAV. Excessive calcification and non-spherical annuli do not play a significant role in SAVR, since the surgeon is able to debride all calcium under direct visual inspection, and the annulus is forced to conform to the circular frame of the valve prosthesis. In contrast, retention of large amounts of calcium debris in non-spherical annuli during TAVI may have deleterious effects on short-term complications such as annular rupture, PVL, pacemaker requirement and increased gradients due to non-uniform expansion of the TAVI device, as well as long-term complications such as coronary access difficulties, accelerated valve degeneration due to non-uniform device expansion, and decreased space allowing for future TAV-in-TAV procedures.

Furthermore, it is commonly known that BAV is associated with aortopathy and aortic complications. For this reason, SAVR with replacement of the ascending aorta is recommended in AS patients with an ascending aorta >4.5 cm in diameter[6,9]. What is less known is that BAV is also associated with several coronary artery anomalies. The most frequent anomaly is a hypoplastic right coronary artery, whose ostium frequently lies close to the right non-coronary commissure and therefore may be at risk of occlusion during TAVI or future TAV-in-TAV procedures.

Lifetime management of AS patients is a topic that is gaining increasing attention within the medical and patient communities. One of the dictums of lifetime management is that, if SAVR is performed, the largest possible valve prosthesis should be implanted to lower the risk of patient-prosthesis mismatch and to facilitate future TAVI valve-in-valve procedures. BAV patients are known to have larger annuli than TAV patients, allowing the insertion of larger SAVR prostheses[8]. In addition, we know that SAVR post-TAVI results are uniformly poor, being much worse than those for TAVI post-SAVR. In a meta-analysis of 10 studies with 1,690 SAVR post-TAVI patients, 30-day mortality (16.7%) was more than twice as high as the STS Predicted Risk of Mortality and was independent of endocarditis[10]. One of the reasons for the excess mortality was necessary concomitant procedures, the most common being aortic repair in 29% of patients[10]. SAVR is particularly challenging

post-insertion of a self-expanding TAVI device because of aortic ingrowth that occurs into the high-riding stent frame, the high aortotomy required, and the resulting challenging surgical exposure. Future transcatheter coronary access is also known to be more challenging in patients receiving self-expanding TAVI devices.

In summary, multiple reasons support the use of SAVR as the initial intervention of choice in young BAV patients. TAVI should not be performed in such patients, unless within the confines of a properly designed randomised controlled trial.

## Conflict of interest statement

M. Borger declares that his hospital receives speakers' honoraria and/or consulting fees on his behalf from Edwards Lifesciences, Medtronic, Abbott and Artivion.

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# TAVI in asymptomatic patients with severe aortic stenosis: pros and cons

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## Pros: early TAVI, a pre-emptive strategy

**Philippe Généreux, MD**

Aortic stenosis is a progressive disease with an unpredictable evolution. While some phases of the disease are latent, the left ventricle and other cardiac structures are constantly exposed to an increasing overload of pressure, with silent cardiac damage (structural and functional) accumulating over time. Often, the expression of symptoms among patients with progressive aortic stenosis appears at a point when a second or third cardiac "disease" occurs, such as a decrease in left ventricle function, diastolic dysfunction, or atrial fibrillation, which all could be irreversible once the aortic stenosis is fixed. Similarly, it is extremely difficult to predict how a patient will "land" in the symptomatic zone, whether it will be a "crash and burn" scenario, more safe with some degree of turbulence, or more smooth and uneventful. Current guidelines recommend surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis if 1) symptoms occur spontaneously or are triggered during a low-level stress test, or among asymptomatic patients if 2) left ventricle function is depressed (<50%), or 3) another open heart surgery is required[1]. Potential benefits of early intervention include reduced mortality, reduced rehospitalisation for cardiovascular reasons, improvement in quality of life, and prevention of progression and occurrence of cardiac damage. Recently, 2 small randomised trials of approximatively 150 patients each demonstrated the benefits of SAVR among patients with asymptomatic critical aortic stenosis (~65 years old, peak velocity ~5 m/s, and no stress test performed)[2] and asymptomatic very severe aortic stenosis (~65 years old, peak velocity ~4.5 m/s)[3].

The current guidelines are silent about the role of transcatheter aortic valve implantation (TAVI) in asymptomatic patients with severe aortic stenosis. Whether TAVI should be performed instead of SAVR is another question. Given the recent data showing the equivalence and even the superiority of TAVI at short- and mid-term follow-up, a less invasive approach may be preferred in asymptomatic patients if cardiac function is to be preserved. We recently demonstrated that SAVR was associated with the occurrence or progression of cardiac damage after aortic valve replacement compared with TAVI, mainly due to the onset of new atrial fibrillation, the lack of regression of left ventricular hypertrophy (remodelling), and the occurrence of new right ventricular dysfunction due to the on-pump phenomenon[4].

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The relative enhanced safety and reduced invasiveness of TAVI compared with SAVR has some appeal if a pre-emptive strategy is contemplated among asymptomatic patients with normal left ventricular function.

Some opponents of TAVI may argue that the durability of TAVI prostheses is still unknown and may preclude the use of TAVI among asymptomatic patients; however, it was shown that most asymptomatic patients with severe aortic stenosis will become symptomatic and require aortic valve replacement ~2 years after their diagnosis, with approximatively 1-2% mortality per year while waiting for symptoms to occur. TAVI valves have demonstrated at least similar valve durability up to 5 years among intermediate- and high-risk patients and should be preferred among this segment of the population to prevent cardiac depletion and the occurrence of adverse events. The role of TAVI among younger patients (65-75 years) is still a matter of active debate, and longer-term follow-up in ongoing trials will help answer this question. If anatomical suitability for initial and subsequent TAVI implantation is confirmed, it is expected that TAVI will become the preferred intervention among both symptomatic and asymptomatic patients. In this regard, the Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis (EARLY TAVR) trial (ClinicalTrials.gov: NCT03042104) has recently completed its enrolment (~1,000 patients) and is expected to answer this exact question in the near future[5].

## Conflict of interest statement

P. Généreux has been a consultant for Abbott Vascular, Abiomed, BioTrace Medical, Boston Scientific, CARANX, Cardiovascular Systems Inc (for the PI Eclipse Trial), Edwards Lifesciences, GE Healthcare, iRhythm Technologies, Medtronic, Opsens, Pi-Cardia, Puzzle Medical, Saranas, Shockwave, Siemens, Soundbite Medical Inc, Teleflex, and 4C Medical for the PI Feasibility study; an advisor to Abbott Vascular, Abiomed, BioTrace Medical, Edwards Lifesciences, and Medtronic; has received speaker fees from Abbott Vascular, Abiomed, BioTrace Medical, Edwards Lifesciences, Medtronic, and Shockwave; has been a proctor for Edwards Lifesciences; and has equity in Pi-Cardia, Puzzle Medical, Saranas, and Soundbite Medical Inc.

## Cons: insufficient evidence for TAVI in asymptomatic AS

Bernard Iung, MD

While symptomatic severe aortic stenosis (AS) has been an undisputed indication for intervention for decades, asymptomatic patients with severe AS generally undergo follow-up until symptom onset. Historically, the low rate of cardiac events in asymptomatic AS supported conservative management. Over the last decades, European and American guidelines have defined indications for intervention in selected asymptomatic patients with high rates of cardiac events reported in observational studies[1,6]. Conversely, an argument that supports earlier intervention – as soon as AS becomes severe without waiting for symptoms – is that the risk of delay in the identification of symptom onset thereby exposes the patient to the inherent risk of symptomatic AS.

Recently, intervention in asymptomatic AS has gained new attention due to the RECOVERY and AVATAR randomised trials, which included 145 and 157 patients, respectively, and led to consistent findings supporting early surgery in asymptomatic AS[2,3]. The occurrence of the primary endpoint of operative mortality or postoperative cardiovascular mortality in the RECOVERY trial and all-cause death or major adverse cardiac events in AVATAR was significantly reduced in the early surgery group versus the conservative management group.

The two randomised trials represent a major step forward in evidence-based treatment of asymptomatic AS. However, they do not close the debate. In the RECOVERY trial, AS was more severe than the usual criteria delineate, and the absence of symptoms was based on patient history without systematic exercise testing, while the AVATAR trial included patients with common definitions of severe AS and mandatory negative exercise testing. Primary endpoints were composite in both trials, and the decrease in all-cause mortality was significant only in the RECOVERY trial. The robustness of both trials is limited by the cumulative number of 302 patients and 51 primary events.

The results of the RECOVERY and AVATAR trials support early surgical aortic valve replacement in relatively young (mean age 64 and 67 years, respectively) and very low-risk patients (mean EuroSCORE II 0.9% in RECOVERY and mean Society of Thoracic Surgeons [STS] score 1.7% in AVATAR), who do not represent the majority of AS patients, even the asymptomatic ones. These findings cannot be translated to elderly patients due to the higher risk of procedural complications and the competing risks between AS prognosis and the impact of comorbidities and frailty.

In asymptomatic patients, TAVI is particularly attractive since a minimally invasive intervention seems more acceptable than surgery in patients who do not complain of any symptoms. The recent extension of indications for TAVI to low-risk patients provides the opportunity to consider TAVI in asymptomatic patients, who are frequently at low risk for surgery. However, performing TAVI at an earlier stage of AS leads to interventions in patients with longer life expectancies, and this raises concerns regarding the long-term consequences of TAVI. While paravalvular leak is now less frequent and less severe, the incidence of conduction disorders has not decreased with recent devices. Uncertainties remain on the long-term impact of coronary access and structural valve deterioration[7]. Present data on clinical and echocardiographic follow-up after TAVI are mostly limited to 5-8 years, mostly in

EuroIntervention 2022;18:793-795

octogenarians at increased risk for surgery, and cannot be extrapolated to asymptomatic patients with severe AS who do not present with the same features.

Despite recent trials supporting early intervention, it is not time to recommend TAVI in asymptomatic AS. The evidence supporting intervention in asymptomatic AS is currently limited to surgical aortic valve replacement in selected low-risk patients and cannot support unrestricted indications of TAVI in asymptomatic AS. The 20-year story of TAVI has been paved with a succession of randomised trials leading to a progressive extension of indications. We should not abandon this virtuous example and instead should wait for the results from ongoing trials before considering TAVI in asymptomatic AS.

## Conflict of interest statement

B. Iung has no conflicts of interest to declare.

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# Long-term risk of unplanned percutaneous coronary intervention after transcatheter aortic valve replacement

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**KEYWORDS**

- coronary artery disease
- normal coronary arteries
- TAVI

## Abstract

**Background:** Coronary access after transcatheter aortic valve replacement (TAVR) can be challenging and complicate percutaneous coronary intervention (PCI).

**Aims:** We aimed to investigate the incidence, characteristics, and predictors of unplanned PCI after TAVR.

**Methods:** In a single-centre registry, TAVR candidates were systematically screened for concomitant coronary artery disease (CAD) through the use of coronary angiography prior to TAVR. Rates of unplanned PCI were prospectively collected and independently adjudicated.

**Results:** Among 3,015 patients undergoing TAVR between August 2007 and December 2020, 67 patients (2.2%) underwent unplanned PCI after TAVR. The indication for unplanned PCI was acute coronary syndrome in more than half of the cases. Patients with unplanned PCI were younger (80.2±6.5 years vs 81.9±6.4 years; p=0.028) and more likely to be male (75% vs 50%; p<0.001) than those without unplanned PCI. In a multivariable analysis, the number of diseased vessels, male sex, and younger age were independently associated with an increased risk of unplanned PCI. The cumulative incidence rates of unplanned PCI at 1, 5, and 10 years were 0.1%, 0.4%, and 0.6% in patients with no CAD at the time of TAVR, 0.7%, 2.5%, and 3.4% in patients with single-vessel disease, and 1.5%, 5.4%, and 7.4% in patients with multivessel disease, respectively.

**Conclusions:** The lifetime risk of unplanned PCI after TAVR is low in patients with no CAD at the time of TAVR but accumulates over time in patients with known CAD, particularly multivessel disease. ClinicalTrials.gov: NCT01368250.

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## Abbreviations

| | |
|---|---|
| **AS** | aortic stenosis |
| **CAD** | coronary artery disease |
| **LAD** | left anterior descending |
| **LCx** | left circumflex artery |
| **LMT** | left main trunk |
| **NSTEMI** | non-ST-elevation myocardial infarction |
| **PCI** | percutaneous coronary intervention |
| **RCA** | right coronary artery |
| **SAVR** | surgical aortic valve replacement |
| **STEMI** | ST-elevation myocardial infarction |
| **TAVI** | transcatheter aortic valve implantation |

## Introduction

A majority of patients with severe aortic stenosis (AS) can be safely and effectively treated with both transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) based on periprocedural risk and anatomic criteria[1,2]. However, the lifetime management of patients with AS introduces an additional level of complexity to the Heart Team's decision. The selection of the optimal treatment strategy for younger patients with a longer life expectancy requires the integration of downstream cardiac risk due to concomitant coronary artery disease (CAD), combined valvulopathies, and repeat and future cardiac interventions[3].

Coronary access after TAVR is a concern with important repercussions on lifetime management of patients with severe AS. Previous studies have detailed the challenges of selective coronary access for percutaneous coronary intervention (PCI) after TAVR, particularly in the presence of supra-annular devices featuring tall stent frames[1,2]. The need for repeat TAVR in younger patients is anticipated to further exacerbate the complexity of coronary access, particularly in the setting of low coronary offtake in relation to the neoskirt and misalignment of the two stent frames[3-5]. The complexity of coronary access directly translates into adverse clinical outcomes in patients presenting with acute coronary syndrome (ACS)[6] and needs to be anticipated before the implantation of the first transcatheter heart valve (THV). Thus, in order to tailor lifetime management to an individual context, it is crucial to estimate during treatment for AS the probability that PCI will be required in the future.

In the present study, we aimed to evaluate the incidence, characteristics, and predictors of unplanned PCI after TAVR in a prospective TAVR registry.

## Methods

### STUDY POPULATION

The Bern TAVR registry is a prospective registry enrolling consecutive patients undergoing TAVR at Bern University Hospital, which forms part of the nationwide SwissTAVI Registry (ClinicalTrials.gov: NCT01368250). The registry was approved by the ethics committee, and all patients provided written informed consent for participation. The study was conducted in compliance with the Declaration of Helsinki.

Patients undergoing TAVR were systematically screened for concomitant CAD by means of coronary angiography prior to TAVR. Concomitant CAD was treated with PCI before, during, or after TAVR based on the Heart Team's decision, taking into account myocardium at risk, lesion complexity, and symptom status[7]. Functional ischaemia testing was not routinely performed during the study period.

### DATA COLLECTION AND OUTCOME MEASURES

Baseline clinical characteristics, procedural, and follow-up data were prospectively recorded in a web-based database. Computed tomographic imaging data were independently re-evaluated by dedicated imaging specialists, as previously described, and integrated into the database[8]. The presence of CAD was defined by a history of surgical and/or percutaneous coronary revascularisation, previous myocardial infarction (MI), and/or at least 1 significant lesion (diameter stenosis ≥50%) in a major native coronary artery by visual assessment with coronary angiography prior to TAVR[9].

Regular clinical follow-up was scheduled at 30 days, 1 year, 5 years, and 10 years after TAVR, and the data were obtained by standardised interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events, including unplanned PCI, were systematically collected and adjudicated by a dedicated clinical event committee. The Clinical Trials Unit Bern was responsible for central data monitoring to verify the completeness and accuracy of data, and to perform independent statistical analysis. In the registry, unplanned PCI included all PCI following TAVR, excluding staged PCI planned at the time of TAVR. PCI was performed in accordance with guidelines at the corresponding time of intervention[7]. For the purpose of the present study, coronary revascularisation resulting from mechanical coronary obstruction complicating TAVR was excluded.

### STATISTICAL ANALYSIS

Categorical variables are reported as frequencies and percentages. Continuous variables are presented as mean values±standard deviation (SD) or median values with interquartile ranges (IQR). Univariable Cox proportional hazard models were used to calculate hazard ratios (HR), 95% confidence intervals (CI), and p-values. The cumulative rate of PCI over time was represented through a cumulative incidence curve. Multivariable Fine and Gray regressions (with all-cause death as a competing risk) were used to build a prediction model for the incidence of unplanned PCI. All variables potentially related to unplanned PCI were tested in a univariable model, and variables with a p-value <0.2 were subsequently entered into a multivariable model. All p-values were 2-sided, and a p-value <0.05 was considered significant for all tests. All statistical analyses were performed with Stata 17.0 (StataCorp).

## Results

### INCIDENCE OF UNPLANNED PCI

Among 3,015 patients undergoing TAVR between August 2007 and December 2020, 109 patients (3.6%) underwent staged PCI after TAVR and 67 patients (2.2%) underwent unplanned PCI

during follow-up. The median follow-up time available for living patients was 1,095 (IQR 366-1,824) days, and the median time to death was 799 (IQR 268-1,485) days. The cumulative incidence rates of unplanned PCI were 0.4%, 1.6%, and 2.3% at 1, 5, and 10 years, respectively **(Figure 1)**. The median interval from TAVR to unplanned PCI was 605 (IQR 292-1,340) days.

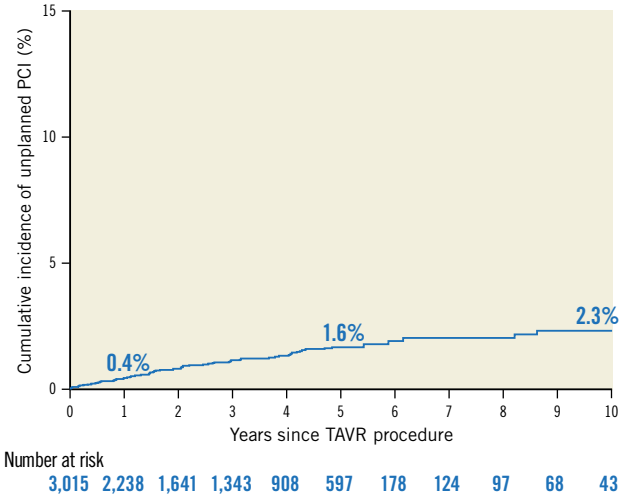



**Figure 1.** *Lifetime risk of unplanned PCI after TAVR. Cumulative incidence of unplanned PCI after TAVR considering competing risk with death is shown. PCI: percutaneous coronary intervention; TAVR: transcatheter aortic valve replacement*

## BASELINE AND PROCEDURAL CHARACTERISTICS

Baseline characteristics of patients with and without unplanned PCI after TAVR are shown in **Table 1**. Patients who underwent unplanned PCI after TAVR were younger (80.2±6.5 years vs 81.9±6.4 years; p=0.028), more likely to be male (75% vs 50%; p<0.001), and more frequently had peripheral artery disease (21% vs 13%; p=0.048) than those without unplanned PCI. There were no significant differences in traditional risk factors (hypertension, diabetes mellitus, and dyslipidaemia), chronic kidney disease, or previous cerebrovascular events between the 2 groups. Pre-TAVR coronary angiographies revealed that 94% of patients who underwent unplanned PCI had CAD at baseline, compared with 59% of patients who did not undergo unplanned PCI (p<0.001). CAD was more likely to be multivessel disease in patients with unplanned PCI than in those without unplanned PCI (p=0.025). Patients with unplanned PCI were more likely to have had previous myocardial infarction (30% vs 14%; p<0.001) and a history of PCI (52% vs 26%; p<0.001).

Details of TAVR procedures are shown in **Table 1**. TAVR was performed via transfemoral access in 90% of patients, without a significant difference between groups. There was no significant difference in the type of THV used between groups.

## PREDICTORS OF UNPLANNED PCI

In a multivariable model, the number of diseased vessels, male sex, and younger age were independently associated with an increased risk of unplanned PCI after TAVR, while traditional risk factors, previous peripheral artery disease, previous myocardial infarction and a history of PCI were not **(Table 2, Supplementary Figure 1, Supplementary Figure 2)**. The cumulative incidence curves stratified by the presence of CAD and number of diseased vessels prior

**Table 1. Baseline characteristics.**

| | Cohort | Control | Unplanned PCI | *p*-value* |
|---|---|---|---|---|
| | N=3,015 | N=2,948 | N=67 | |
| Age, years | 81.9±6.4 | 81.9±6.4 | 80.2±6.5 | 0.028 |
| Gender, male | 1,521 (50%) | 1,471 (50%) | 50 (75%) | <0.001 |
| Body mass index, kg/cm$^2$ | 26.6±5.3 | 26.6±5.3 | 27.6±5.0 | 0.154 |
| STS calculated risk of mortality | 5.2±4.1 | 5.2±4.1 | 4.6±2.8 | 0.176 |
| **Risk factors** | | | | |
| Hypertension | 2,628 (87%) | 2,566 (87%) | 62 (93%) | 0.128 |
| Diabetes mellitus | 805 (27%) | 785 (27%) | 20 (30%) | 0.240 |
| Dyslipedaemia | 2,009 (67%) | 1,957 (66%) | 52 (78%) | 0.060 |
| Renal failure (GFR<60) | 2,027 (67%) | 1,983 (67%) | 44 (66%) | 0.941 |
| History of cerebrovascular accident | 352 (12%) | 342 (12%) | 10 (15%) | 0.288 |
| Peripheral artery disease | 408 (14%) | 394 (13%) | 14 (21%) | 0.048 |
| **Coronary artery disease** | | | | |
| Coronary artery disease | 1,797 (60%) | 1,734 (59%) | 63 (94%) | <0.001 |
| Number of vessels involved | n=1,797 | n=1,734 | n=63 | 0.025 |
| 1VD | 656 (37%) | 64 (37%) | 13 (21%) | |
| 2VD | 510 (28%) | 490 (28%) | 20 (32%) | |
| 3VD | 631 (35%) | 601 (35%) | 30 (48%) | |
| History of MI | 429 (14%) | 409 (14%) | 20 (30%) | <0.001 |
| Previous CABG | 347 (12%) | 335 (11%) | 12 (18%) | 0.170 |
| Previous PCI | 806 (27%) | 771 (26%) | 35 (52%) | <0.001 |
| **Computed tomography** | | | | |
| Left coronary height, mm | 14.8±3.6 | 14.8±3.6 | 15.2±3.8 | 0.230 |
| Right coronary height, mm | 17.7±3.4 | 17.7±3.4 | 18.3±2.7 | 0.024 |
| Aortic valve calcium volume, mm$^3$ | 307.9±329.5 | 309.0±331.5 | 259.3±228.5 | 0.138 |
| Sinus of Valsalva diameter, mm | 32.1±4.7 | 32.0±4.7 | 32.9±2.7 | 0.298 |
| **Procedural data** | | | | |
| Femoral main access | 2,728 (90%) | 2,669 (91%) | 59 (88%) | 0.816 |
| Transcatheter heart valve type | n=3,011 | n=2,944 | n=67 | 0.936 |
| Balloon-expandable | 1,530 (51%) | 1,497 (51%) | 33 (49%) | |
| Self-expanding | 1,334 (44%) | 1,304 (44%) | 30 (45%) | |
| Mechanically expandable | 147 (5%) | 143 (5%) | 4 (6%) | |
| Concomitant revascularisation | 243 (8%) | 238 (8%) | 5 (7%) | 0.479 |

**p*-values from univariable Cox regressions with time-to-unplanned PCI as the outcome. Aortic valve calcium volume was quantified as previously described[8]. CABG: coronary artery bypass surgery; GFR: glomerular filtration rate; MI: myocardial infarction; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons; VD: vessel disease

**Table 2. Predictors of unplanned PCI under competing risk with death.**

| Variables | Subhazard ratio (95% CI) | *p*-value |
|---|---|---|
| **Univariable** | | |
| Coronary artery disease | | |
| None | [Ref.] | |
| Single-vessel disease | 5.59 (1.82-17.14) | 0.003 |
| Multivessel disease | 12.26 (4.43-33.90) | <0.001 |
| Age, years | 0.96 (0.93-0.99) | 0.006 |
| Gender, male | 3.03 (1.75-5.26) | <0.001 |
| Body mass index, kg/m² | 1.04 (1.00-1.07) | 0.058 |
| Hypertension | 2.02 (0.81-5.01) | 0.130 |
| Diabetes mellitus | 1.22 (0.72-2.05) | 0.462 |
| Dyslipidaemia | 1.83 (1.03-3.25) | 0.040 |
| Peripheral artery disease | 1.60 (0.89-2.88) | 0.117 |
| History of MI | 2.46 (1.47-4.14) | 0.001 |
| Previous CABG | 1.54 (0.84-2.83) | 0.163 |
| Previous PCI | 2.95 (1.83-4.76) | <0.001 |
| Concomitant PCI | 0.72 (0.29-1.81) | 0.489 |
| Aortic valve calcification, mm³* | 1.00 (1.00-1.00) | 0.099 |
| **Multivariable** | | |
| Coronary artery disease | | |
| None | [Ref.] | |
| Single-vessel disease | 4.10 (1.29-13.10) | 0.017 |
| Multivessel disease | 8.63 (2.85-26.09) | <0.001 |
| Age, years | 0.96 (0.92-1.00) | 0.039 |
| Gender, female | 0.37 (0.20-0.67) | 0.001 |
| Body mass index, kg/m² | 1.04 (0.99-1.09) | 0.141 |
| Hypertension | 1.84 (0.64-5.22) | 0.255 |
| Dyslipidaemia | 0.85 (0.44-1.64) | 0.631 |
| Peripheral artery disease | 1.16 (0.61-2.22) | 0.655 |
| History of MI | 1.36 (0.74-2.48) | 0.320 |
| History of PCI | 1.14 (0.63-2.06) | 0.669 |
| Previous CABG | 0.50 (0.24-1.03) | 0.061 |
| Aortic valve calcification, cm³* | 0.46 (0.19-1.11) | 0.085 |

*Aortic valve calcification was quantified in contrast-enhanced images using a predefined Hounsfield unit threshold of 850, as previously described[8]. Multivariable model selecting variables with a *p*-value <0.2 in the univariable analysis. Multivariable analysis was based on 2,460 patients with CT imaging data. Single imputation of the mode (or mean for BMI) for missing data: n=3 CABG, n=3 PCI and n=10 BMI. A multivariable model without aortic valve calcification in the entire cohort (N=3,015) is shown in **Supplementary Table 1**. A multivariable model with a limited number of variables with a *p*-value <0.1 in the univariable analysis is shown in **Supplementary Table 2**. BMI: body mass index; CABG: coronary bypass grafting; CT: computed tomography; MI: myocardial infarction; PCI: percutaneous coronary intervention

to TAVR are shown in the **Central illustration**. The cumulative incidence rates of unplanned PCI at 1, 5, and 10 years were 0.1%, 0.4%, and 0.6%, respectively, in patients with no CAD. In patients with single-vessel disease, the unplanned PCI rates were 0.7%, 2.5%, and 3.4%, respectively. In patients with multivessel disease, unplanned PCI was performed in 1.5%, 5.4%, and 7.4% at 1, 5 and 10 years, respectively. The effect of CAD was largely consistent after excluding patients with a history of coronary artery bypass grafting **(Supplementary Figure 1)**.

## CLINICAL INDICATIONS AND PROCEDURAL CHARACTERISTICS OF UNPLANNED PCI

The clinical indications and procedural characteristics of unplanned PCI are shown in **Table 3**. More than half of the patients underwent unplanned PCI for treatment of ACS (56%). Non-ST-elevation myocardial infarction (NSTEMI) was the most frequent indication (30%), followed by ST-elevation myocardial infarction (STEMI; 16%), and unstable angina pectoris (UAP; 10%) **(Central illustration)**. The most frequent target vessels were, in descending order, the left anterior descending artery (LAD; 51%), followed by the right coronary artery (RCA; 30%), the left circumflex artery (LCx; 18%), the left main (LM; 16%), and coronary artery bypass grafts (9%). Sixty-seven percent of lesions were *de novo* lesions, 33% were restenotic lesions, and 3% of lesions occurred in the setting of stent thromboses **(Central illustration)**. Femoral access was preferentially used over radial access, and PCI of the target vessel was successful in 99% of cases.

**Table 3. Clinical indication for unplanned PCI.**

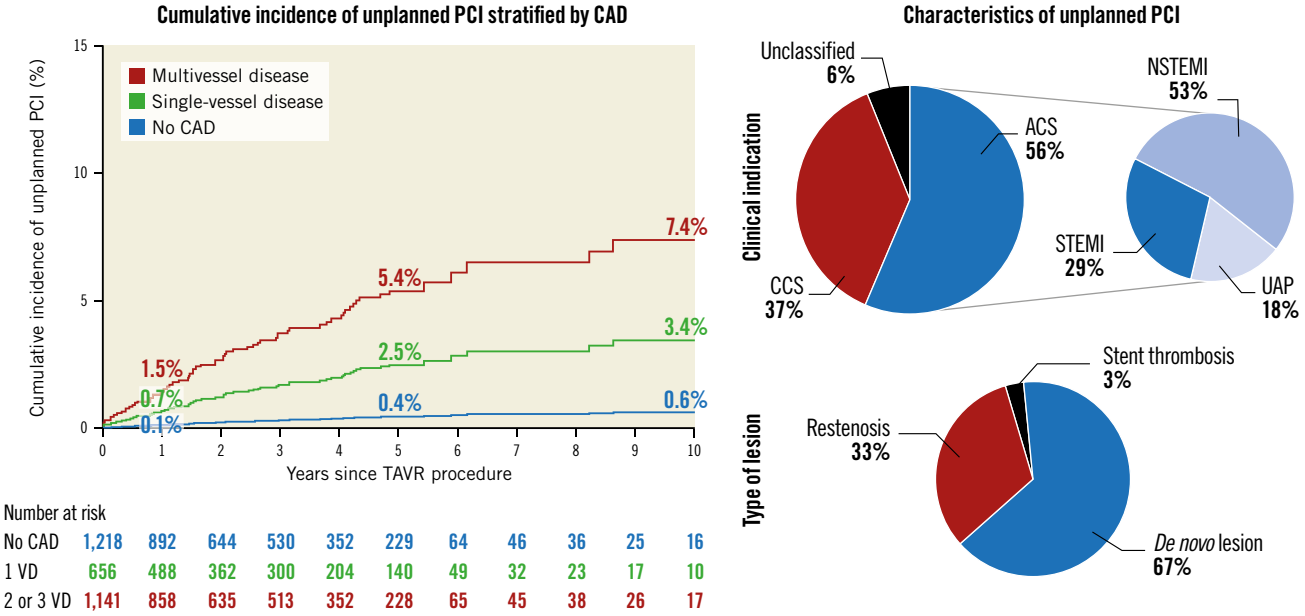
| | Unplanned PCI |
|---|---|
| | N=67 |
| Days between TAVR and unplanned PCI | 817±711 |
| median (25%; 75% IQR) | 605 (292; 1,340) |
| Reason for unplanned PCI | |
| Chronic coronary syndrome | 25 (37%) |
| Unstable angina pectoris | 7 (10%) |
| NSTEMI | 20 (30%) |
| STEMI | 11 (16%) |
| Others | 4 (6%) |
| Successful PCI | 66 (99%) |
| Type of lesion | |
| *De novo* stenosis | 45 (67%) |
| Restenosis | 22 (33%) |
| Stent thrombosis | 2 (3%) |
| Target vessel | |
| Left main trunk | 11 (16%) |
| Left anterior descending artery | 34 (51%) |
| Left circumflex artery | 12 (18%) |
| Right coronary artery | 20 (30%) |
| Graft | 6 (9%) |
| Vascular access | |
| Femoral | 37 (61%) |
| Radial | 24 (39%) |

IQR: interquartile range; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TAVR: transcatheter aortic valve replacement

EuroIntervention

## CENTRAL ILLUSTRATION Long-term risk of unplanned PCI after TAVR.

✓ **Prospective TAVR registry (n=3,015)**
✓ **Concomitant CAD:** Systematically screened by the use of coronary angiography prior to TAVR
✓ **Unplanned PCI:** Prospectively collected and adjudicated at regular follow-up (30 days, 1 year, 5 years and 10 years)




*Cumulative incidence curve of unplanned PCI after TAVR stratified by baseline CAD. The red line denotes multivessel disease, the green line denotes single-vessel disease, and the blue line denotes no CAD. Clinical indications and types of lesions of unplanned PCI after TAVR. ACS: acute coronary syndrome; CAD: coronary artery disease; CCS: chronic coronary syndrome; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TAVR: transcatheter aortic valve replacement; UAP: unstable angina pectoris; VD: vessel disease*

## Discussion

In this prospective TAVR registry, the incidence of unplanned PCI after TAVR was 0.4%, 1.6%, and 2.3% at 1, 5, and 10 years, respectively. The number of diseased vessels diagnosed by pre-TAVR coronary angiography, male sex, and younger age were independently associated with an increased risk of unplanned PCI after TAVR. Fewer than 1% of patients without CAD before TAVR underwent unplanned PCI within 10 years after TAVR, while 3% and 7% of patients with single-vessel disease and multivessel disease, respectively, underwent unplanned PCI within 10 years. The primary indication for unplanned PCI was ACS in more than half of the cases; the LAD was the most frequent target vessel and most lesions were *de novo*. Unplanned PCI was successful in 99% of patients.

The high PCI success rate in the present study is in line with the 96-100% success rate in previous studies[10-16]. However, the relatively high rate of femoral access for PCI (61%) may indicate the operators' anticipation of challenging coronary cannulation. In a recent, dedicated, prospective study, Reobtain Coronary Ostia Cannulation Beyond Transcatheter Aortic Valve Stent (RE-ACCESS), unsuccessful coronary cannulation was observed in 7.7% of patients with a previously implanted THV, and semi-selective cannulation was reported in 12.0% for the left coronary artery and in 31.7% for the RCA. Difficulties in achieving selective cannulation after TAVR were also reflected by the longer times and the larger amounts of contrast dye used to engage each coronary ostium. Challenging cannulation was more commonly observed in patients treated with the Evolut R/PRO (Medtronic) THV[2]. The TAVR with Commissural Alignment Followed by Coronary Access (ALIGN-ACCESS) study demonstrated that commissural alignment improves the rate of selective coronary access after TAVR with supra-annular THV; however, aligned supra-annular THV still carry a higher risk of unfeasible/non-selective coronary access than the SAPIEN 3 (Edwards Lifesciences) THV[17]. Along the same lines, in a multicentre study including 118 patients presenting with STEMI after TAVR, the PCI failure rate, median door-to-balloon time, procedural time, fluoroscopy time, dose-area product, and contrast volume were all higher in TAVR patients presenting with STEMI compared with all-comer STEMI patients[6]. Furthermore, it can be expected that coronary access will be even more challenging after repeat TAVR[3-5]. Thus, the risk of unplanned PCI after TAVR should always be taken into account

during the Heart Team decision-making process, particularly in younger patients at risk of requiring repeat TAVR in the future.

Evidence on the incidence and characteristics of unplanned PCI following TAVR is scarce. The Revascularization After Transcatheter Aortic Valve Implantation (REVIVAL) study summarised unplanned PCI cases after TAVR from several centres. Estimates of PCI after TAVR may have been biased by selective reporting and retrospective data collection. In addition, the study did not have a control group and did not differentiate PCI for mechanical obstruction complicating TAVR from PCI due to CAD[18]. Thus, the present study is the first to systematically report the incidence, characteristics, and predictors of unplanned PCI after TAVR from a prospective registry. In line with the previous multicentre study, unplanned PCI after TAVR was infrequent, and the most common indication for PCI was ACS. In contrast to the study by Stefanini and colleagues, we documented no acute decrease in the incidence of unplanned PCI over time, and the median interval from TAVR to unplanned PCI was longer. Both of these observations may be explained by the exclusion of unplanned PCI for acute coronary obstruction due to TAVR and the high completeness of follow-up in the present study.

To the best of our knowledge, our study is the first to identify baseline clinical factors associated with an increased risk of unplanned PCI after TAVR. Patients with single-vessel disease and multivessel disease had a 4-fold and 9-fold increased risk of unplanned PCI after TAVR, respectively, compared to those without CAD. Male sex and younger age were also independently associated with an increased risk of unplanned PCI. This finding has important clinical implications for the lifetime management of patients with AS. If no relevant CAD is documented at the time of intervention for AS, the long-term risk of unplanned PCI later in life is exceedingly low. This observation seems to expand the range of transcatheter treatment options for low-risk patients with isolated AS to all THV, irrespective of the height of the stent frame. Conversely, if a TAVR candidate does have relevant CAD at the time AS requires intervention, is male, and has a long life expectancy, it may be preferable to consider surgery or preserve future coronary access by using an intra-annular THV with a short stent frame.

## Study limitations

The findings of our cohort study should be interpreted in light of several limitations. First, although the current study was based on a large prospective TAVR registry including over 3,000 patients, the incidence of unplanned PCI was relatively rare, and the number of patients with unplanned PCI after TAVR was modest. Furthermore, more detailed data reflecting the complexity of selective coronary cannulation, such as procedural duration, fluoroscopic time, the amount of contrast dye used, and the number of catheters used, were not systematically collected. On the other hand, the robustness of our findings is enhanced by the prospective data collection and independent event adjudication as well as the systematic assessment of CAD through the use of coronary angiography prior to TAVR. Second, although the data on unplanned PCI were systematically collected at regular follow-ups, the number of patients reaching 10-year follow-up was limited. Finally, the present cohort predominantly included octogenarians at increased surgical risk. As shown in this study, the risk of unplanned PCI is higher in younger patients due to their longer life expectancy. The overall incidence of unplanned PCI after TAVR is expected to further increase as the indication for TAVR is expanded to younger and low-risk patient populations.

## Conclusions

Unplanned PCI after TAVR is rare in patients with no CAD prior to TAVR, while it is more common in those with CAD, particularly in the setting of multivessel disease. The assessment of CAD prior to TAVR is essential in the lifetime management of patients with AS.

## Impact on daily practice

PCI after TAVR can be challenging due to impaired coronary access. In a prospective TAVR registry, the number of diseased vessels diagnosed by pre-TAVR coronary angiography, male sex, and younger age were independently associated with an increased risk of unplanned PCI after TAVR. Unplanned PCI after TAVR is rare in patients with no CAD prior to TAVR, while it is more common in those with CAD, particularly in the setting of multivessel disease. The assessment of concomitant CAD prior to TAVR is crucial for optimal lifetime management of patients with severe AS.

## Conflict of interest statement

S. Windecker reports research and educational grants to the institution from Abbott, Abiomed, Amgen, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardinal Health, CardioValve, Corflow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pfizer, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed, Terumo, Vifor, and V-Wave. S. Windecker serves as unpaid advisory board member for and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, AstraZeneca, Bayer, Boston Scientific, Biotronik, Bristol-Myers Squibb, Edwards Lifesciences, Janssen, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, V-Wave, and Xeltis, but has not received personal payments from pharmaceutical companies or device manufacturers. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding from industry without impact on his personal remuneration. S. Windecker is an unpaid member of the Pfizer Research Award selection committee in Switzerland and of the Women as One Awards Committee. He is member of the Clinical Study Group of the Deutsches Zentrum für Herz Kreislauf-Forschung and of the Advisory Board of the

Australian Victorian Heart Institute. He is chairperson of the ESC Congress Program Committee and Deputy Editor of JACC CV Interventions. T. Pilgrim received research grants to the institution from Boston Scientific, Edwards Lifesciences, and Biotronik; speaker fees/consultancy from Boston Scientific, Biotronik, Medtronic, and Abbott; and consultancy (clinical event adjudication committee) for HighLife SAS. D. Heg has no personal conflicts; his employer, CTU Bern, University of Bern, has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in the design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organisations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. The other authors have no conflicts of interest to declare with regards to the contents of this article.

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## Supplementary data

**Supplementary Table 1.** Predictors of unplanned PCI under competing risk with death (model excluding aortic valve calcification).

**Supplementary Table 2.** Predictors of unplanned PCI under competing risk with death (model including variables with a p-value <0.1).

**Supplementary Figure 1.** Cumulative incidence curve of unplanned PCI after TAVR by baseline CAD in patients without a history of coronary artery bypass grafting.

*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00342*

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# Haemodynamic performance and clinical outcomes of transcatheter aortic valve replacement with the self-expanding ACURATE neo2

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**KEYWORDS**

- aortic stenosis
- atrio-ventricular block
- conduction abnormalities
- TAVR

## Abstract

**Background:** Transcatheter aortic valve replacement (TAVR) with the ACURATE *neo* device has been associated with a non-negligible incidence of paravalvular aortic regurgitation (AR). The new-generation ACURATE *neo2* has been designed to mitigate this limitation.

**Aims:** The aim of the study was to compare TAVR with the ACURATE *neo* and *neo2* devices.

**Methods:** The NEOPRO and NEOPRO-2 registries retrospectively included patients undergoing transfemoral TAVR with self-expanding valves at 24 and 20 centres, respectively. Patients receiving the ACURATE *neo* and *neo2* devices (from January 2012 to December 2021) were included in this study. Predischarge and 30-day VARC–3 defined outcomes were evaluated. The primary endpoint was predischarge moderate or severe paravalvular AR. Subgroup analyses per degree of aortic valve calcification were performed.

**Results:** A total of 2,026 patients (*neo*: 1,263, *neo2*: 763) were included. Predischarge moderate or severe paravalvular AR was less frequent for the *neo2* group (2% vs 5%; p<0.001), resulting in higher VARC-3 intended valve performance (96% vs 90%; p<0.001). Furthermore, more patients receiving the *neo2* had none/trace paravalvular AR (59% vs 38%; p<0.001). The reduction in paravalvular AR with *neo2* was mainly observed with heavy aortic valve calcification. New pacemaker implantation and VARC-3 technical and device success rates were similar between the 2 groups; there were more frequent vascular and bleeding complications for the *neo* device. Similar 1-year survival was detected after TAVR (*neo2*: 90% vs *neo*: 87%; p=0.14).

**Conclusions:** TAVR with the ACURATE *neo2* device was associated with a lower prevalence of moderate or severe paravalvular AR and more patients with none/trace paravalvular AR. This difference was particularly evident with heavy aortic valve calcification.

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## Abbreviations

**AR** aortic regurgitation
**PPI** permanent pacemaker implantation
**TAVR** transcatheter aortic valve replacement
**THV** transcatheter heart valve
**VARC** Valve Academic Research Consortium

## Introduction

Transcatheter aortic valve replacement (TAVR) is an established treatment option for patients with symptomatic severe aortic stenosis[1,2]. As TAVR candidates are increasingly younger and at lower surgical risk, it has become crucial to minimise potential procedural complications and to provide surgical-like long-term outcomes. Post-procedural moderate or severe paravalvular aortic regurgitation (AR) is a relevant complication after TAVR that has been found to be associated with adverse short- and long-term outcomes[3]. In the last few years, the first-generation ACURATE *neo* (Boston Scientific) transcatheter heart valve (THV) has emerged as a widely adopted self-expanding device for TAVR, associated with good procedural and clinical outcomes[4-9]. However, 2 randomised trials have recently reported a higher rate of moderate or severe paravalvular AR with the ACURATE *neo* as compared to other new-generation self-expanding and balloon-expandable THVs[10,11]. This complication was more frequent with increased device landing zone calcification[5]. For this reason, careful patient selection, proper sizing, and appropriate positioning were proposed to optimise procedural outcomes[9].

In September 2020, the new-generation ACURATE *neo2* THV was commercially released in Europe. This latest iteration of the ACURATE *neo* platform has been specifically designed to minimise the occurrence of paravalvular AR by utilising a 60% larger sealing skirt. Quantitative aortographic assessments have shown promising results in terms of paravalvular AR reduction with the ACURATE *neo2* device[12]. However, no large, real-world data have compared the performance of ACURATE *neo* and *neo2*. With this background, our study aimed to investigate the haemodynamic performance and clinical outcomes after transfemoral TAVR with the ACURATE *neo2* compared to the first-generation ACURATE *neo* THV.

## Methods

### STUDY POPULATION

The observational, retrospective NEOPRO (A Multicenter Comparison of Acurate NEO Versus Evolut PRO Transcatheter Heart Valves) registry included a total of 1,551 patients who underwent transfemoral TAVR with either ACURATE *neo* (n=1,263) or Evolut PRO (n=288; Medtronic) devices between January 2012 and March 2018 at 24 centres[4]. The NEOPRO-2 registry was designed to expand the previous registry to include procedures performed with the new-generation ACURATE *neo2* (n=763) and Evolut PRO or PRO+ (n=1,412) devices up to December 2021 at 20 centres. All consecutive patients treated with transfemoral TAVR for symptomatic, severe aortic stenosis of the native aortic valve (AV) with the implantation of the aforementioned self-expanding devices were included in the registries. For the purposes of the present study, only patients treated with ACURATE *neo* or *neo2* THVs were analysed. The number of patients included from each participating centre is detailed in **Supplementary Table 1**. The treatment period was from January 2012 to March 2018 for the *neo* THV and from September 2020 to December 2021 for the *neo2* device. Data obtained from 29 participating centres were included in the present analysis: 18 centres implanting the ACURATE *neo* (NEOPRO) and 16 centres using the *neo2* device (NEOPRO-2). Local multidisciplinary Heart Teams evaluated each case and confirmed eligibility for transfemoral TAVR. All patients provided written informed consent for the procedure and subsequent data collection per local practice for retrospective data. The study complied with the Declaration of Helsinki and was approved by local ethics committees. Preprocedural screening was performed by means of clinical assessment (patient demographics, symptoms, comorbidities, laboratory examinations, and risk evaluation), echocardiography and multidetector computed tomography.

### DEVICE DESCRIPTION

The ACURATE *neo2* bioprosthesis is a self-expanding THV with a supra-annular leaflet design. Three sizes are currently available (small, medium, and large) and correspond to annular diameters of 21-23, 23-25, and 25-27 mm, respectively. The *neo2* THV is implanted using a dedicated transfemoral delivery system inserted through a 14 Fr expandable sheath (iSleeve [Boston Scientific]). The deployment is performed in a top-down sequence, starting with the release of the stabilisation arches, and does not require rapid pacing. The self-expanding nitinol frame is wrapped with a pericardial sealing skirt on the outer and inner surface of the stent body that extends 60% higher from the inflow part of the stent frame as compared to the first-generation ACURATE *neo*. The skirt's extended dimensions have the potential of providing a more synchronous adaptation to the native aortic annulus during the different phases of the cardiac cycle, especially in irregular and calcified anatomies. Furthermore, a radiopaque marker has been added to the delivery system to navigate accurate positioning of the THV at the aortic annulus.

### STUDY ENDPOINTS AND DEFINITIONS

The primary study endpoint was the occurrence of moderate or severe paravalvular AR at predischarge transthoracic echocardiography. Secondary endpoints were Valve Academic Research Consortium (VARC)-3 defined clinical outcomes at 30 days[13], including the need for permanent pacemaker implantation (PPI), and 1-year overall survival.

Paravalvular AR severity was assessed with Doppler echocardiography according to VARC-3 criteria and classified as follows: none or trace, mild, moderate, and severe[13]. Native aortic valve and left ventricular outflow tract calcifications from multidetector computed tomography scans were classified and graded using a semiquantitative scoring system, as previously described[6,14].

### STATISTICAL ANALYSIS

Continuous variables are reported as mean±standard deviation or median (interquartile range [IQR]) and compared with the Student's unpaired t-test (parametric test) or the Wilcoxon rank-sum test (non-parametric test), according to their distribution. Categorical variables were reported as absolute and relative frequencies and compared with the $\chi^2$ test with Yates' correction for continuity or Fisher's exact test, as appropriate. Survival curves with their 95% confidence interval (CI) were plotted using the Kaplan-Meier estimator and compared with the log-rank test. A subgroup analysis testing the primary and secondary endpoints across different degrees of aortic valve calcification was also performed. For all analyses, a two-sided p-value <0.05 was considered to be significant. Statistical analyses were performed using R, version 4.0.2 (R Foundation).

## Results

### BASELINE PATIENT CHARACTERISTICS

A total of 2,026 patients in the NEOPRO and NEOPRO-2 registries underwent transfemoral TAVR with the self-expanding ACURATE *neo* or *neo2* THVs and were included in this study. Of these, 1,263 patients received the first-generation ACURATE *neo*, whereas 763 were treated using the new ACURATE *neo2* device. Baseline characteristics of the study population are reported in **Table 1**. The mean age was 82.0±5.8 years, and 66% of patients were women. Patients treated with the ACURATE *neo* were more frequently in New York Heart Association (NYHA) Functional Class III or IV (78% vs 55%; p<0.001), and were deemed at higher surgical risk (STS score: 4.1 [IQR 2.9-6.1] vs 3.5 [IQR 2.5-5.0], EuroSCORE II: 4.4 [IQR 2.7-7.2] vs 3.1 [IQR 2.1-5.1]; p<0.001). Patients receiving the ACURATE *neo2* were characterised by smaller anatomies of the aortic valve (area and perimeter) and of the TAVR femoral access (minimal diameter: 7.14±1.13 vs 7.95±1.37; p<0.001). The severity of aortic valve calcification was higher in the *neo* group, whereas mild and moderate left ventricular outflow tract calcifications were more frequent in *neo2* patients.

### PROCEDURAL RESULTS

Procedural characteristics are depicted in **Table 2**. Valve sizes were equally distributed within the 2 groups. Implantation of the *neo* THV was more frequently performed under general anaesthesia (13% vs 1%; p<0.001) and completed with final post-dilatation (42% vs 31%; p<0.001). The prevalence of procedural complications (namely: death, valve embolisation, the need for a second THV, annular rupture, pericardial tamponade, aortic dissection, coronary occlusion, and conversion to open-heart surgery) was low with no differences between the *neo* and *neo2* groups.

### CLINICAL OUTCOMES

Clinical outcomes assessed at 30 days post-TAVR are shown in **Table 3** and the **Central illustration**. VARC-3 defined technical (*neo*: 91% vs *neo2*: 93%; p=0.117) and device success (*neo*: 81% vs *neo2*: 84%; p=0.119) were similar in the 2 groups. The VARC-3 defined intended performance of the valve was more frequently met in the *neo2* group (96% vs 90%; p<0.001). This result was mainly driven by a lower rate of moderate or severe paravalvular AR in the *neo2* group (2% vs 5%; p<0.001). The prevalence of none/trace paravalvular AR was significantly higher

**Table 1. Baseline characteristics.**

| | | Total (2,026) | ACURATE *neo* (1,263) | ACURATE *neo2* (763) | *p*-value |
|---|---|---|---|---|---|
| **Clinical characteristics** | | | | | |
| Age, years | | 82±5.8 | 82±5.8 | 82±5.9 | 0.822 |
| Male | | 694 (34) | 444 (35) | 250 (33) | 0.303 |
| BMI | | 27±5 | 27±5 | 27±5 | 0.281 |
| BSA | | 1.82±0.21 | 1.82±0.21 | 1.82±0.22 | 0.314 |
| Hypertension | | 1,726 (87) | 1,079 (88) | 647 (85) | 0.055 |
| Diabetes mellitus | | 598 (30) | 379 (30) | 219 (29) | 0.571 |
| Atrial fibrillation | | 648 (32) | 408 (33) | 240 (32) | 0.772 |
| Previous stroke | | 209 (10) | 126 (10) | 83 (11) | 0.719 |
| Peripheral vascular disease | | 271 (13) | 156 (12) | 115 (15) | 0.093 |
| Previous myocardial infarction | | 220 (11) | 138 (12) | 82 (11) | 0.689 |
| Previous PCI | | 582 (29) | 370 (29) | 212 (28) | 0.496 |
| Previous CABG | | 194 (10) | 147 (12) | 47 (6) | <0.001 |
| COPD | | 369 (18) | 244 (19) | 125 (16) | 0.114 |
| eGFR, ml/min/1.73m$^2$ | | 60±25 | 58±22 | 64±29 | <0.001 |
| Prior PM/ICD | | 219 (11) | 158 (12) | 61 (8) | 0.002 |
| NYHA Class III/IV | | 1,397 (69) | 981 (78) | 416 (55) | <0.001 |
| EuroSCORE II | | 3.9 [2.5-6.6] | 4.4 [2.7-7.2] | 3.1 [2.1-5.1] | <0.001 |
| STS score (mortality) | | 4.0 [2.8-5.8] | 4.1 [2.9-6.1] | 3.5 [2.5-5.0] | <0.001 |
| **Echocardiographic data** | | | | | |
| Mean aortic gradient, mmHg | | 44±16 | 43±17 | 45±14 | 0.057 |
| AVA, cm$^2$ | | 0.71±0.22 | 0.71±0.19 | 0.71±0.26 | 0.523 |
| Indexed AVA, cm$^2$/m$^2$ | | 0.39±0.10 | 0.39±0.11 | 0.39±0.09 | 0.891 |
| LVEF, % | | 57±11 | 57±12 | 58±10 | 0.032 |
| **CT analysis** | | | | | |
| Aortic valve area, mm$^2$ | | 429±64 | 432±67 | 424±59 | 0.015 |
| Aortic valve perimeter, mm | | 74±6 | 75±6 | 74±5 | <0.001 |
| Aortic valve calcification | None or mild | 470 (29) | 286 (29) | 184 (29) | 0.02 |
| | Moderate | 739 (46) | 428 (44) | 311 (50) | |
| | Heavy | 396 (25) | 263 (27) | 133 (21) | |
| LVOT calcification | None | 693 (53) | 541 (56) | 152 (46) | 0.01 |
| | Mild | 379 (29) | 265 (27) | 114 (35) | |
| | Moderate | 152 (12) | 107 (11) | 45 (14) | |
| | Severe | 78 (6) | 62 (6) | 16 (5) | |
| Femoral access*, mm | | 7.78±1.36 | 7.95±1.37 | 7.14±1.13 | <0.001 |

*Minimal lumen diameter of the femoral artery used to deliver the valve. Values are n (%), mean±standard deviation, or median [interquartile range]. AVA: aortic valve area; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PM: pacemaker; STS: Society of Thoracic Surgeons

**Table 2. Procedural characteristics.**

| | | Total (2,026) | ACURATE *neo* (1,263) | ACURATE *neo2* (763) | *p*-value |
|---|---|---|---|---|---|
| Valve size, mm | 23 | 533 (26) | 348 (28) | 185 (24) | 0.255 |
| | 25 | 847 (42) | 520 (41) | 327 (43) | |
| | 27 | 645 (32) | 394 (31) | 251 (33) | |
| General anaesthesia | | 175 (9) | 168 (13) | 7 (1) | <0.001 |
| Predilatation | | 1,706 (84) | 1,051 (83) | 655 (86) | 0.141 |
| Post-dilatation | | 759 (38) | 526 (42) | 233 (31) | <0.001 |
| Death | | 2 (0.3) | 0 (0.0) | 2 (0.3) | 1.000 |
| Valve embolisation | | 21 (1) | 13 (1) | 8 (1) | 1.000 |
| Second THV implanted | | 20 (1) | 14 (1) | 6 (1) | 0.634 |
| Annular rupture | | 5 (0.2) | 4 (0.3) | 1 (0.1) | 0.656 |
| Pericardial tamponade | | 27 (1) | 20 (2) | 7 (1) | 0.286 |
| Aortic dissection | | 1 (0.0) | 1 (0.1) | 0 (0.0) | 1.000 |
| Coronary occlusion | | 4 (0.2) | 2 (0.2) | 2 (0.3) | 1.000 |
| Conversion to open-heart surgery | | 16 (1.0) | 13 (1.0) | 3 (0.4) | 0.191 |

Values are expressed as n (%). THV: transcatheter heart valve

after TAVR with the *neo2* THV (59% vs 38%; p<0.001). Slightly increased mean aortic gradients were found in the *neo2* group (*neo*: 8.0±3.3 mmHg vs *neo2*: 8.9±4.1 mmHg; p<0.001), and no differences were found in terms of aortic valve area. The need for a new PPI was similar in the 2 groups (*neo*: 9% vs *neo2*: 8%; p=0.46). Patients receiving the *neo2* THV experienced fewer vascular (p<0.001) and bleeding (p=0.020) complications.

Patients were followed up for a median time of 83 [IQR 30-261] days. As shown in the Kaplan-Meier analysis **(Figure 1)**, all-cause mortality at 1-year follow-up was not significantly different between the *neo2* and *neo* groups (90%, 95% CI: 83-98 vs 87%, 95% CI: 84-90; p=0.14).

## SUBGROUP ANALYSIS ON AORTIC VALVE CALCIFICATION SEVERITY

As shown in **Table 4**, clinical outcomes were further analysed stratifying the overall population for baseline aortic valve calcification grades (none or mild, moderate, and heavy). The significant reduction of moderate or severe paravalvular AR in the *neo2* group was observed in the subgroup of patients with heavy aortic valve calcification (2% vs 9%; p=0.018); consequently, VARC-3 intended performance of the valve was more frequently met among patients receiving *neo2* THV in the heavy aortic valve calcification subgroup (97% vs 88%; p=0.005). No significant differences were observed for these 2 endpoints between the *neo* and *neo2* groups in the other calcification subgroups **(Table 4)**.

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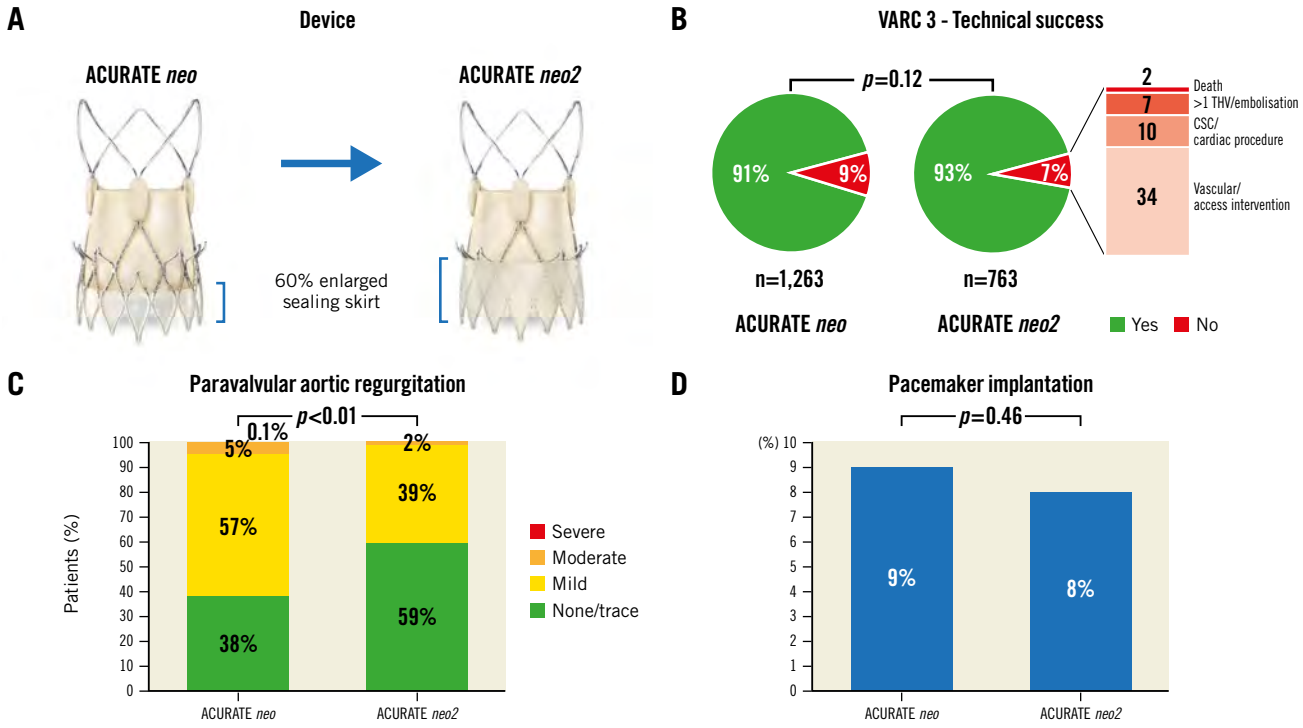
CENTRAL **ILLUSTRATION** Comparison of the ACURATE *neo* and the ACURATE *neo2* THVs.




*A) Device characteristics, B) VARC-3 technical success, C) predischarge paravalvular aortic regurgitation, and D) the need for permanent pacemaker implantation after transcatheter aortic valve replacement. Device illustrations reproduced with permission from Boston Scientific. CSC: cardiac structural complication; THV: transcatheter heart valve; VARC: Valve Academic Research Consortium*

**Table 3. 30-day outcomes.**

| | | Total (2,026) | ACURATE *neo* (1,263) | ACURATE *neo2* (763) | *p*-value |
|---|---|---|---|---|---|
| All-cause death | | 61 (3) | 39 (3) | 22 (3) | 0.903 |
| VARC 3 – technical success | | 1,859 (92) | 1,149 (91) | 710 (93) | 0.117 |
| VARC 3 – device success | | 1,630 (82) | 1,024 (81) | 606 (84) | 0.119 |
| VARC 3 – intended performance | | 1,286 (93) | 572 (90) | 714 (96) | <0.001 |
| PM implantation | | 147 (8) | 96 (9) | 51 (8) | 0.460 |
| Acute kidney injury (stage 2-3) | | 58 (3) | 37 (3) | 21 (3) | 0.953 |
| Vascular complications | None | 1,700 (87) | 1,032 (83) | 668 (94) | <0.001 |
| | Minor | 156 (8) | 138 (11) | 18 (2) | |
| | Major | 98 (5) | 75 (6) | 23 (3) | |
| Bleeding complications | None | 1,638 (86) | 1,011 (85) | 627 (88) | 0.020 |
| | Type 1 | 104 (6) | 65 (6) | 39 (6) | |
| | Type 2 | 79 (4) | 56 (5) | 23 (3) | |
| | Type 3 | 74 (4) | 56 (5) | 18 (2) | |
| | Type 4 | 2 (0.1) | 0 (0.0) | 2 (0.3) | |
| Mean aortic gradient, mmHg | | 8.5±3.8 | 8±3.3 | 8.9±4.1 | <0.001 |
| AVA, $cm^2$ | | 1.8±0.4 | 1.8±0.4 | 1.8±0.4 | 0.826 |
| Indexed AVA, $cm^2/m^2$ | | 0.96±0.20 | 0.96±0.20 | 0.96±0.20 | 0.769 |
| Moderate or severe paravalvular AR* | | 75 (4) | 62 (5) | 13 (2) | <0.001 |

*Predischarge assessment. Values are n (%) or mean±standard deviation. AR: aortic regurgitation; AVA: aortic valve area; PM: pacemaker; VARC: Valve Academy Research Consortium

All the remaining clinical outcomes were consistent with the primary analysis with no significant differences between both groups across all aortic valve calcification subgroups. In detail, the rates of new PPI were similar between *neo* and *neo2* THVs in each subgroup (none/mild: 9% vs 7%, moderate: 10% vs 9%, heavy: 8% vs 6%; all p-values >0.05, p for interaction=0.982).

## Discussion

The main findings of our multicentre, observational, real-world comparison between ACURATE *neo* and *neo2* devices in a total of 2,026 patients undergoing transfemoral TAVR (from the NEOPRO/NEOPRO-2 registries) are as follows: 1) the latest-generation ACURATE *neo2* THV was associated with a significant reduction in post-procedural moderate or severe paravalvular AR as compared to the first-generation *neo* THV; 2) a similar need for new PPI was observed between *neo2* and *neo* devices; 3) the superior performance of the ACURATE *neo2* THV was particularly evident in severely calcified aortic valve anatomies; 4) TAVR with the ACURATE *neo2* in combination with the expandable iSleeve is associated with reduced rates of vascular complications.

In our study, procedural outcomes after ACURATE *neo2* THV implantation suggest acceptable safety and efficacy with rates of 3% for 30-day mortality, 93% for VARC-3 technical success, 84% for VARC-3 device success, and 96% for VARC-3 intended performance of the valve. These results compare favourably with available evidence on the first-generation *neo* device reporting an equal 30-day mortality rate (3%) and similar rates of procedural complications[5,10,11]. Interestingly, we observed fewer vascular and bleeding complications in the *neo2* group as compared to the *neo* group. It must be acknowledged that all the procedures were transfemoral

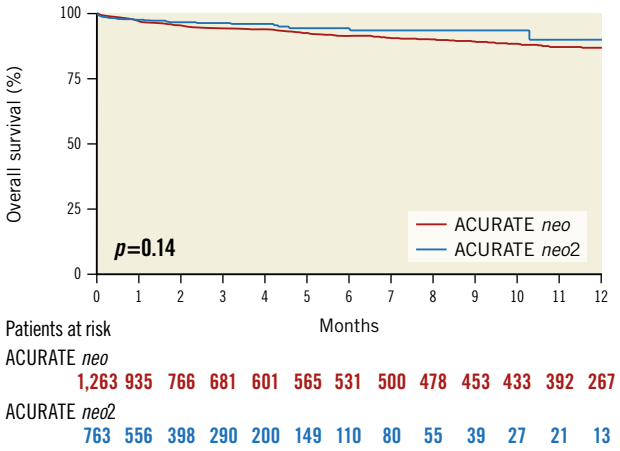



**Figure 1.** *Kaplan-Meier analysis of overall survival in ACURATE neo vs ACURATE neo2 transcatheter aortic valves.*

**Table 4. 30-day outcomes stratified per aortic valve calcification grade.**

| | None or mild calcification | | | Moderate calcification | | | Heavy calcification | | | *p*-value for interaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | ACURATE *neo* (286) | ACURATE *neo2* (184) | *p*-value | ACURATE *neo* (428) | ACURATE *neo2* (311) | *p*-value | ACURATE *neo* (263) | ACURATE *neo2* (133) | *p*-value | |
| All-cause death | 9 (3) | 6 (3) | 1.000 | 11 (3) | 9 (3) | 0.962 | 9 (4) | 0 (0) | 0.070 | 0.418 |
| VARC 3 - technical success | 250 (87) | 167 (91) | 0.332 | 390 (91) | 287 (92) | 0.669 | 240 (91) | 128 (96) | 0.105 | 0.404 |
| VARC 3 - device success | 229 (80) | 150 (84) | 0.311 | 346 (81) | 244 (83) | 0.524 | 203 (78) | 100 (85) | 0.172 | 0.691 |
| VARC 3 - intended performance | 262 (97) | 178 (97) | 0.937 | 377 (93) | 293 (95) | 0.298 | 214 (88) | 127 (97) | 0.005 | 0.899 |
| PM implantation | 21 (9) | 11 (7) | 0.605 | 40 (10) | 23 (9) | 0.535 | 17 (8) | 6 (6) | 0.705 | 0.982 |
| Mean aortic gradient, mmHg | 7.6±3.4 | 8.5±4.2 | 0.023 | 8.0±3.2 | 9.0±4.1 | 0.001 | 8.2±3.6 | 8.9±3.9 | 0.023 | 0.141 |
| AVA, $cm^2$ | 1.7±0.4 | 1.7±0.4 | 0.867 | 1.7±0.4 | 1.7±0.4 | 0.731 | 1.8±0.4 | 1.9±0.4 | 0.867 | 0.135 |
| Indexed AVA, $cm^2/m^2$ | 0.96±0.20 | 0.96±0.20 | 0.979 | 0.93±0.20 | 0.94±0.20 | 0.589 | 0.96±0.20 | 1.0±0.2 | 0.979 | 0.208 |
| Moderate or severe paravalvular AR* | 6 (2) | 1 (0.5) | 0.317 | 21 (5) | 7 (2) | 0.077 | 23 (9) | 3 (2) | 0.018 | 0.671 |

*Predischarge assessment. Values are n (%) or mean±standard deviation. AR: aortic regurgitation; AVA: aortic valve area; PM: pacemaker; VARC: Valve Academic Research Consortium

with smaller accesses for *neo2* recipients (minimal lumen diameter 7.14±1.13 vs 7.95±1.37; p<0.001), similar baseline patient characteristics (age: 82±6 years, atrial fibrillation: 33% vs 32%, peripheral vascular disease: 12% vs 15%), and lower surgical risk scores for the *neo2* group, in accordance with TAVR indication expanding to lower-risk patients over time. Even if speculative, the fewer bleeding and vascular complications observed with the implantation of the *neo2* THV may be explained by a combination of the redesigned expandable introducer with a low-profile (iSleeve; Boston Scientific), increased operator experience with the ACURATE system, and improved vascular access/complication management.

The only VARC-3 defined outcome that was significantly different between the *neo* and *neo2* devices was the intended performance of the valve (*neo2*: 96% vs *neo*: 90%; p<0.001). This composite endpoint is achieved with a mean transvalvular gradient <20 mmHg, peak velocity <3 m/s, Doppler velocity index ≥0.25, and less than moderate AR[13]. The improved performance of the *neo2* THV was driven by a reduction in moderate or severe paravalvular AR compared to the first-generation *neo* THV. In the overall population, the 5% rate of moderate or severe paravalvular AR that occurred after the ACURATE *neo* implantation was significantly higher than the 2% rate observed with the *neo2* THV (p<0.001). The rate of paravalvular AR in our *neo* group (5%) is lower than those reported by the randomised SCOPE 1 (9.4%) and SCOPE 2 (9.6%) trials[10,11]. This finding may be explained by differences in outcome adjudication (core lab vs centre-reported) and baseline patient characteristics. Although these trials excluded severe eccentric aortic valve calcifications, they did not report the degrees of overall calcifications which have been demonstrated by Kim et al as having a significant impact on moderate or severe paravalvular AR rates (mild: 0.8%, moderate: 5%, severe: 13%)[5]. Accordingly, our subgroup analysis reported a similarly increasing trend for paravalvular AR in the *neo* group, starting from 2% for none/mild aortic valve calcifications, up to 5% for moderate and 9% for heavy calcifications. On the contrary, the rate of moderate or severe paravalvular AR after TAVR with the *neo2* THV was consistent among these 3 calcification subgroups (none/mild: 0.5%, moderate: 2%, heavy: 2%). Similar rates of moderate or severe paravalvular AR (1.7-2.5%) were reported in other exploratory analyses evaluating TAVR with the ACURATE *neo2* device[12,15]. Furthermore, 59% of patients treated with the new-generation *neo2* device showed none/trace paravalvular AR after TAVR, which is significantly higher than the 38% obtained with the *neo* THV (p<0.001). This finding also compares favourably with the frequency of none/trace paravalvular AR observed after *neo* implantation in the SCOPE 1 (40%) and SCOPE 2 trials[10,11]. These results are promising as they demonstrate how the engineering refinements translate into better performance of the ACURATE *neo2* THV. Moreover, they indicate that the caveat of avoiding patients with severe aortic calcifications may no longer be appropriate for the ACURATE *neo2* system[9]. Pending further supporting evidence, it seems that this new-generation device can provide favourable performance with a low rate of significant paravalvular AR, even in the more challenging calcific anatomies. The observed gradient with *neo2* in our population (8.9±4.1 mmHg) is similar to the one reported in patients with small annuli included in the TAVI-SMALL registry and receiving the *neo* device (9.6±0.3 mmHg)[16]. An inverse correlation between annular dimensions and post-procedural gradients has been previously demonstrated with better haemodynamic performance of self-expanding supra-annular THVs in this anatomical setting[17,18].

Another relevant clinical outcome after TAVR is represented by the need for new PPI. Previous studies investigating the ACURATE *neo* system reported a 10-11% rate of PPI[5,10,11],which was found to be independent of device landing zone calcification[5]. Our analysis confirms these findings for the *neo2* THV, showing a rate of new PPI equal to 8% with no significant differences across the aortic valve calcification subgroups. These results are even more meaningful when compared with the 17-18% of PPI after TAVR with the self-expanding CoreValve Evolut platform (Medtronic)[10,19]. A stable and precise (less protrusion in the left ventricular outflow tract) valve implantation with top-down deployment and radiopaque positioning markers, a moderate device radial force, and the temporal shift from the left anterior oblique to cusp overlap view for the THV implantation are the technical factors explaining this relatively low PPI rate. Keeping this figure as low as possible has a great clinical value and may be used to guide device selection in patients at high risk of permanent conduction disturbances after TAVR[20].

At 1-year follow-up, we did not observe a significant difference in all-cause mortality between the *neo2* and *neo* groups (10% vs 13%; p=0.14). The 1-year mortality rate observed in this real-world experience with ACURATE *neo* is in line with rates recently reported by the randomised SCOPE 1 (11%) and SCOPE 2 (13%) trials[10,11]. Given the prognostic impact of moderate or severe paravalvular AR[3] and its significant reduction using the ACURATE *neo2*, further analyses with larger sample sizes and longer follow-up are eagerly awaited to better explore long-term outcomes after TAVR with this new self-expanding platform.

## Limitations

The main limitation of this study is related to its retrospective observational design, with no core laboratory analysis of procedural results and echocardiographic readings or independent adjudication of clinical events. The investigated THVs were implanted in consecutive time periods, and unmeasured confounding factors (e.g., operator experience, valve preference) may have affected the presented results. The use of multiple different sheaths with the ACURATE *neo* may be a major contributor to the differences in peripheral vascular characteristics compared to the *neo2*, which was implanted through a redesigned expandable introducer with a low-profile (iSleeve; Boston Scientific). Given the recent release of the ACURATE *neo2* device (September 2020), available follow-up time is currently limited, and future studies will be needed to assess if lower paravalvular AR is sustained over time and how it impacts on long-term clinical outcomes. Whilst waiting for the results of ongoing registries (Early *neo2* Registry of the Acurate *neo2* TAVI Prosthesis [ClinicalTrials.gov: NCT04810195]) and randomised controlled trials (ACURATE IDE: Safety and Efficacy

Study of Acurate Valve for Transcatheter Aortic Valve Replacement [ClinicalTrials.gov: NCT03735667]), these exploratory analyses can provide immediate assistance in THV selection for TAVR.

## Conclusions

The latest-generation ACURATE *neo2* THV is associated with a lower rate of moderate or severe paravalvular AR, when compared to the first-generation ACURATE *neo*, in patients undergoing transfemoral TAVR. As a result, a greater percentage of patients receiving the *neo2* THV have none/trace paravalvular AR. The superior performance of the *neo2* device is particularly evident among patients with heavy aortic valve calcification.

## Impact on daily practice

TAVR with the ACURATE *neo* THV was associated with a non-negligible rate of moderate or severe paravalvular AR, which is known to have an adverse prognostic impact. TAVR with the ACURATE *neo2* device is associated with a lower rate of moderate or severe paravalvular AR when compared with the first-generation ACURATE *neo*. The superior performance of the *neo2* device is particularly evident among patients with heavy aortic valve calcification. Further studies with larger sample sizes and longer follow-up are needed to confirm these preliminary findings.

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## Guest editor

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## Conflict of interest statement

A. Latib has served on advisory boards or as a consultant for Medtronic, Boston Scientific, Philips, Edwards Lifesciences, and Abbott. W-K. Kim is a proctor for Boston Scientific and Abbott Vascular; and has received speaker fees from Edwards Lifesciences. U. Schäfer is proctor for Boston Scientific and Medtronic and has received lecture fees and travel support from both companies. M. Barbanti has served as a consultant for Edwards Lifesciences. D. Hildick-Smith is an advisor and a proctor for Boston Scientific, Symetis, and Medtronic. A. Wolf is a proctor for Medtronic and Boston Scientific. N. Van Mieghem has received research grant support from Boston Scientific, Abbott Vascular, Medtronic, Claret, and Essential Medical. S. Toggweiler is a consultant and proctor for Boston Scientific, Medtronic, Abbott, and Biosensors; is a consultant for Medira, Atheart Medical, Veosource, Shockwave, and Teleflex; has received institutional research grants from Boston Scientific and Fumedica AG; and holds equity in Hi-D Imaging. D. Mylotte is a proctor for Medtronic and Microport. V. Veulemans has received lecture fees and travel support from Medtronic and Edwards Lifesciences. S. Windecker has received grants from Abbott Vascular, Biotronik, Boston Scientific, Edwards Lifesciences, and Medtronic. D. Siqueira is proctor for Medtronic, Symetis, and Edwards Lifesciences. M. Adamo reports speaker honoraria from Abbott Vascular and Medtronic. J-M. Sinning is a proctor for Medtronic and Boston Scientific; and has received speaking honoraria and research grants from Medtronic, Edwards Lifesciences, and Boston Scientific. D.A. Wood has received grant support from Boston Scientific; and is a consultant for Medtronic. L. Sondergaard has received consultant

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## Supplementary data

**Supplementary Table 1.** NEOPRO and NEOPRO-2 participating centres.

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# Dual ProGlide versus ProGlide and FemoSeal for vascular access haemostasis after transcatheter aortic valve implantation

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**KEYWORDS**

- access site
- bleeding
- femoral
- TAVI

## Abstract

**Background:** Large-bore arteriotomy for transcatheter aortic valve implantation (TAVI) requires percutaneous vascular closure devices, but real-world data comparing different closure strategies are limited.

**Aims:** We sought to compare a dual ProGlide strategy vs a combination of one ProGlide and one FemoSeal for vascular closure after TAVI.

**Methods:** We retrospectively analysed 874 propensity score-matched patients undergoing TAVI at the Munich University Hospital from August 2018 to October 2020. From August 2018 to August 2019, a dual ProGlide strategy was used for vascular closure. From October 2019 to October 2020, a combination of one ProGlide and one FemoSeal was used. The primary endpoint was defined as access-related major vascular complications or bleeding ≥Type 2 according to Valve Academic Research Consortium 3 criteria.

**Results:** Patients in the dual ProGlide group (n=437) had a higher incidence of the primary endpoint than patients treated with one ProGlide and one FemoSeal (n=437; 11.4% vs 3.0%; p<0.001). Furthermore, they had a higher rate of closure device failure (2.7% vs 0.9%; p=0.044) and more often required unplanned surgery or endovascular treatment (3.9% vs 0.9%; p=0.004). The incidence of death did not differ significantly between groups (3.4% vs 1.6%; p=0.08).

**Conclusions:** A combined ProGlide and FemoSeal strategy might have the potential to reduce access-related vascular complications following TAVI.

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## Abbreviations

| | |
|---|---|
| **CT** | computed tomography |
| **P+F group** | ProGlide and FemoSeal group |
| **P+P group** | Dual ProGlide group |
| **TAVI** | transcatheter aortic valve implantation |
| **VARC** | Valve Academic Research Consortium |
| **VCD** | vascular closure device |

## Introduction

Transcatheter aortic valve implantation (TAVI) is the optimal therapy for patients with symptomatic severe aortic stenosis at high surgical risk[1]. Due to the results of the PARTNER 2 and 3 as well as the SURTAVI and Evolut Low Risk trials, the use of TAVI is increasingly extended to intermediate- and even low-risk patients[2-5].

Access-related vascular complications and bleeding remain the most frequent complications after transfemoral TAVI and are associated with worse short- and long-term outcomes[4,6,7]. Historically, suture-mediated percutaneous vascular closure devices (VCD) have been used for main access closure to avoid surgical cut-down. Among VCD, the Perclose ProGlide (Abbott Vascular) has shown superior results compared to the Prostar XL (Abbott Vascular) and has since become the most widely used suture-based VCD[8,9]. Additionally, a large-bore collagen plug-based VCD (MANTA; Teleflex) has been developed recently. Despite promising results in early feasibility trials and retrospective analyses, MANTA proved inferior to a dual ProGlide strategy in a recent randomised controlled study[10-12].

Initially proposed as a bailout strategy for excessive bleeding, a combination of suture-based VCD with additional collagen plug-based VCD has been reported to be safe and feasible[13,14]. This approach theoretically reduces constriction of the common femoral artery and strain on the arterial wall while maintaining the advantages of both suture- and plug-based VCD. However, real-world data on vascular and bleeding outcomes of this approach are lacking.

Therefore, the objective of this study was to compare the use of a dual ProGlide technique (hereafter referred to as P+P group) and a combination of one ProGlide with the plug-based VCD FemoSeal (P+F group; Terumo) regarding vascular complications and bleeding in patients undergoing transfemoral TAVI.

## Methods

In this retrospective single centre study, consecutive patients that underwent transfemoral TAVI from August 2018 to October 2020 at the Munich University Hospital were included.

From August 2018 to August 2019, vascular closure was performed using a suture-based strategy with 2 diagonally placed ProGlide systems. From October 2019 to October 2020, a combination of a single ProGlide system with a subsequently introduced FemoSeal system was used. Patients treated in September 2019 were excluded from this analysis to minimise the learning curve impact. In total, 1,018 patients underwent transfemoral TAVI during the selected time period. Twenty-nine patients were excluded due to primary use of a different closure device, conversion to open-surgery or death before access-site closure **(Figure 1)**.

All patients initially underwent contrast-enhanced computed tomography (CT) and transthoracic echocardiography in accordance with current European guidelines[15,16]. TAVI was scheduled after obtaining consensus in the Heart Team. Transthoracic echocardiography and a duplex ultrasound of the main access site were performed routinely before discharge.

Patient data were collected from the electronic database that is part of the local EVERY VALVE registry (project number: 19-840) at the University Hospital Munich. The institutional ethics committee approved data acquisition and statistical analysis, and the study adhered to the tenets of the Declaration of Helsinki.

### TAVI PROCEDURE

TAVI was generally performed under local anaesthesia. After the initial puncture of the femoral artery, a routine angiogram was

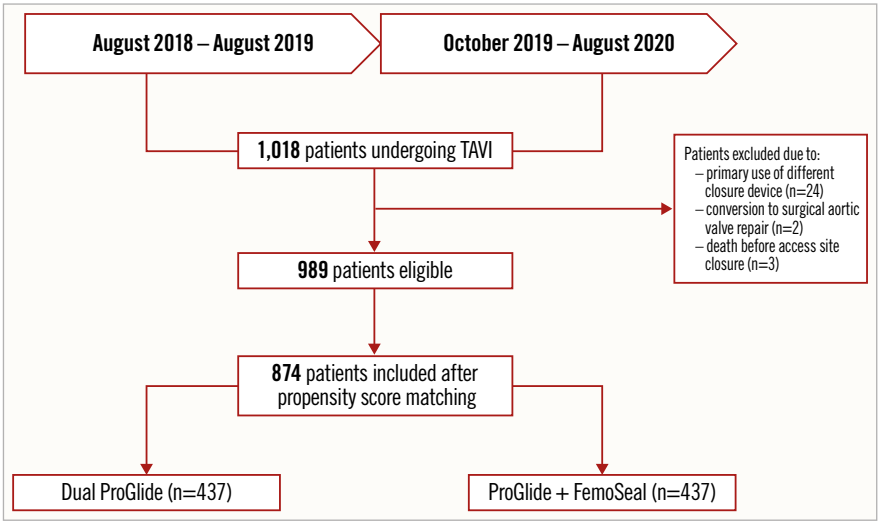


**Figure 1.** *Study flowchart showing time period of inclusion. TAVI: transcatheter aortic valve implantation*

done to confirm puncture height. In the P+P group, 2 VCDs were deployed diagonally (at 10 and 2 o'clock). In the P+F group, 1 ProGlide was inserted at the beginning of the procedure followed by the plug-based FemoSeal system at the end of the procedure. Intraprocedural anticoagulation was achieved with unfractionated heparin (50 to 70 IU/kg body weight) obtaining a target activated clotting time >250 sec. Manual compression was maintained until complete haemostasis was achieved.

### ENDPOINTS

The primary endpoint was defined as a composite of access-related major vascular complications or in-hospital bleeding ≥Type 2 according to the 2021 Valve Academic Research Consortium (VARC-3) criteria[17]. Secondary endpoints included overall vascular complications, closure device failure and bleeding according to the VARC-3 criteria, the need for unplanned surgery or endovascular treatment as well as the need for red blood cell transfusion. Additionally, standard procedural endpoints such as death, the need for a new pacemaker, stroke, unplanned revascularisation and acute kidney injury were obtained from the local registry.

### STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS (version 25; IBM). The Student's t-test and Wilcoxon rank-sum test were used to compare continuous variables as appropriate. The chi-square test was used to compare categorial variables. The normality of data distribution was assessed graphically. All tests were 2-sided and a p-value <0.05 was considered statistically significant. Propensity score matching was performed using the R package MatchIt (version 4.3.3; Ho, Imai, King, and Stuart) with a 1:1 nearest neighbour algorithm, no replacement, a 0.1 calliper and the following variables: age, sex, body mass index, estimated glomerular filtration rate, haemoglobin, diabetes mellitus, atrial fibrillation, history of stroke, left ventricular ejection fraction, oral anticoagulation, peripheral arterial disease, and chronic obstructive pulmonary disease[18].

A logistic regression analysis was used to identify predictors for the primary endpoint. Both groups were divided into tertiles to exclude learning curve effects. Variables with p<0.1 were included in the multivariable analysis.

## Results

### BASELINE CHARACTERISTICS

Baseline characteristics of the 989 unmatched and 874 matched patients included are presented in **Table 1**. Patients were well balanced except for a lower rate of chronic dialysis in the dual ProGlide group (0.5% vs 2.1%; p=0.033). Standardised mean differences are shown in **Supplementary Table 1**. Computed tomography characteristics of the main access vessel are depicted in **Table 2**.

**Table 1. Baseline characteristics.**

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | Dual ProGlide (n=491) | ProGlide+FemoSeal (n=498) | *p*-value | Dual ProGlide (n=437) | ProGlide+FemoSeal (n=437) | *p*-value |
| Age | 81.0±6.7 | 79.9±7.5 | 0.017 | 80.7±7.7 | 80.8±6.9 | 0.81 |
| Female sex | 230 (46.8%) | 210 (42.2%) | 0.14 | 197 (45.1%) | 197 (45.1%) | 1 |
| BMI | 26.5±5.2 | 26.6±4.8 | 0.61 | 26.6±5.2 | 26.4±4.7 | 0.75 |
| Society of Thoracic Surgeons Score | 3.8±2.6 | 3.6±2.7 | 0.12 | 3.8±2.7 | 3.7±2.8 | 0.61 |
| NYHA Class III or IV | 392 (80.0%) | 383 (76.0%) | 0.26 | 350 (80.1%) | 339 (77.6%) | 0.36 |
| Diabetes mellitus | 140 (28.5%) | 118 (23.7%) | 0.08 | 118 (27.0%) | 107 (24.5%) | 0.40 |
| Coronary artery disease | 297 (60.5%) | 303 (60.8%) | 0.91 | 259 (59.3%) | 261 (59.7%) | 0.89 |
| Previous myocardial infarction | 69 (14.1%) | 64 (12.9%) | 0.58 | 57 (13.4%) | 54 (12.4%) | 0.76 |
| Previous PCI | 164 (33.4%) | 158 (31.7%) | 0.57 | 145 (33.2%) | 138 (31.6%) | 0.61 |
| Previous CABG | 41 (8.4%) | 28 (5.6%) | 0.09 | 36 (8.2%) | 24 (5.5%) | 0.11 |
| Previous stroke | 66 (13.4%) | 62 (12.4%) | 0.64 | 59 (13.5%) | 56 (12.8%) | 0.76 |
| Peripheral arterial disease | 53 (10.8%) | 47 (9.4%) | 0.48 | 48 (11.0%) | 46 (10.5%) | 0.83 |
| Atrial fibrillation | 211 (43.0%) | 189 (38.0%) | 0.12 | 188 (43.0%) | 174 (39.8%) | 0.34 |
| COPD | 51 (10.4%) | 66 (13.3%) | 0.16 | 48 (11.0%) | 46 (10.5%) | 0.83 |
| Baseline eGFR | 49.1±20.0 | 51.7±22.9 | 0.06 | 49.6±20.0 | 50.0±20.4 | 0.85 |
| Chronic dialysis | 5 (1.0%) | 10 (2.0%) | 0.20 | 2 (0.5%) | 9 (2.1%) | 0.033 |
| Baseline haemoglobin level (g/dl) | 12.4±1.8 | 12.6±1.9 | 0.10 | 12.4±1.7 | 12.5±1.9 | 0.44 |
| LV ejection fraction (%) | 50.8±8.4 | 51.6±9.4 | 0.18 | 51.1±8.1 | 51.3±9.6 | 0.79 |
| Mean gradient (mmHg) | 37.0±13.3 | 36.3±14.0 | 0.40 | 35.1±13.2 | 36.4±14.4 | 0.49 |
| Aortic valve area ($cm^2$) | 0.75±0.21 | 0.76±0.21 | 0.32 | 0.75±0.20 | 0.76±0.22 | 0.69 |

BMI: body mass index; CABG: coronary artery bypass graft; eGFR: estimated glomerular filtration rate; LV ejection fraction: left ventricular ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention

**Table 2. Computed tomography characteristics of main access site.**

| Variable | | Dual ProGlide (n=437) | ProGlide +FemoSeal (n=437) | *p*-value |
|---|---|---|---|---|
| Minimal lumen diameter (mm) | | 7.7±1.8 | 7.9±1.8 | 0.23 |
| Calcification | None | 22 (5.0%) | 23 (5.7%) | 0.45* |
| | Mild | 162 (37.1%) | 153 (35.0%) | |
| | Moderate | 212 (48.5%) | 216 (49.7%) | |
| | Severe | 26 (5.9%) | 37 (8.5%) | |
| Vessel tortuosity | None | 42 (9.6%) | 31 (7.1%) | 0.017† |
| | Mild (30-60°) | 194 (44.4%) | 175 (40.0%) | |
| | Moderate (60-90°) | 120 (27.5%) | 145 (33.2%) | |
| | Severe (>90°) | 64 (14.6%) | 78 (17.8%) | |

Values are depicted as no. (percentage of total no.) **p*-value refers to comparison of at least moderate calcification; †*p*-value refers to comparison of at least moderate tortuosity

Tortuosity was lower in the dual ProGlide group (42.1% vs 51.0% ≥moderate tortuosity; p=0.017). Antithrombotic therapy is shown in **Supplementary Table 1**.

## PROCEDURAL RESULTS

**Table 3** shows the procedural details. A radial access was more often used as secondary access in the P+P group (76.0% vs 65.4%; p<0.001). The mean sheath size was slightly, but significantly, larger in the P+P group (14.6±1.0 vs 14.3±0.8; p<0.001). The amount of contrast agent applied (122.2±68.7 vs 107.8±61.6; p=0.001) and fluoroscopy time (13.5±7.8 vs 12.4±7.4; p=0.032) were higher in the P+P group.

**Table 3. Procedural details.**

| Variable | | ProGlide (n=437) | ProGlide +FemoSeal (n=437) | *p*-value |
|---|---|---|---|---|
| Main access | Right femoral | 392 (89.7%) | 399 (91.3%) | 0.42 |
| | Left femoral | 45 (10.3%) | 38 (8.7%) | |
| Secondary access | Radial | 332 (76.0%) | 286 (65.4%) | 0.001 |
| | Femoral | 105 (24.0%) | 149 (34.1%) | |
| Sheath size (French) | | 14.6±1.0 | 14.3±0.8 | <0.001 |
| Valve type | SAPIEN 3 | 308 (70.5%) | 316 (72.3%) | 0.55* |
| | Evolut R | 53 (12.1%) | 65 (14.9%) | |
| | Acurate *neo* | 73 (16.7%) | 56 (12.8%) | |
| | LOTUS Edge | 1 (0.2%) | 0 | |
| | Portico | 2 (0.4%) | 0 | |
| Balloon predilation | | 215 (49.2%) | 210 (48.1%) | 0.76 |
| Balloon post-dilation | | 24 (5.5%) | 28 (6.4%) | 0.55 |
| Percutaneous coronary intervention | | 68 (15.6%) | 61 (14.0%) | 0.50 |
| Procedure duration (min) | | 44.6±22.0 | 42.3±19.9 | 0.11 |
| Contrast agent (ml) | | 122.2±68.7 | 107.8±61.6 | 0.001 |
| Fluoroscopy time (min) | | 13.5±7.8 | 12.4±7.4 | 0.032 |

Continuous variables are depicted as mean±standard deviation. Categorical variables are depicted as no. (percentage of total no.). **p*-value refers to comparison of balloon-expandable valves vs self-expanding valves

## IN-HOSPITAL OUTCOMES

The primary composite endpoint of main access-related bleeding ≥Type 2 or main access-related major vascular complications was significantly higher in the P+P group (11.4% vs 3.0%; p<0.001). Further, total vascular complications as well as total bleedings were significantly more frequent in the P+P group **(Table 4)**. Patients in the P+P group had a higher rate of closure device failure (2.7% vs 0.9%; p=0.044) and more often required unplanned surgical or endovascular treatment (3.9% vs 0.9%; p=0.004). There were no differences in the rate of pseudoaneurysms (3.2 vs 3.4%; p=0.85). Details of the vascular complication type are depicted in the **Central illustration** and **Supplementary Table 2**. There was a trend towards a reduced mortality in the P+F group that did not reach statistical significance (3.4% vs 1.6%; p=0.08). The incidence of acute kidney injury, unplanned myocardial revascularisation, new pacemaker implantation and stroke were comparable between both groups **(Table 4)**.

In the multivariable analysis, age and coronary artery disease were independently associated with higher incidences of the primary endpoint (odds ratio 1.04; p=0.049 and 2.28; p=0.001, respectively), while the use of P+F was independently associated with lower incidences of the primary endpoint (odds ratio 0.24; p<0.001) **(Supplementary Table 3)**.

# Discussion

This retrospective single-centre study sought to compare 2 vascular closure strategies in a large real-world patient population undergoing transfemoral TAVI. The incidence of the primary endpoint of main access-related major vascular complications or bleeding ≥Type 2 was significantly higher in the dual ProGlide group than in patients treated with a combination of 1 ProGlide and 1 FemoSeal **(Central illustration)**.

Access-related vascular complications and bleeding remain the most frequent complications in patients undergoing TAVI and are associated with impaired outcomes[4,6,7]. For closure of the large-bore arteriotomy, traditional suture-based VCD have been most frequently used in clinical practice. However, the more recently developed large-bore plug-based VCD MANTA has been established as a widely used alternative strategy for vascular closure. Even though early feasibility trials and retrospective analyses showed promising results, the use of MANTA was associated with higher rates of vascular complication than a Dual ProGlide technique in 2 randomised controlled trials[10-12,19]. As an alternative, suture-based VCD can be combined with smaller sized plug-based VCD, e.g., AngioSeal (Terumo) or FemoSeal. Although initially proposed as a bailout strategy for closure device failure, this combination appeared to be safe and feasible in a smaller study by Ko

**Table 4. In-hospital outcomes.**

| Variable | Dual ProGlide (n=437) | ProGlide +FemoSeal (n=437) | *p*-value |
|---|---|---|---|
| Primary endpoint* | 50 (11.4%) | 13 (3.0%) | <0.001 |
| Vascular complication – main access-related | 67 (15.3%) | 29 (6.6%) | <0.001 |
| Major | 43 (9.8%) | 12 (2.7%) | <0.001 |
| Minor | 24 (5.5%) | 17 (3.9%) | 0.27 |
| Vascular complication – overall | 72 (16.5%) | 37 (8.5%) | <0.001 |
| Major | 48 (10.1%) | 15 (3.4%) | <0.001 |
| Minor | 24 (5.5%) | 22 (5.0%) | 0.76 |
| Closure device failure | 12 (2.7%) | 4 (0.9%) | 0.044 |
| Unplanned surgical or endovascular treatment | 17 (3.9%) | 4 (0.9%) | 0.004 |
| Bleeding – main access-related | 69 (15.8%) | 22 (5.0%) | <0.001 |
| Type 1 | 22 (5.0%) | 9 (2.1%) | 0.017 |
| Type 2 | 35 (8.0%) | 10 (2.3%) | <0.001 |
| Type 3 | 11 (2.5%) | 3 (0.7%) | 0.031 |
| Type 4 | 1 (0.2%) | 0 | 1 |
| Bleeding – overall | 104 (23.8%) | 35 (8.0%) | <0.001 |
| Type 1 | 29 (6.6%) | 13 (3.0%) | 0.011 |
| Type 2 | 48 (11.0%) | 16 (3.7%) | <0.001 |
| Type 3 | 26 (5.9%) | 6 (1.4%) | <0.001 |
| Type 4 | 1 (0.2%) | 0 | 1 |
| Need for red blood cell transfusion | 65 (14.9%) | 43 (9.8%) | 0.024 |
| Delta haemoglobin (g/dl) | –2.0±1.4 | –1.9±1.3 | 0.49 |
| Stroke | 14 (3.2%) | 6 (1.4%) | 0.07 |
| Acute kidney injury | 56 (12.8%) | 48 (11.0%) | 0.40 |
| AKIN 1 | 41 (9.4%) | 41 (9.4%) | 1 |
| AKIN 2 | 5 (1.1%) | 2 (0.5%) | 0.45 |
| AKIN 3 | 6 (1.4%) | 2 (0.5%) | 0.29 |
| New onset of dialysis | 4 (0.9%) | 3 (0.7%) | 1 |
| Unplanned revascularisation | 4 (0.9%) | 3 (0.7%) | 0.69 |
| New pacemaker | 67 (15.3%) | 63 (14.4%) | 0.70 |
| Death | 15 (3.4%) | 7 (1.6%) | 0.08 |

Continuous variables are depicted as mean±standard deviation. Categorical variables are depicted as no. (percentage of total no.). Vascular complications, closure device failure and bleedings are defined according to VARC-3 criteria. *Primary endpoint: composite endpoint of main access-related bleeding ≥Type 2 or main access related major vascular complication. AKIN: acute kidney injury network

et al[14]. In the recently published study by Costa et al, a combined approach reduced major vascular complications and bleeding[20]. However, the study was limited by a small sample size and heterogenic use of suture-based devices: the majority of patients were treated with 1 Prostar XL even though the ProGlide has proven to be superior[8,9]. One major concern when combining multiple VCD is constriction of the arterial lumen as described earlier with a consequent risk of peripheral ischaemia[21]. Hence, Ko et al combined a single ProGlide with one AngioSeal and even though no significant differences in overall vascular complications and bleeding were found, the authors reported a significantly lower rate of arterial stricture compared to a dual ProGlide approach. Nevertheless, larger studies comparing this hybrid technique to the standard dual ProGlide technique are lacking.

In our study, we compared the 2 strategies in a large real-world population at a tertiary European centre. In this setting, the primary endpoint of main access-related major vascular complications or bleeding ≥Type 2 was significantly higher in the dual ProGlide group than in patients treated with 1 ProGlide and 1 FemoSeal. Similar to a randomised controlled trial recently published by Abdel-Wahab et al and the study by Costa et al, this result was mainly driven by a high number of access bleeding and consequent haematomas, while the overall rate of other vascular complications such as arterial dissection or peripheral ischaemia was low in both groups[10,20]. Nonetheless, the rate of unplanned surgical or endovascular treatments as well as the need for transfusion was significantly higher in the dual ProGlide group, implying clinical relevance of the observed

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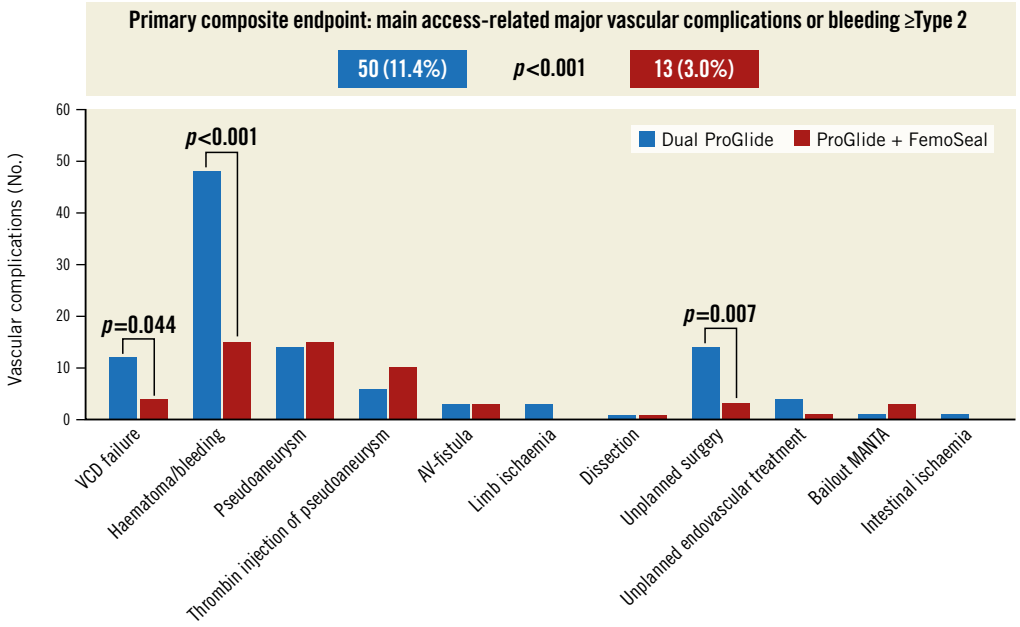
CENTRAL **ILLUSTRATION** Primary endpoint and vascular complications.




*Minor and major vascular complications (absolute numbers) in both study groups stratified according to type of vascular complication. AV-fistula: arteriovenous fistula; Bailout MANTA: bailout strategy using the MANTA vascular closure device; Haematoma/bleeding: combined endpoint of VARC-3 bleeding and/or VARC-3 vascular complication due to haematoma; VCD: vascular closure device*

complications. The rate of pseudoaneurysms was relatively high in this series of patients, which might be due to the systematic duplex ultrasound exam of the access site. However, routine ultrasound-guided puncture might reduce this rate. Major vascular complications and bleedings are known to be associated with increased mortality[4,6,7]. In our study, there was a trend towards higher mortality in the dual ProGlide group that did not reach statistical significance. However, retrospective analyses are prone to bias, and prospective studies are needed to confirm this observation.

As mentioned above, deployment of multiple ProGlide VCD significantly reduces the minimal vessel diameter. In our study, 3 patients in the dual ProGlide group underwent unplanned surgery for peripheral ischaemia, while this was not the case in the ProGlide+FemoSeal group. This finding is in line with the higher rate of arterial stricture in patients treated with multiple ProGlide VCD found by Ko et al and supports concerns of inducing haemodynamically relevant stenoses. In the published randomised controlled trials, 35-59% of the patients treated with a dual ProGlide technique needed additional VCD to achieve complete haemostasis[10,19]. These additional VCD could reduce the residual arterial lumen and, hence, increase the risk of peripheral ischaemia even further. In our study, the incidence of closure device failure among patients treated with 1 ProGlide and 1 FemoSeal was low. Therefore, a combination of a single ProGlide with 1 small-sized plug-based VCD might, in fact, be advantageous, as it showed not only high efficacy but was associated with a reduced risk of subsequent peripheral ischaemia.

Compared to the randomised controlled study by Abdel-Wahab et al, we found a similar incidence of major vascular complications and bleeding ≥Type 2 in the ProGlide+FemoSeal group, but higher incidences in the dual ProGlide group. Rates of minor vascular complications or bleeding were lower in our study compared to the recent randomised controlled trials. We explain this with the retrospective nature of this study, as small haematomas without a relevant drop in haemoglobin might not be documented and, thus, remain undetected in retrospective analyses. However, these minor complications without clinical consequences are of questionable relevance.

## Limitations

Even though propensity score matching resulted in equally balanced study groups, this is a retrospective analysis with its inherent limitations. All patients were treated at 1 large European TAVI centre. Further, there were some significant differences between the 2 groups. Main vessel tortuosity was higher in the P+F group. In contrast, the degree of calcification as well as the minimum lumen diameter of the main access vessel and the prevalence of peripheral arterial disease did not differ between groups, implying comparable vascular status. A radial access was more often used as secondary access in the dual ProGlide group. Finally, patients in the P+P group had a higher mean sheath size, which might lead to an increased bleeding risk.

## Conclusions

The combination of suture-based with plug-based vascular closure devices might have the potential to reduce access-related major vascular complications and bleedings and, therefore, unplanned surgical or endovascular treatment in patients following TAVI.

## Impact on daily practice

Vascular closure after transcatheter aortic valve implantation using a combined suture- and plug-based strategy (1 ProGlide and 1 FemoSeal) might result in reduced access-related major vascular complications and bleeding and, therefore, unplanned surgical or endovascular treatment, compared to an exclusively suture-based strategy (dual ProGlide).

## Conflict of interest statement

M. Orban reports speaker honoraria from Abbott Medical, AstraZeneca, Abiomed, Bayer Vital, BIOTRONIK, Bristol-Myers Squibb, CytoSorbents, Daiichi Sankyo Deutschland, Edwards Lifesciences, and Sedana Medical; support for attending meetings from AstraZeneca; stocks from Abbott Laboratories, AbbVie, AstraZeneca, Bayer, Biontech, Bristol-Myers Squibb, Curevac, Draegerwerk, Fresenius Medical Care, Gilead Sciences, Inari Medical, Johnson&Johnson, Linde, Merck US, Moderna, NovoNordisk, Nuance Communications, Pfizer, Proctor&Gamble, Roche, SAP, Siemens Healthineers, and Zoom. D. Braun reports speaker honoraria from Abbott Vascular and Edwards Lifesciences. J. Hausleiter reports speaker honoraria and consulting fees from Abbott Vascular and Edwards Lifesciences. S. Deseive reports speaker honoraria from AstraZeneca. S. Peterß reports speaker honoraria from AstraZeneca. C. Scherer reports speaker honoraria from AstraZeneca. J. Mehilli reports institutional research grants from Boston Scientific and speaker honoraria from AstraZeneca, Pfizer, SIS Medical, Daiichi Sankyo. J. Steffen reports speaker honoraria from AstraZeneca and Travel support from the German Center for Cardiovascular Research (DZHK). The other authors have no conflicts of interest to declare.

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## Supplementary data

**Supplementary Table 1.** Antithrombotic therapy.

**Supplementary Table 2.** Details of vascular complications.

**Supplementary Table 3.** Predictors of the primary endpoint.

**Supplementary Figure 1.** Standardised mean differences before and after propensity score matching.

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# Coronary access techniques following ACURATE neo2 implantation in surgical bioprosthesis

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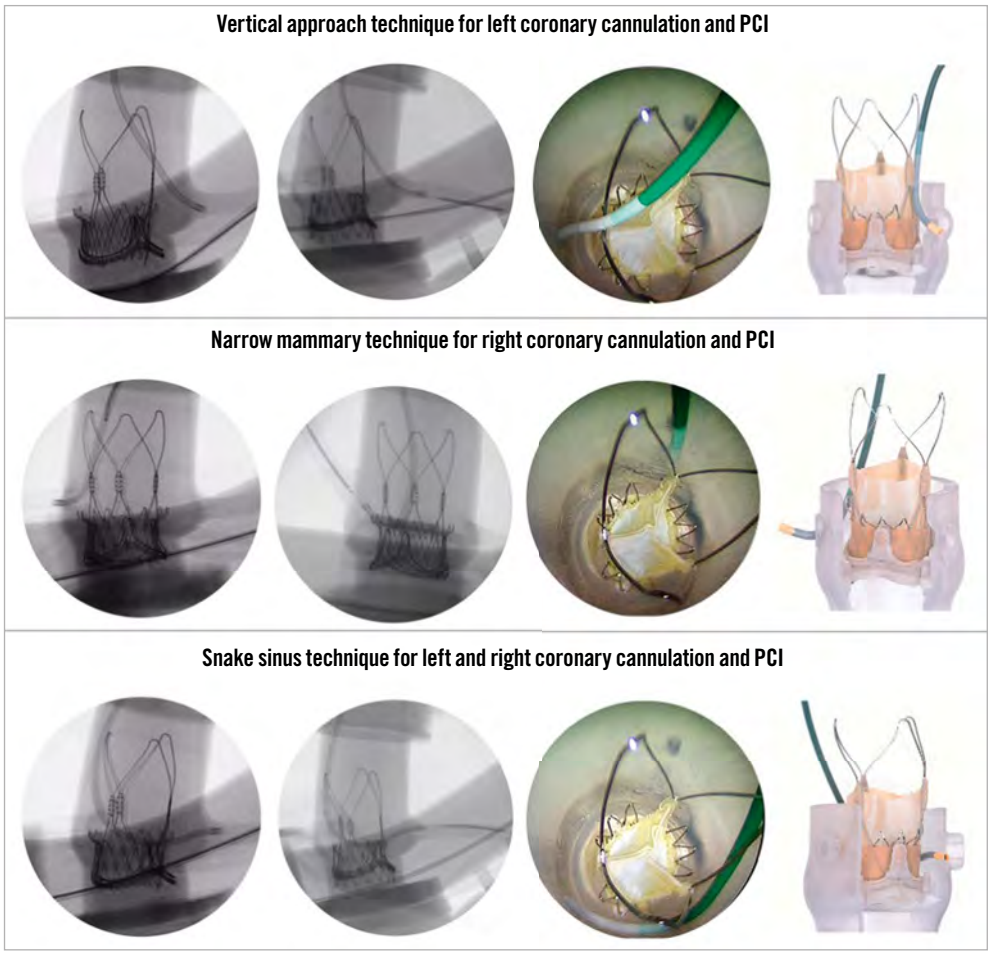


**Figure 1.** *Novel coronary access techniques to bypass the ACURATE neo2 valve frame following ViV-TAVI. The vertical approach, narrow mammary and snake sinus techniques are presented with (from left to right): fluoroscopic images of diagnostic cannulation, percutaneous coronary intervention, internally mounted borescope view and ex vivo modelling. PCI: percutaneous coronary intervention; ViV-TAVI: valve-in-valve transcatheter aortic valve implantation*

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Coronary access after transcatheter aortic valve implantation (TAVI) procedures can be challenging due to anatomical, procedural or valve-related factors[1,2]. This challenge is further augmented during valve-in-valve (ViV) procedures due to the additional presence of transcatheter or surgical valve frames and leaflets[3]. Dedicated valve-specific cannulation techniques are required for operators to achieve coronary access, particularly in challenging scenarios[2,4]. To date, specific coronary cannulation techniques have only been described for the CoreValve/Evolut (Medtronic) and SAPIEN (Edwards Lifesciences) valve platforms following native aortic valve TAVI[2,4].

Therefore, we performed *ex vivo* simulations of coronary access in a computed tomography-derived patient-specific pulsatile flow ViV-TAVI model consisting of an ACURATE *neo2* (Boston Scientific) valve implanted inside a Carpentier-Edwards Perimount 25 mm surgical bioprosthesis (Edwards Lifesciences).

A challenging cannulation was simulated by selecting a patient with low coronary heights and narrow aortic sinus dimensions. An ACURATE *neo2* valve was positioned at a high implantation depth and with severe commissural misalignment between the transcatheter and surgical valve posts **(Supplementary Figure 1)**. Expert operators attempted to cannulate the left and right coronary arteries under fluoroscopic guidance using a wide range of differently sized and shaped catheters. The different cannulation approaches were visualised using an internally mounted borescope camera.

We describe three novel cannulation techniques, the vertical approach, narrow mammary and snake sinus, which all allow the obstructive elements of the ACURATE *neo2* valve frame to be bypassed by a catheter **(Figure 1, Supplementary Figure 2, Moving image 1- Moving image 3)**. These techniques are preferable in the setting of severe commissural misalignment and/or if the coronary ostia arise below the level of the upper crown adjacent to the pericardially covered stent frame. The vertical approach and internal mammary techniques are used for left and right coronary cannulation respectively, whilst the snake sinus technique can be used for cannulation of either ostium.

The reported techniques were reproduced by different operators using both 6 Fr diagnostic and guiding catheters. Adequate guiding catheter support was assessed for by simulating a percutaneous coronary intervention procedure. Delivery of an intracoronary wire, 3.0 non-compliant balloon and a 4.0×24 mm drug-eluting stent was feasible with all three techniques.

These techniques were specific to the ACURATE *neo2* valve because of its unique split-level design with a short lower-stent frame and large open upper stabilisation arches. These techniques could not be replicated with the Evolut valve, due to the larger outflow portion of the valve, which leaves less room for a catheter to bypass the valve frame. All cannulations were performed from the femoral access route. Whilst the left radial access route may achieve similar results, we cannot comment on the feasibility of these cannulation techniques using the right radial approach, particularly in the presence of tortuous brachiocephalic anatomy. The safety and efficacy of these novel cannulation techniques has to be determined in different anatomical settings before further *in vivo* validation.

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## Conflict of interest statement

D. Dudek is on the advisory board for Boston Scientific. The other authors have no conflicts of interest to declare.

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## Supplementary data

**Supplementary Figure 1.** Challenging configuration of ACURATE *neo2* implantation inside Carpentier-Edwards surgical aortic bioprosthesis.

**Supplementary Figure 2.** Three-dimensional digital reconstructions of the proposed novel techniques demonstrating how the catheters bypass the obstructive elements of the ACURATE *neo2* valve frame (Boston Scientific).

**Moving image 1.** *Ex vivo* simulation of the vertical approach cannulation technique.

**Moving image 2.** *Ex vivo* simulation of the snake sinus cannulation technique.

**Moving image 3.** *Ex vivo* simulation of the narrow mammary cannulation technique.

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# Commissural alignment with the novel Hydra transcatheter heart valve during aortic valve replacement

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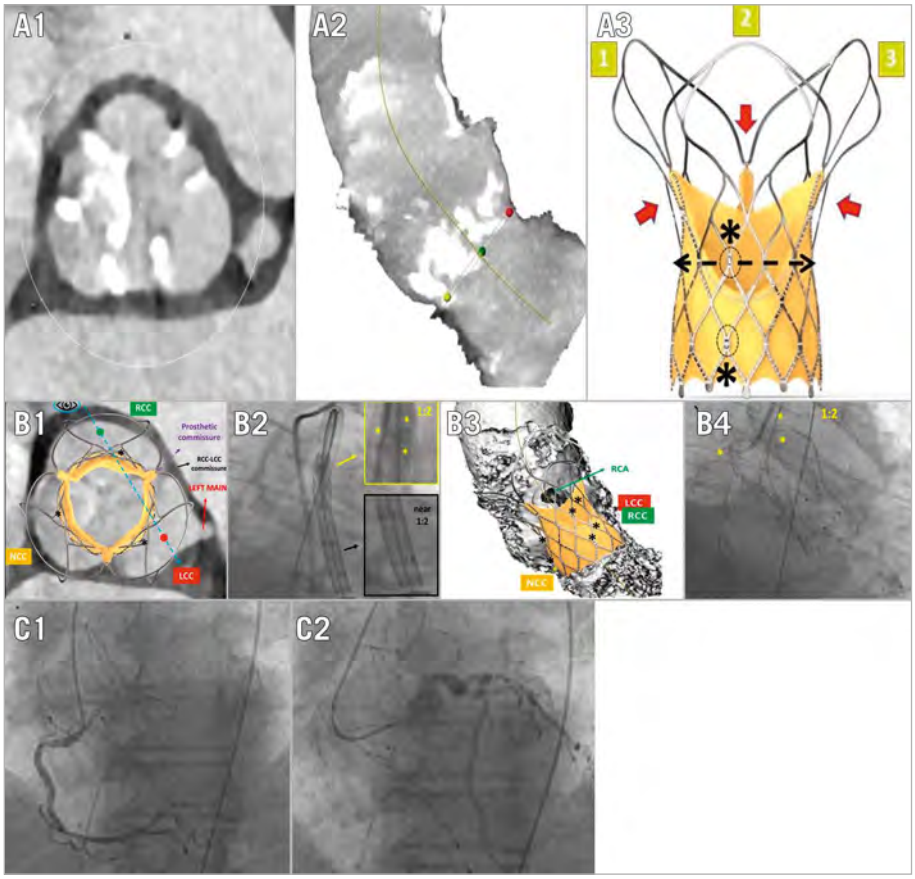


**Figure 1.** *Commissural alignment with Hydra THV. Computed tomography showing severe aortic valve stenosis (A1), with 3-cusp view reconstruction (A2). The novel Hydra THV (A3) with the three-tentacle design (1,2,3) and commissural posts (red arrows) at their bases; six radiopaque markers are located three by three in two rows (black asterisks), each asymmetrically positioned between two prosthetic commissures (dashed lines). Proper commissural alignment (B1) is achieved using the RCC-LCC overlap view (B2, blue dashed line in B1) when one tentacle is on the left and the other two appear on the right (yellow box in B3); the radiopaque markers are seen in a "near 1:2 pattern", without complete overlap of those located on the right side (black box in B3). Final angiographic result in RCC-LCC overlap view (B4). Easy right (C1) and left (C2) coronary artery reaccess. LCC: left coronary cusp; NCC: non-coronary cusp; RCA: right coronary artery; RCC: right coronary cusp; THV: transcatheter heart valve*

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An 83-year-old gentleman with severe aortic valve stenosis was deemed eligible for transfemoral transcatheter aortic valve replacement (TAVR) after a Heart Team evaluation. Cardiac computed tomography showed severe calcification of the native aortic valve leaflets **(Figure 1A1, Figure 1A2)**. A 30 mm self-expanding Hydra (Sahajanand Medical Technologies) transcatheter heart valve (THV) was chosen **(Moving image 1)**. This novel supra-annular THV has a nitinol frame with large stent cells (≥15 Fr) and a three-tentacle design at the stent outflow. Bovine pericardium leaflets are attached to the stent by three commissures, placed between the three tentacles. Six radiopaque markers, aligned three by three in two rows, are positioned on the THV frame and guide the implantation depth during valve deployment. The location of the lower row of these markers on the stent frame corresponds to the base of each of the three cusps, but with a slightly asymmetrical distance to the middle of the base. Consequently, each of the prosthetic commissures is situated between the markers, also with a slightly asymmetrical distance **(Figure 1A3)**. Currently, there are no specific recommendations concerning the optimal implantation technique to achieve a patient-specific commissural alignment (CA) with the Hydra THV[1]. Such a CA would require positioning the tentacles of the Hydra THV exactly above the base of each cusp of the native aortic valve, which would accordingly align each of the three prosthetic commissures with the native commissures **(Figure 1B1, Figure 1B2)**. Patient-specific CA with the Hydra THV can be achieved using the angiographic right coronary cusp (RCC)-left coronary cusp (LCC) overlap view. In this projection, before valve deployment, one tentacle should be isolated on the left side of the screen and the other two tentacles should be overlapping on the right side of the screen ("1:2 pattern"); such positioning would be indicative of a proper CA, considering that one prosthetic commissure is placed exactly between the two overlapping tentacles **(Figure 1B3)**. However, the tentacles are poorly visible when clustered within the catheter prior to valve deployment. Since the alignment of each of the six markers on the stent frame is much easier to assess in our patient, we tried to achieve CA by considering the orientation of these markers. A near-perfect CA can be achieved, if one of the base markers in the RCC-LCC overlap view is isolated on the left side of the screen and the other two base markers are situated on the right side of the screen; the same pattern can then be seen in the upper row of the stent markers. Keeping in mind the asymmetric distance between the markers and the prosthetic commissures placed between them, we call this a "near 1:2 pattern" **(Figure 1B1-Figure 1B3)**. Employing this technique, we safely implanted the Hydra THV **(Figure 1B4)**. After the THV deployment, we were able to easily recannulate both the right and left coronary arteries **(Moving image 2, Figure 1C1, Figure 1C2)**. This empirically demonstrated, at least, a near-perfect patient-specific CA. Preserving coronary artery reaccess has become imperative in TAVR scenarios, and different techniques have been described to achieve a reliable CA with other commercially available THVs[2,3]. Hereby, we described a potential method for reaching a satisfactory CA with the novel Hydra THV. In the event that the alignment of the stent in the RCC-LCC view required some rotation of the delivery catheter, pulling back the delivery system into the descending aorta and turning it there could potentially modify the orientation of the stent markers. We do not suggest performing this manoeuvre in the aortic annulus or the ascending aorta, since the Hydra delivery catheter is not primarily designed to be rotated whilst curved (given the absence of a spine). Clearly, more robust clinical and post-implantation imaging data are needed to assess the safety and efficacy of the described technique in a broader patient population.

## Conflict of interest statement

G. Bieliauskas received consulting fees from Sahajanand Medical Technologies. The other authors have no conflicts of interest to declare.

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## Supplementary data

**Moving image 1.** Hydra implantation with commissural alignment.
**Moving image 2.** Coronary artery reaccess.

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# Transcatheter valve-in-valve implantation versus redo surgical mitral valve replacement in patients with failed mitral bioprostheses

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**KEYWORDS**

- mitral regurgitation
- mitral stenosis
- mitral valvuloplasty

## Abstract

**Background:** Data on the safety of valve-in-valve transcatheter mitral valve replacement (ViV-TMVR) compared with redo surgical mitral valve replacement (SMVR) in patients with a history of bioprosthetic mitral valve (MV) remain limited.

**Aims:** We aimed to evaluate the in-hospital, 30-day and 6-month readmission outcomes of ViV-TMVR compared with redo-SMVR in a real-world cohort.

**Methods:** The Nationwide Readmission Database was utilised, analysing data from 2015 to 2019. To determine the adjusted odds ratio (aOR), we used the propensity-matched analysis for major outcomes at index hospitalisation, 30 days, and 6 months during the episode of readmission.

**Results:** A total of 3,691 patients were included, of these, 24.2% underwent ViV-TMVR and 75.8% underwent redo-SMVR. Patients undergoing ViV-TMVR were older with higher rates of comorbidities. The mean length of stay (15 days vs 4 days) and cost of hospitalisation ($76,558 vs $46,743) were significantly higher for redo-SMVR. The rate of in-hospital all-cause mortality was also significantly lower in ViV-TMVR (2.6% vs 7.3%). By contrast, 30-day all-cause mortality during the episode of readmission (aOR 1.01, 95% confidence interval [CI]: 0.40-2.55) and all-cause readmission rates (aOR 0.82, 95% CI: 0.66-1.02) were similar between both groups. The incidence of all-cause readmissions at 6 months (aOR 0.83, 95% CI: 0.65-1.05) and all-cause mortality during the episode of readmission at 6 months (aOR 1.84, 95% CI: 0.54-6.36) were also comparable. The utilisation of the ViV-TMVR procedure increased significantly during our study duration, from 5.2% to 36.8%, ($p_{trend}$<0.01).

**Conclusions:** ViV-TMVR is associated with lower odds of in-hospital mortality, complications, and resource utilisation. The all-cause readmissions and 30-day and 6-month mortality during the episode of readmissions were comparable between both groups.

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## Abbreviations

| | |
|---|---|
| **AHRQ** | Agency for Healthcare Research and Quality |
| **CCR** | cost-to-charge ratio |
| **CMS** | Centers for Medicare and Medicaid Services |
| **FDA** | Food and Drug Administration |
| **HCUP** | Healthcare Cost and Utilization Project |
| **ICD-10-CM** | International Classification of Diseases, 10th Revision Clinical Modifications |
| **IQR** | interquartile range |
| **IRB** | institutional review board |
| **NRD** | National Readmission Database |
| **SD** | standard deviation |
| **ViV-TMVR** | valve-in-valve transcatheter mitral valve replacement |
| **redo-SMVR** | redo surgical mitral valve replacement |

## Introduction

Bioprosthetic valves have an advantage over mechanical valves due to a lower risk of thrombotic complications and a shorter duration of anticoagulation[1]. However, these benefits are offset by the frequent degenerative changes seen with bioprosthetic valves, leading to an increased need for repeat intervention[2]. Redo surgical mitral valve replacement (redo-SMVR) has been the treatment of choice in about one-third of patients with bioprosthetic mitral valve complications[3]. However, redo-SMVR has been linked with high morbidity and periprocedural mortality, due to the risks of an open surgical procedure, longer bypass time, and the complex anatomy of the prosthetic valves[3-5]. Valve-in-valve transcatheter mitral valve replacement (ViV-TMVR) is emerging as a viable alternative to redo-SMVR in high surgical risk patients with prosthetic mitral valve disease[6,7]. Following the success of valve-in-valve transcatheter aortic valve replacement (ViV-TAVR), the US Food and Drug Administration (FDA) has now approved ViV-TMVR use for degenerated bioprosthetic mitral valves, but data on the comparative outcomes of ViV-TMVR and redo-SMVR remain limited[8]. The current study aims to evaluate the in-hospital and short-term outcomes of ViV-TMVR compared with redo-SMVR in a real-world cohort.

## Methods

### DATA SOURCE

This is a retrospective analysis of the National Readmission Database (NRD) using data from September 2015 to November 2019. The NRD is a database provided by the Agency for Healthcare Research and Quality (AHRQ) and developed through the Federal-State industry partnership. The Healthcare Cost and Utilization Project (HCUP) maintains data on approximately 35 million annual weighted discharges. The discharge data are available from 28 states, representing 59.7% of the US population and 58.7% of in-patient hospitalisations[9]. It is an all-payer database that captures nationally representative records on hospital readmissions and resource utilisation. For tracing readmissions within a calendar year, each patient is assigned a unique randomly generated identifier code (NRD_visitLink) to protect their confidentiality. The "NRD days-to-event" variable is utilised to capture and trace readmissions from January until the end of December in a calendar year but cannot trace across different years. A timing variable called "admittime" was computed to calculate the timing of readmission after discharge from the index hospitalisation. The provided data are compliant with the HCUP guidelines with observations <11 not reported in the available tables. This study was exempted from the institutional review board (IRB) approval as it was performed on publicly available de-identified data.

The NRD contains data on the total in-patient charges billed by the hospital and differs from the actual cost, which includes the total expense needed for hospital services including utilities, wages, and supplies. To further calculate the cost, the HCUP provides cost-to-charge ratio (CCR) files that provide hospital-level data, including hospital-specific ratios or weighted average ratios, to supplement the original NRD file. Cost information is obtained from the accounting reports of the participating hospitals, which are collected by the Centers for Medicare and Medicaid Services (CMS), with some imputation of missing values as deemed necessary[10]. For our study, the provided adjusted cost of care is calculated by multiplying the element of the total charges provided by the NRD and the CCR.

### STUDY SAMPLE AND PATIENT SELECTION

We extracted data using the International Classification of Diseases, 10th Revision Clinical Modifications (ICD-10-CM) **(Supplementary Table 1)**. All patients with a history of bioprosthetic mitral valve (MV) undergoing ViV-TMVR or redo-SMVR were selected using NRD data from the fourth quarters (Q4) of 2015 to November 2019. The ICD-10-CM codes for prosthetic valve dysfunction and history of prosthetic valve (T82.01XA, T82.02XA, T82.03XA, T82.09XA, T82.221A, T82.222A, T82.223A, T82.228A, Z45.09, T82.857 and Z95.2) were used to identify admissions with a degenerated bioprosthetic valve. We excluded patients with aortic valve disease, tricuspid valve disease, pulmonic valve disease, coronary artery bypass graft surgeries, surgical aortic valve replacement, tricuspid/pulmonic valve surgery, transcatheter aortic valve replacement, atrial/ventricular septal defect closures, and infective endocarditis. We defined index admissions for patients undergoing ViV-TMVR or redo-SMVR and who were discharged alive with no missing variables critical for identifying readmissions (i.e., length of stay, mortality, or days-to-event variables). For in-hospital index hospitalisation and their 30-day readmissions, December admissions were excluded to allow for the calculation of 30-day readmissions rates. For the 6-month readmission analysis, July to December admissions were excluded to allow for the calculation of 6-month readmission rates. Baseline patient characteristics, including sex, age, hospital characteristics (i.e., teaching status and bed size), and median household income, and patient comorbidities (i.e., hypertension, diabetes, etc.) were included in the current study. For patients who had multiple readmissions, only the first hospitalisation is

included in the analysis. Readmission was defined as the first elective or non-elective admission after discharge. Readmission mortality was defined as mortality during re-hospitalisation, and it did not include patients that died outside the hospital or out of the state. For readmission outcomes, we reported 30-day and 6-month readmission rates and mortality rates during the episode of readmission follow-up. We used the discharge weights provided by the NRD to provide nationally representative data. A detailed methods flow chart of the study is shown in **Figure 1**.

## STUDY OUTCOMES

The primary outcomes were in-hospital mortality, 30-day, and 6-month all-cause readmissions, and mortality during the episode of readmission after ViV-TMVR in comparison with redo-SMVR. The secondary outcomes included disposition, temporal trends, procedural complications, and measures of utilisation of resources (i.e., adjusted hospitalisation cost and length of hospital stay).

## STATISTICAL ANALYSIS

Statistical analysis was performed using RStudio software for statistical computing version 4.3 (Rstudio). Categorical variables were expressed as frequencies and percentages, and continuous variables were reported as medians with an interquartile range (IQR). Baseline characteristics were compared using Pearson's chi-square or Fisher's exact tests for categorical variables and the Mann-Whitney U test for continuous variables. For the weighted analysis of data, we used a survey package of R[11]. The Cochrane-Armitage test was used for trend analysis. The survey package takes into consideration the nationally weighted data and clustering outcomes within hospitals to report nationally representative proportions of readmissions[11]. To account for potential confounding and selection bias, a propensity score matching model using R's MatchIt package[12] was developed using logistic regression to derive 2 nearly matched groups for comparative outcomes analysis of ViV-TMVR versus redo-SMVR. A nearest-neighbour variable ratio, parallel, balanced propensity matching model was made using a calliper width of 0.1 standard deviations (SD). The variables used in the propensity matching model included: age, sex, mode of admission (elective versus non-elective), median household income, insurance status, and baseline comorbidities (anaemia, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, coronary artery disease, cerebrovascular disease, diabetes, hypertension, liver disease, obesity, peripheral vascular disease, prior pacemaker, chronic kidney disease, end-stage renal disease and smoking). All variables considered clinically meaningful on an *a priori* basis were selected regardless of the significance of the p-value. Covariate balance before and after propensity matching is shown in **Figure 2**. R's survival package[13] was also used for cumulative incidences, using a log-rank test to assess the timing of readmissions within 30 days, and 6 months. A falsification[14] and E-value analysis[15] to evaluate for the presence of residual confounding for in-hospital mortality, and 30-day and 6-month readmission mortality were performed. The E-value provides an estimate of the minimum strength of association for an

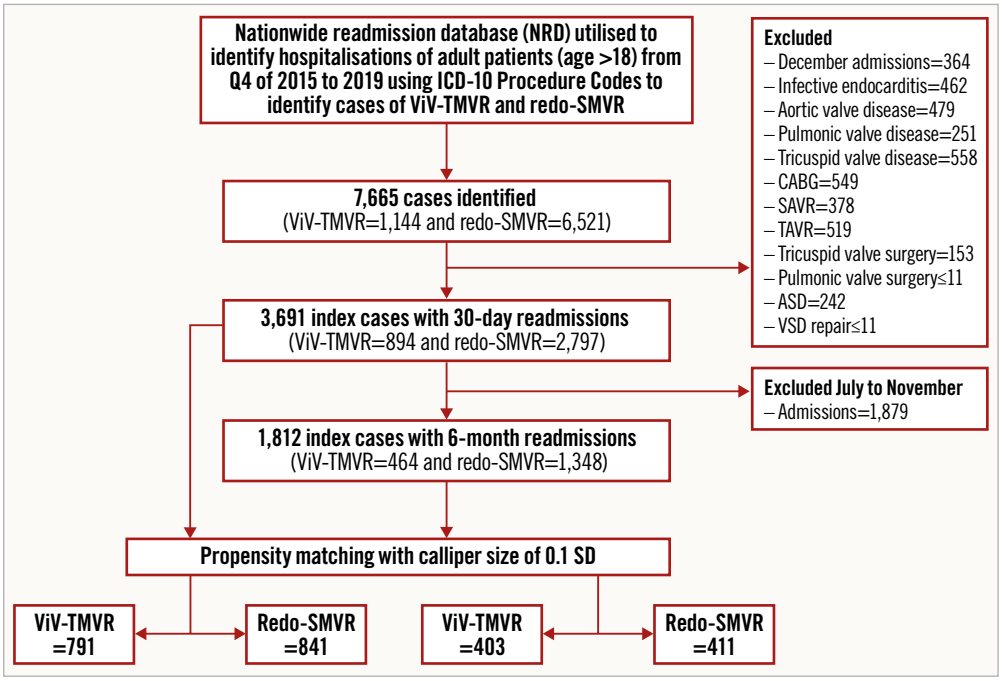



**Figure 1.** *Study flow diagram. ASD: atrial septal defect; CABG: coronary artery bypass graft; ICD-10: International Classification of Diseases 10th Revision; SAVR: surgical aortic valve replacement; SD: standard deviation; SMVR: surgical mitral valve replacement; TAVR: transcatheter aortic valve replacement; ViV-TMVR: valve-in-valve transcatheter mitral valve replacement; VSD: ventricular septal defect repair*

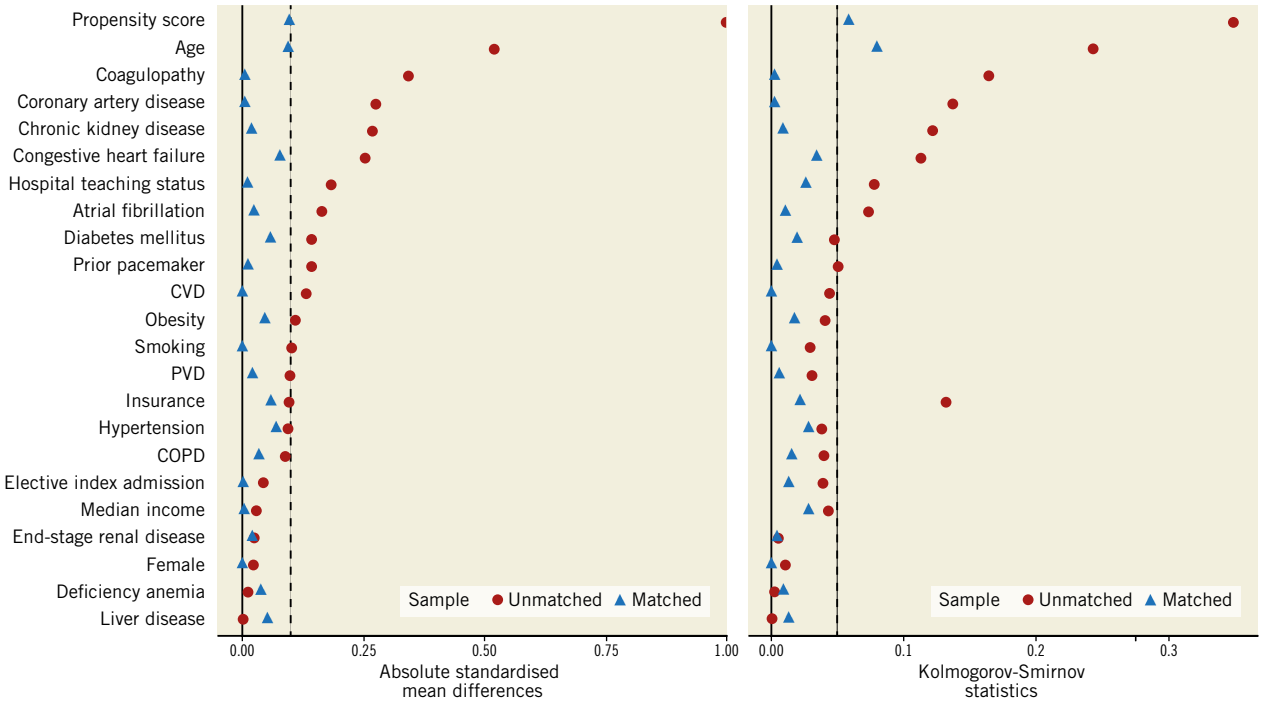



**Figure 2.** *Covariate balance before and after propensity matching. COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; PVD: peripheral vascular disease*

unmeasured confounder with both the outcome and the treatment group to entirely explain the treatment-outcome association, conditional on the measured covariates. For the falsification analysis, 2 outcomes that are not expected to be associated with the treatment were selected. The falsification endpoints included hip/femur fracture and acute chronic obstructive pulmonary disease (COPD) exacerbation. A lack of association of falsification endpoints with the intervention supports a causal association between the treatment and study outcomes. For all analyses, a 2-tailed p-value of 0.05 is considered statistically significant.

## Results

### SELECTION OF CASES

A total of 7,665 patients were identified during the initial screening. After applying the exclusion criteria (i.e., excluding coronary artery bypass graft surgeries, aortic valve disease, tricuspid valve disease, pulmonic valve disease, surgical aortic valve replacement, tricuspid/pulmonic valve surgery, transcatheter aortic valve replacement, atrial/ventricular septal defect closures, and infective endocarditis), 3,691 index hospitalisations with 30-day readmissions were selected. Of these, 23.2% underwent ViV-TMVR (n=894) and 76.8% underwent redo-SMVR (n=2,797). Amongst the ViV-TMVR procedures, 84.2% (n=875) were performed via the transseptal approach. On propensity matching, 791 cases of ViV-TMVR were matched with 841 cases of redo-SMVR.

### BASELINE CHARACTERISTICS

On crude analysis, patients undergoing ViV-TMVR (76 years, IQR 68-81) were significantly older than those undergoing redo-SMVR (69 years, IQR 60-76). In terms of comorbidities, the frequency of congestive heart failure (84.3% vs 72.8%; p<0.01), coronary artery disease (60.6% vs 45.7%; p<0.01), and chronic kidney disease (41.3% vs 31%; p<0.01) were significantly higher in ViV-TMVR compared with the redo-SMVR group, respectively. On propensity score-matched analysis, balanced comparison groups with no significant differences in the baseline characteristics were selected **(Table 1)**.

### IN-HOSPITAL ALL-CAUSE MORTALITY AND PROCEDURAL COMPLICATIONS

On crude analysis of the index hospitalisation, the unadjusted all-cause mortality and in-hospital complications were significantly higher with redo-SMVR. A propensity score-matched analysis mirrored the findings of the crude analysis. The adjusted odds of all-cause mortality remained significantly higher in patients undergoing redo-SMVR (7.3%) compared with ViV-TMVR (2.6%, odds ratio [OR] 1.55, 95% confidence interval [CI]: 1.05-2.27). The odds of non-home facility discharge were 2-fold higher with redo-SMVR (77.2%) compared with ViV-TMVR (46.1%, OR 2.64, 95% CI: 2.26-3.08). Similarly, the in-hospital complication rates, including stroke, need for transfusions, and need for permanent pacemaker (PPM) implantation were higher for the surgery group compared with the transcatheter approach. The median length of stay on index hospitalisation (15 days vs 4 days; p<0.01) and adjusted cost of hospitalisation ($76,558 vs $46,743; p<0.01) were also significantly higher for redo-SMVR compared with the ViV-TMVR group, respectively **(Table 2, Figure 3)**.

**Table 1. Baseline characteristics of the study population.**

| Variable, n (%) | | Unmatched | | Propensity matched | | |
|---|---|---|---|---|---|---|
| | | ViV-TMVR (n=894) | Redo-SMVR (n=2,797) | ViV-TMVR (n=791) | Redo-SMVR (n=841) | *p*-value |
| Age, median (IQR), years | | 76 (68-81) | 69 (60-76) | 75 (67-79) | 73 (65-79) | <0.01 |
| Female | | 484 (54.2) | 1,537 (54.9) | 438 (55.4) | 455 (54.1) | 0.61 |
| Elective index admission | | 577 (64.5) | 1,723 (61.6) | 509 (64.4) | 549 (65.3) | 0.69 |
| Deficiency anaemia | | 48 (5.4) | 151 (5.4) | 39 (4.9) | 38 (4.5) | 0.71 |
| Atrial fibrillation | | 582 (65.1) | 1,993 (71.3) | 528 (66.8) | 559 (66.5) | 0.88 |
| Congestive heart failure | | 754 (84.3) | 2,035 (72.8) | 654 (82.7) | 658 (78.2) | 0.02 |
| Chronic obstructive pulmonary disease | | 289 (32.3) | 755 (27.0) | 259 (32.8) | 243 (28.9) | 0.09 |
| Coagulopathy | | 181 (20.3) | 1,002 (35.8) | 181 (22.9) | 182 (21.7) | 0.55 |
| Coronary artery disease | | 542 (60.6) | 1,278 (45.7) | 454 (57.4) | 478 (56.9) | 0.82 |
| Cerebrovascular disease | | 78 (8.7) | 378 (13.5) | 77 (9.7) | 84 (10.0) | 0.86 |
| Diabetes mellitus | | 64 (7.1) | 369 (13.2) | 64 (8.1) | 91 (10.9) | 0.06 |
| Hypertension | | 747 (83.5) | 2,260 (80.8) | 657 (83.1) | 681 (81.0) | 0.27 |
| Liver disease | | 59 (6.6) | 195 (7.0) | 46 (5.9) | 65 (7.7) | 0.13 |
| Obesity | | 114 (12.7) | 483 (17.3) | 111 (14.0) | 130 (15.5) | 0.42 |
| Peripheral vascular disease | | 63 (7.1) | 310 (11.1) | 62 (7.8) | 69 (8.2) | 0.79 |
| Prior pacemaker | | 181 (20.2) | 423 (15.1) | 158 (20.0) | 164 (19.5) | 0.81 |
| Chronic kidney disease | | 369 (41.3) | 868 (31.0) | 318 (40.2) | 345 (41.1) | 0.72 |
| End-stage renal disease | | 45 (5.0) | 137 (4.9) | 41 (5.2) | 47 (5.6) | 0.71 |
| Smoking | | 59 (6.6) | 256 (9.1) | 56 (7.1) | 54 (6.4) | 0.59 |
| Hospital teaching status | Metropolitan non-teaching | 56 (6.3) | 382 (13.6) | 65 (8.3) | 89 (10.6) | <0.01 |
| | Metropolitan teaching | 821 (91.8) | 2,329 (83.3) | 720 (91.0) | 717 (85.3) | |
| | Non-metropolitan hospital | 17 (1.9) | 86 (3.1) | <11 (<1.4)* | 34 (4.0) | |
| Median quartile of income | 0-25$^{th}$ percentile | 186 (20.8) | 719 (25.7) | 170 (21.5) | 209 (24.9) | 0.42 |
| | 26-50$^{th}$ percentile | 224 (25.0) | 678 (24.2) | 191 (24.2) | 199 (23.6) | |
| | 51-75$^{th}$ percentile | 229 (25.6) | 711 (25.4) | 205 (26.0) | 205 (24.4) | |
| | 76-100$^{th}$ percentile | 241 (27.0) | 613 (21.9) | 213 (26.9) | 211 (25.0) | |
| Insurance | Medicare | 734 (82.1) | 1,909 (68.3) | 633 (80.1) | 644 (76.6) | 0.03 |
| | Medicaid | 40 (4.5) | 230 (8.2) | 40 (5.1) | 47 (5.6) | |
| | Private insurance | 100 (11.1) | 567 (20.3) | 97 (12.2) | 127 (15.1) | |
| | Self-pay | <11 (1.2)* | 39 (1.4) | <11 (<1.4)* | <11 (1.3)* | |
| | Others | 17 (1.9) | 46 (1.7) | 17 (2.2) | <11 (1.3)* | |

*Observations <11 are not reported as per HCUP guidelines. HCUP: Healthcare Cost and Utilization Project; IQR: interquartile range; SMVR: surgical mitral valve replacement; ViV-TMVR: valve-in-valve transcatheter mitral valve replacement

### TEMPORAL TRENDS UTILISATION AND PROCEDURAL OUTCOMES FOR VIV-TMVR VERSUS REDO-SMVR DURING THE STUDY PERIOD

The annual utilisation of ViV-TMVR ($p_{trend}$<0.01) increased significantly (5.2% to 36.8%) during the study period (Q4 2015-2019), while the trend of redo-SMVR ($p_{trend}$ <0.01) procedures decreased from 94.8% in 2015 to 63.2% in 2019 **(Figure 4A)**. Mortality rates decreased for the ViV-TMVR ($p_{trend}$ =0.01) group from 6.8% in 2016 to 2.0% in 2019 **(Figure 4B)**. Similarly, complication rates also decreased from 59.7% in 2016 to 43.0% in 2019 for ViV-TMVR ($p_{trend}$ =0.01) **(Figure 4C)**. All-cause 30-day and 6-month readmission rates remained steady for both ViV-TMVR ($p_{trend}$ =0.79) and redo-SMVR ($p_{trend}$ =0.47) **(Supplementary Figure 1, Supplementary Figure 2)**. Among the ViV-TMVR group, the utilisation of transseptal ($p_{trend}$ <0.01) ViV-TMVR increased, whereas the use of the transapical ($p_{trend}$ <0.01) approach decreased during the study period **(Supplementary Figure 3)**.

### READMISSION OUTCOMES AT 30 DAYS

The mortality rate during the episode of readmission at 30 days (<1.2% vs <1.1%, OR 1.01, 95% CI: 0.40-2.55) and all-cause readmission rates (14.9% vs 13.4%, OR 0.82, 95% CI: 0.66-1.02) were not significantly different in ViV-TMVR compared with redo-SMVR **(Figure 5, Figure 6)**. ViV-TMVR had a similar risk for the need for transfusions, incidence of stroke, vascular complication, and the need for PPM implantation compared

**Table 2. Hospitalisation outcomes at 30 days and 6 months after the procedure.**

| Variable, N (%) | Unadjusted | | | Propensity matched | | |
|---|---|---|---|---|---|---|
| | ViV-TMVR (n=894) | Redo-SMVR (n=2,797) | *p*-value | ViV-TMVR (n=791) | Redo-SMVR (n=841) | *p*-value |
| **In-hospital outcomes** | | | | | | |
| Mortality | 33 (3.7) | 156 (5.6) | 0.03 | 21 (2.6) | 61 (7.3) | <0.01 |
| Home discharge | 470 (52.5) | 826 (29.5) | <0.01 | 426 (53.9) | 192 (22.8) | <0.01 |
| Skilled nursing care | 426 (47.5) | 1,968 (70.6) | | 365 (46.1) | 649 (77.2) | |
| Cardiogenic shock | 93 (10.4) | 400 (14.3) | <0.01 | 68 (8.6) | 93 (11.0) | 0.11 |
| Stroke | 13 (1.4) | 148 (5.3) | <0.01 | 13 (1.6) | 36 (4.3) | <0.01 |
| Vascular complications | 85 (9.5) | 523 (18.7) | <0.01 | 73 (9.2) | 126 (15.0) | <0.01 |
| Blood transfusion | 110 (12.3) | 876 (31.3) | <0.01 | 96 (12.1) | 245 (29.1) | <0.01 |
| Cardiac arrest with CPR | <11 (<1.2)* | 55 (2.0) | 0.03 | <11 (<1.4)* | 20 (2.4) | 0.02 |
| Pneumonia | 63 (7.0) | 343 (12.2) | <0.01 | 58 (7.4) | 102 (12.2) | <0.01 |
| Urinary tract infection | 77 (8.6) | 277 (9.9) | 0.25 | 63 (8.0) | 79 (9.4) | 0.31 |
| Pericardial effusion | 14 (1.5) | 78 (2.8) | 0.04 | 12 (1.6) | 26 (3.1) | 0.04 |
| PPM | 26 (2.9) | 272 (9.7) | <0.01 | 23 (2.9) | 93 (11.1) | <0.01 |
| Resource utilisation | | | | | | |
| Length of stay, median (IQR), days | 4 (2-10) | 15 (8-26) | <0.01 | 4 (2-11) | 15 (8-25) | <0.01 |
| Cost of hospitalisation, median (IQR), $ | 49,019 (38,102-89,688) | 73,879 (52,613-106,736) | <0.01 | 46,743 (35,997-89,834) | 76,558 (50,148-142,501) | <0.01 |
| **Readmission outcomes at 30 days** | | | | | | |
| All-cause readmissions | 131 (14.7) | 345 (12.3) | 0.07 | 120 (15.1) | 119 (14.2) | 0.57 |
| 30-day readmission mortality | <11 (<1.2)* | 19 (0.7) | 0.98 | <11 (1.4)* | <11 (<1.3)* | 0.36 |
| Cardiogenic shock | 0 (0.0) | <11 (<0.4)* | 0.07 | 0 (0.0) | <11 (<1.3)* | 0.04 |
| Stroke | <11 (<1.2)* | <11 (<0.4)* | 0.81 | <11 (1.4)* | <11 (<1.3)* | 0.99 |
| Vascular complications | <11 (<1.2)* | 24 (0.9) | 0.59 | <11 (1.4)* | <11 (<1.3)* | 0.41 |
| Blood transfusion | 16 (1.8) | 33 (1.2) | 0.17 | 15 (1.9) | <11 (<1.3)* | 0.20 |
| Cardiac arrest with CPR | <11 (<1.2)* | 4 (0.1) | 0.60 | <11 (1.4)* | <11 (<1.3)* | 0.99 |
| Pneumonia | 13 (1.4) | 38 (1.4) | 0.83 | <11 (1.4)* | <11 (<1.3)* | 1.00 |
| Urinary tract infection | <11 (<1.2)* | 35 (1.3) | 0.75 | <11 (1.4)* | <11 (<1.3)* | 0.80 |
| Pericardial effusion | <11 (<1.2)* | 14 (0.5) | 0.27 | <11 (1.4)* | <11 (<1.3)* | 0.25 |
| PPM | <11 (<1.2)* | <11 (<0.4)* | 0.25 | <11 (1.4)* | 0 (0.0) | 0.08 |
| Falsification outcome | | | | | | |
| Hip/femur fracture | 0 (0) | <11 (<0.4)* | 0.57 | 0 (0) | <11 (<1.3)* | 0.33 |
| Acute COPD exacerbation | <11 (<1.2)* | <11 (<0.4)* | 0.54 | <11 (1.4)* | <11 (<1.3)* | 0.61 |
| Resource utilisation | | | | | | |
| Length of stay, median (IQR), days | 5 (3-11) | 4 (2-8) | 0.16 | 5 (3-11) | 4 (2-9) | 0.10 |
| Cost of hospitalisation, median (IQR), $ | 10,309 (4,207-18,794) | 7,105 (4,277-15,855) | 0.28 | 10,298 (4,420-17,023) | 8,327 (4,509-16,823) | 0.67 |
| **Readmission outcomes at 6 months** | **(n=464)** | **(n=1,348)** | | **(n=403)** | **(n=411)** | |
| All-cause readmissions | 126 (27.1) | 317 (23.5) | 0.12 | 101 (25.2) | 123 (29.8) | 0.13 |
| Mortality | <11 (<2.4)* | 16 (1.2) | 0.33 | <11 (<2.4)* | <11 (<0.8)* | 0.11 |
| Falsification outcome | | | | | | |
| Hip/femur fracture | <11 (<2.4)* | <11 (<0.8)* | 0.43 | <11 (<2.4)* | <11 (<0.8)* | 0.99 |
| Acute COPD exacerbation | <11 (<2.4)* | <11 (<0.8)* | 0.27 | <11 (<2.4)* | <11 (<0.8)* | 0.46 |
| Resource utilisation | | | | | | |
| Length of stay, median (IQR), days | 4 (2-9) | 4 (2-8) | 0.94 | 4 (2-9) | 4 (2-8) | 0.85 |
| Cost of hospitalisation, median (IQR), $ | 9,472 (4,072-19,549) | 8,427 (4,706-18,635) | 0.54 | 8,904 (3,943-15,998) | 8,723 (4,981-17,080) | 0.25 |

*Observations <11 are not reported as per HCUP guidelines. COPD: chronic obstructive pulmonary disease; CPR: cardiopulmonary resuscitation; HCUP: Healthcare Cost and Utilization Project; IQR: interquartile range; PPM: permanent pacemaker; SMVR: surgical mitral valve replacement; ViV-TMVR: valve-in-valve transcatheter mitral valve replacement

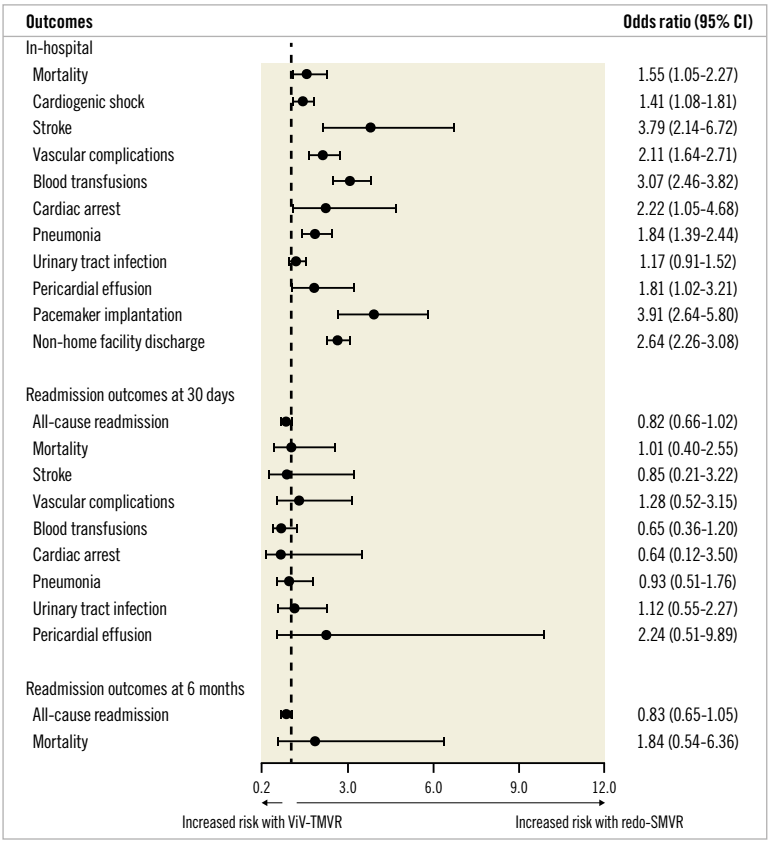



**Figure 3.** *Adjusted odds ratio for in-hospital outcomes. Adjusted outcomes are based on propensity-matched analysis. Propensity matching model adjusted for: age, sex, mode of admission (elective versus non-elective), median household income, insurance status and baseline comorbidities (anaemia, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, coronary artery disease, cerebrovascular disease, diabetes, hypertension, liver disease, obesity, peripheral vascular disease, chronic kidney disease, end-stage renal disease and smoking). CI: confidence interval; SMVR: surgical mitral valve replacement; ViV-TMVR: valve-in-valve transcatheter mitral valve replacement*

with redo-SMVR. In terms of resource utilisation, the readmission length and cost of hospitalisation were also similar for the 2 groups **(Table 2)**. The cumulative incidence of 30-day readmission rates was comparable as shown by the log-rank test (log-rank p-value=0.55) **(Table 2, Figure 5)**.

## READMISSION OUTCOMES AT 6 MONTHS

A total of 1,812 index cases and their 6-month readmissions were included in the analysis. Of the included cases, 24.4% underwent ViV-TMVR (n=464) whereas 75.6% had redo-SMVR (n=1,348). After propensity matching, 403 ViV-TMVR cases were matched

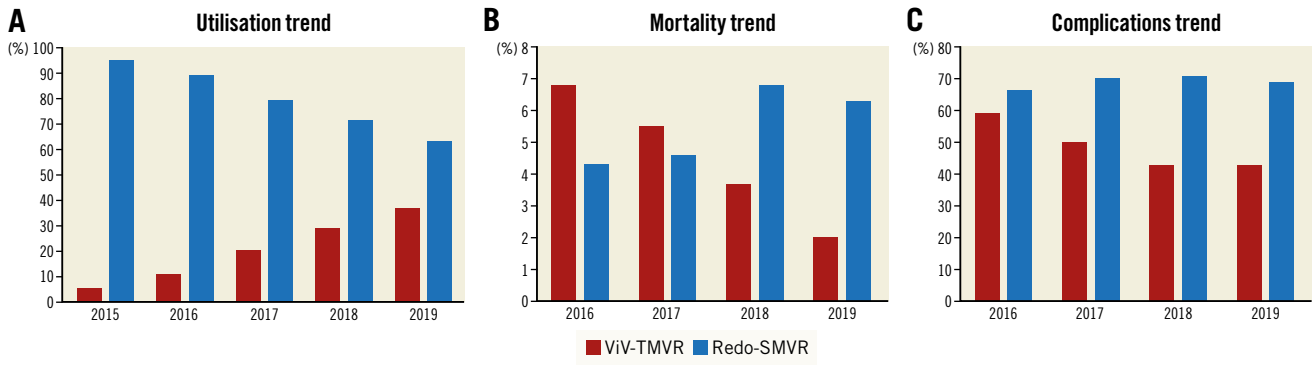



**Figure 4.** *Trends in utilisation, mortality and complications of ViV-TMVR compared with redo-SMVR. A) Utilisation trend. B) Mortality trend. C) Complications trend. Complication rates include a composite of cardiogenic shock, AKI, stroke, vascular complications, bleeding, cardiac arrest, pericardial effusions, need for PPM and infections. AKI: acute kidney injury; PPM: permanent pacemaker; SMVR: surgical mitral valve replacement; ViV-TMVR: valve-in-valve transcatheter mitral valve replacement*

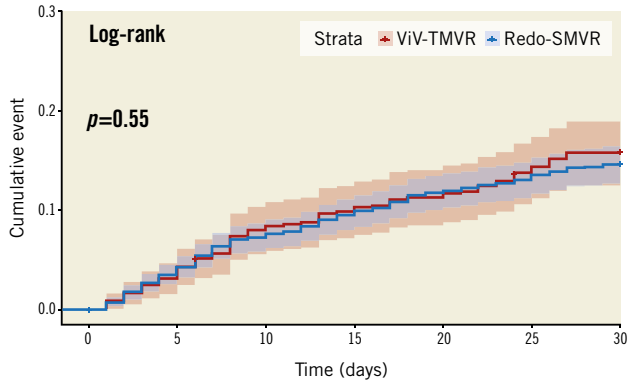



**Figure 5.** *Cumulative incidence of 30-day readmission. SMVR: surgical mitral valve replacement; ViV-TMVR: valve-in-valve transcatheter mitral valve replacement*

with 411 redo SMVR procedures. All-cause readmissions at 6 months (30.1% vs 27.5%, OR 0.83, 95% CI: 0.65-1.05) and all-cause readmission mortality (<2.3% vs <2.4%, OR 1.84, 95% CI: 0.54-6.36) remained non-significant between ViV-TMVR and redo-SMVR, respectively. Similarly, there was no difference in terms of the length and cost of hospitalisation. The cumulative incidence of the 6-month readmission was also similar between the 2 groups (log-rank p-value=0.26) **(Table 2, Figure 6)**. The **Central illustration** provides a graphical summary of our study findings.

### TRANSSEPTAL AND TRANSAPICAL VIV-TMVR VERSUS REDO-SMVR FOR IN-HOSPITAL OUTCOMES

The baseline characteristics of transseptal and transapical ViV-TMVR compared with redo-SMVR are summarised in **Supplementary Table 2** and **Supplementary Table 3**. The crude mortality rate and the adjusted mortality rate were lower for transseptal ViV-TMVR compared with redo-SMVR. On adjusted analysis, the procedural complication rates of stroke, need for transfusion, vascular complications and need for PPM were lower for the transseptal group **(Supplementary Table 4)**.

There was no difference in terms of unadjusted or adjusted mortality rates or procedural complications for the transapical approach when compared with conventional surgery. PPM implantation rates were lower with the transapical approach when compared with surgery **(Supplementary Table 5)**.

### E-VALUE ANALYSIS AND FALSIFICATION ENDPOINTS

In terms of E-value analysis, the observed effect size for mortality could be explained by unmeasured confounding with an OR of at least 2.7 (in-hospital mortality) and 2.0 (30-day and 6-month readmission mortality) above the measured confounding. Furthermore, there was no significant difference in terms of falsification outcomes during the 30-day and 6-month episode of readmission for hip/femur fracture and acute COPD exacerbation **(Table 2)**.

## Discussion

Our contemporary study evaluated the safety of minimally invasive ViV-TMVR compared with redo-SMVR. The principal findings of our adjusted analysis are as follows: 1) the in-hospital odds of all-cause mortality, and post-procedural complications such as vascular complications, stroke, need for transfusions, and need for PPM were significantly higher with redo-SMVR compared with ViV-TMVR at index hospitalisation. 2) Similarly, redo-SMVR appears to be associated with a higher resource utilisation as indicated by a significantly higher mean length of stay, and a greater average cost of hospitalisation. 3) The benefits of ViV-TMVR were attenuated during the episode of 30-day readmission, showing no significant differences in all-cause readmissions, post-procedure stroke,

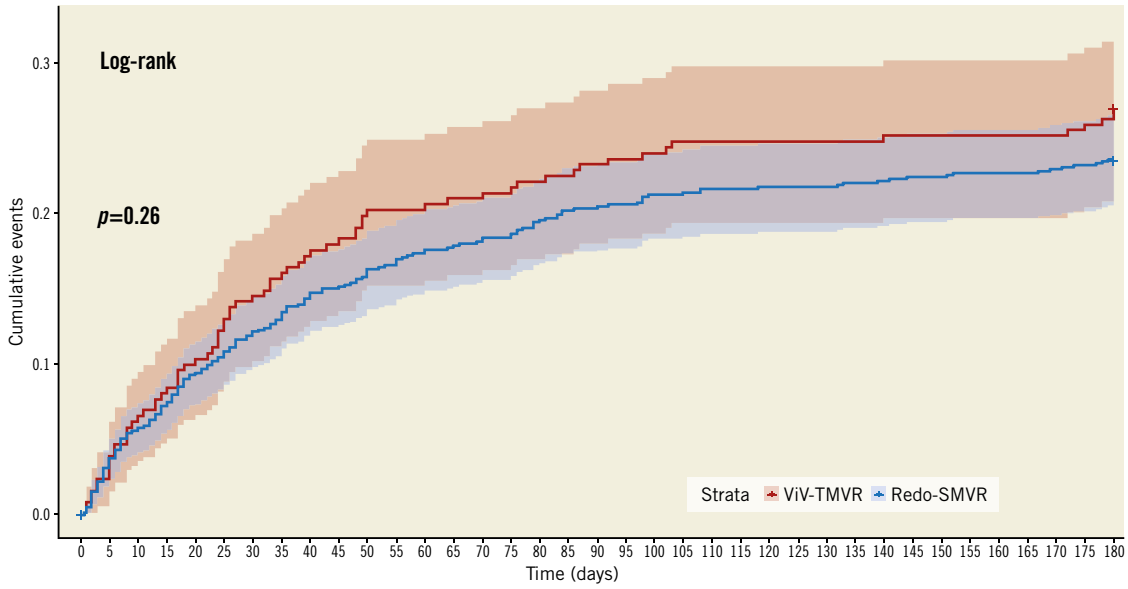
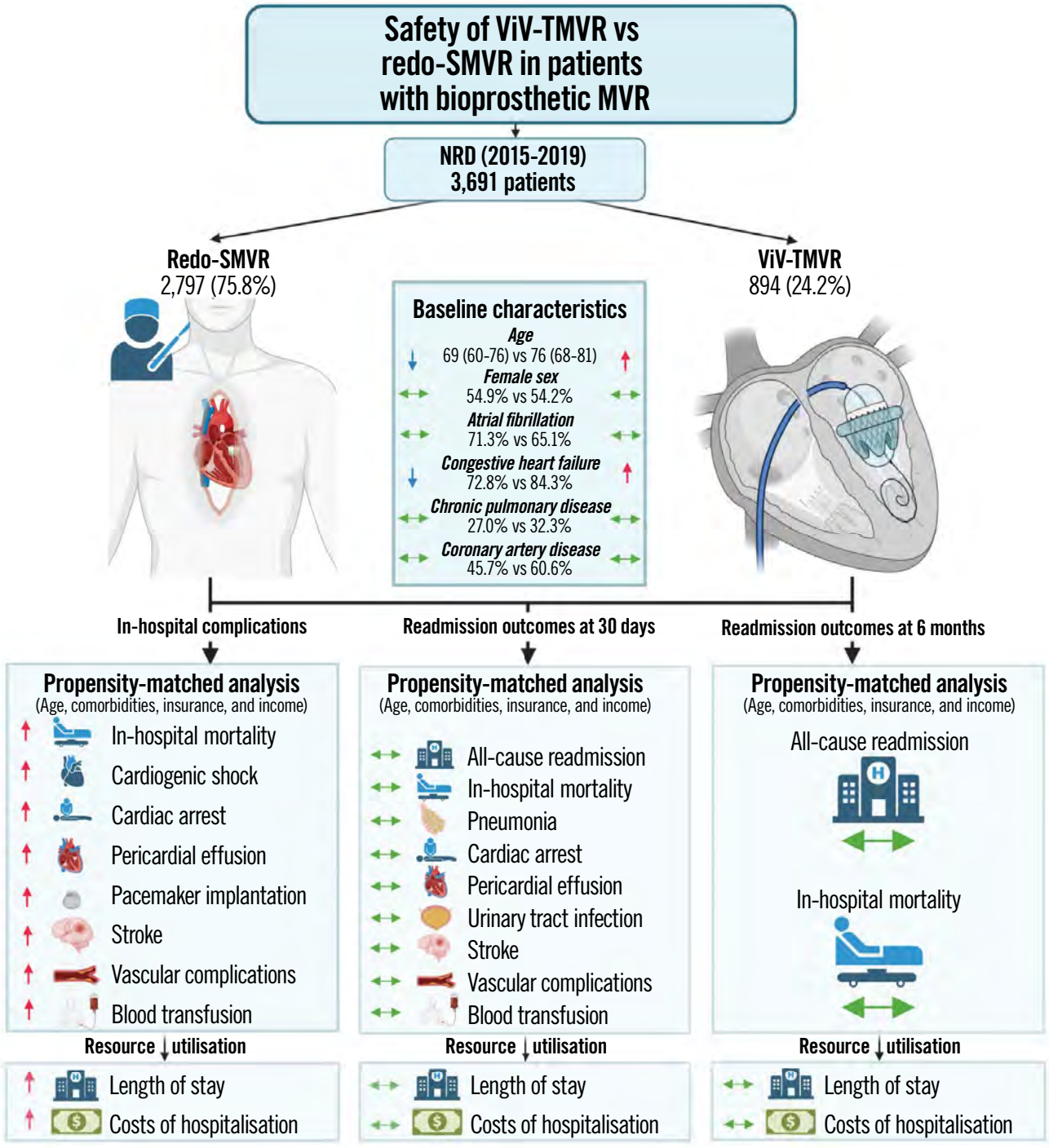



**Figure 6.** *Cumulative incidence of 6-month readmission. SMVR: surgical mitral valve replacement; ViV-TMVR: valve-in-valve transcatheter mitral valve replacement*

CENTRAL **ILLUSTRATION** **Transcatheter valve-in-valve implantation versus redo surgical mitral valve replacement in patients with failed mitral bioprostheses.**




vascular complications, and need for PPM during the episode of readmission. 4) During the 6-month readmission episode, the incidence of mortality and all-cause readmissions remained similar between the 2 groups, indicating a similar safety and efficacy of the transcatheter approach compared with the surgical option. 5) The annual trend of ViV-TMVR utilisation showed an exponential increase peaking at 36.8% in 2019. Furthermore, along with increased utilisation, there was an improvement in ViV-TMVR procedural outcomes, with a decrease in mortality and complication rates over the study duration.

Our study revealed that, despite a higher burden of baseline comorbidities in patients undergoing ViV-TMVR, the crude and adjusted survival rate favoured the ViV-TMVR group. This indicates that redo-SMVR carries inherent risks of periprocedural complications that can translate into high in-hospital mortality. However, as evidenced by the similar outcomes on follow-up data of up to 6 months, the estimates of all-cause mortality and complication rate decreased substantially with time, implying that the periprocedural complications might not have long-term sequelae. Patients who survive the immediate post-operative phase of redo-SMVR might subsequently have similar outcomes. These findings also indicate that, although ViV-TMVR is a novel procedure for degenerated MV and is performed on a sicker population, in terms of efficacy it might be non-inferior to SMVR on follow-up up to 6 months.

The major caveat to these observations is that only patients who were readmitted within this time frame were assessed, and events occurring outside the hospital admission or emergency department (ED) admissions could not be captured. It is important to note that these findings were in contrast to the conclusions of some of the small-scale prior studies. Kamioka et al reported a higher baseline comorbidity burden with higher Society of Thoracic Surgeons (STS) predicted mortality scores in ViV-TMVR, yet the in-hospital mortality rate was comparable between the 2 groups (n=2 deaths, for both groups)[16]. The study by Murzi et al also showed an increased baseline mean age of ViV-TMVR, and numerically lower mortality rates compared with a surgical approach, but it did not reach the threshold of statistical significance due to a small sample size (n=61)[17]. Similar findings were echoed by an Italian study comprising 78 procedures[18]. Nonetheless, the conclusions of a recent meta-analysis and subsequent database studies were in concordance with our study, showing a higher in-hospital mortality compared with ViV-TMVR[5,19]. In the context of disputed results of prior studies, our large scale adjusted analysis provides a benchmark against which future studies could be compared.

Our reported estimates of mortality with ViV-TMVR (5.4%) on NRD were closer to those reported by the TVT and TMVR registry study[20]. The higher in-hospital complication rates with redo-SMVR translate into an increased length of stay and higher adjusted cost of hospitalisation. These findings are in agreement with the prior study by Kamioka et al who reported increased ICU and hospital length of stay with redo-SMVR[16]. Prior studies have reported a significant risk of PPM implantation with redo-SMVR, whereas ViV-TMVR is associated with a negligible risk[21-25]. These findings were complemented by our study which reports a 4-fold higher risk of PPM with a surgical approach compared with catheter-based treatment. The plausible explanation for these findings could be the proximity of the MV and increased chances of injury to the conduction system with an open surgical approach.

Our findings at short-term follow-up validate the results of prior studies. Kamioka et al reported a similar 30-day mortality between ViV-TMVR (3.2%) and redo-SMVR (3.4%)[16]. Similarly, Simonetta and colleagues also observed no significant difference in the 30-day mortality difference between the 2 treatment strategies (p=0.41)[18]. However, the application of the individual studies was limited, due to the small sample size, lack of power to detect the primary outcomes, unadjusted analysis, and single-centre experiences.

Our study provides contemporary evidence on the safety of ViV-TMVR compared with redo-SMVR for up to 6 months post-procedure. Additionally, our study provides insights into the yearly utilisation of the ViV-TMVR approach in the USA. We observed that ViV-TMVR utilisation has increased by more than 300% from 2015 to 2019. These findings suggest a trend towards an increased adoption of this technique in the US for degenerated bioprosthetic valves. Moreover, we also report novel findings of improved temporal trends of procedural complication and mortality rates with ViV-TMVR from 2016 to 2019, which have not been explored previously in a US national database.

## Limitations

Our study is constrained by the following limitations. As mentioned above, the NRD cannot capture deaths that occur outside of the hospital or out of state, which might have led to an underestimation of the pooled benefits of ViV-TMVR. Moreover, data on medication use, blood chemistry, echocardiographic data such as left ventricular ejection fraction, mode of valve failure, presence of concomitant tricuspid valve disease, and right ventricular systolic pressure and medication use are lacking, precluding our ability to account for its impact on outcomes. Furthermore, though ViV-TMVR may be associated with better short-term outcomes, data on long-term outcomes and durability are lacking. For evaluating 6-month outcomes, more than 50% of the cases had to be excluded to allow for a 6-month readmission analysis. For temporal trends, we had to exclude the fourth quarter of 2015, due to <11 observations for the ViV-TMVR group for mortality and procedural complication. On subset-analysis (transseptal and transapical ViV-TMVR versus redo-SMVR), due to a reduced sample size, 30-day and 6-month readmission outcome analyses could not be performed. Though it was rare, we could not exclude patients who might have had a failed mechanical valve due to a lack of specific ICD codes. In the ViV-TMVR group, only balloon-expandable valves can be used. Furthermore, data on the size and iteration of the device are not available. Certain outcomes such as acute kidney injury were not assessed, as it is not possible to determine if the outcome occurred prior to the procedure or after the procedure. The low sample size on subset-analysis might have been underpowered to detect a statistically significant difference with respect to mortality and complication rates. The NRD is an administrative claims-based database that uses ICD-10-CM codes for diagnosis Although procedural codes are less prone to error, coding errors cannot be completely excluded. The NRD collects data on in-patient discharges, and each admission is registered as an independent event. Like any observational, retrospective study, association does not imply

causation and conclusions are hypothesis-generating and should be drawn cautiously.

## Conclusions

ViV-TMVR utilisation in patients with degenerated bioprosthetic MV has increased exponentially in recent years. ViV-TMVR is associated with lower in-hospital mortality, periprocedural complications, and resource utilisation compared with redo-SMVR on index hospitalisation. The all-cause readmissions and 30-day and 6-month mortality during the episode of readmissions were comparable between both groups. In addition to the increased utilisation of ViV-TMVR, procedural outcomes have also improved with time. Future large-scale, controlled studies are needed to confirm these findings and to evaluate the long-term outcomes and durability of ViV-TMVR.

## Impact on daily practice

The current guidelines approved the use of ViV-TMVR as an alternative to surgery, especially in patients who are at high surgical risk and have a failed bioprosthetic mitral valve. Based on our findings, the redo-SMVR is associated with increased periprocedural complications and increased resource utilisation including costs and length of hospitalisation. However, there are no differences in terms of 30-day and 6-month outcomes during the episode of readmission. In the absence of randomised trials, our study findings provide initial data supporting the safety of ViV-TMVR for patients with prohibitive surgical risk. The current data can also aid in shared decision-making between the patient and the Heart Team.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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## Supplementary data

**Supplementary Table 1.** ICD-10 codes.

**Supplementary Table 2.** Baseline characteristics of transseptal ViV-TMVR compared with redo-SMVR.

**Supplementary Table 3.** Baseline characteristics of transapical ViV-TMVR compared with redo-SMVR.

**Supplementary Table 4.** Crude and propensity matched outcomes of transseptal ViV-TMVR compared with redo-SMVR.

**Supplementary Table 5.** Crude and propensity matched outcomes of transapical ViV-TMVR compared with redo-SMVR.

**Supplementary Figure 1.** Temporal trend of 30-day readmission for ViV-TMVR versus redo-SMVR.

**Supplementary Figure 2.** Temporal trend of 6-month readmission for ViV-TMVR versus redo SMVR.

**Supplementary Figure 3.** Trend of utilisation of transapical versus transseptal ViV-TMVR.

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# Extracardiac basal annuloplasty for the treatment of secondary mitral regurgitation

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## Introduction

Among the 24 million people affected worldwide by mitral regurgitation[1], almost two-thirds suffer from secondary mitral regurgitation (SMR)[2]. Moreover, the presence of symptomatic SMR in patients with heart failure (HF) remains a marker of increased mortality and rehospitalisation risk whatever its severity[2]. Thus, recent guidelines recommend downsized mitral annuloplasty as a standalone procedure (Class IIb) or as a concomitant procedure combined with coronary artery bypass grafting (CABG; Class I in European and IIa in American guidelines) for the management of SMR[3,4]. However, standard annuloplasty remains an intracardiac procedure requiring aortic cross-clamping and cardiopulmonary bypass and is thus associated with an increased risk of perioperative complications.

We aimed to evaluate the safety and efficacy of a new surgical procedure of extracardiac annuloplasty using the BACE (Basal Annuloplasty of the Cardia Externally) device (Phoenix Cardiac Devices) for the management of SMR in patients with systolic HF.

## Methods

Forty-seven symptomatic patients with significant SMR (i.e., at least moderate or grade 2+) and systolic HF (i.e., left ventricular ejection fraction [LVEF] between 25% and 50%) referred for a surgical mitral valve (MV) intervention were prospectively recruited in 12 multinational centres between November 2012 and July 2019. Specific inclusion and exclusion criteria are described at ClinicalTrials.gov: NCT02701972. Patients had baseline, preoperative, 1-, 3-, 6-, 12-, and 24-month assessments including medical history, functional status (i.e., New York Heart Association [NYHA]), quality of life (i.e., Minnesota Living with Heart Failure Questionnaire [MLHFQ]) and echocardiography analysed by the independent echocardiography core laboratory based at the Quebec Heart & Lung Institute and following the American Society of Echocardiography standards and recommendations[5]. This study was conducted in conformity with the Declaration of Helsinki and Good Clinical Practice principles and approved by local ethics committees and respective health authorities. All patients provided informed written consent.

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The primary safety endpoint was the freedom from major device- or surgery-related adverse events at 6 months following the procedure and was adjudicated by an independent Data Safety & Monitoring Board. The primary efficacy endpoint was the reduction of the SMR grade to ≤mild at 6 months. It was then evaluated in the subset (n=35) which had the 6-month follow-up (FU). Secondary endpoints were freedom from major device-related adverse events, and changes in the SMR grade, NYHA class and MLHFQ score between baseline and FU.

## Results

Among the 47 patients recruited, implantation of the device was attempted but was not completed in 3 patients. Thus, procedural success was 94% **(Figure 1)**. In the 44 patients (mean age±standard deviation [SD]: 62±12 years, 73% male, median [interquartile range] Charlson Comorbidity Index: 3 [2-4]) who were treated with the device, the majority (35 patients; 80%) underwent concomitant CABG, whereas 9 (20%) patients had a standalone

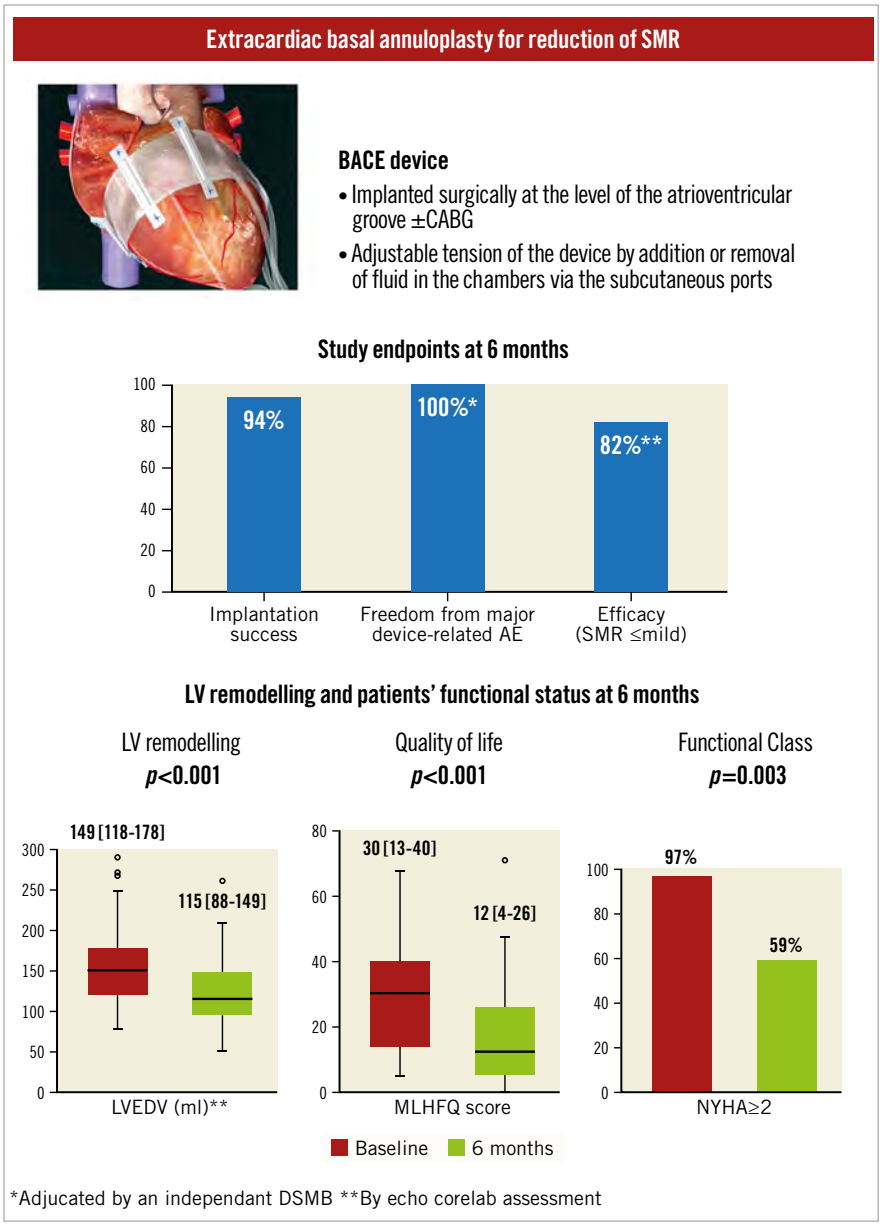


**Figure 1.** *Study endpoints and changes in mitral regurgitation severity, LV remodelling, quality of life and functional status at 6 months following the implantation of the BACE device. Illustration of the BACE device, which provides external annuloplasty of the cardiac base in order to reduce secondary mitral regurgitation severity and left ventricular dilation, and the main characteristics of the device (top); results of feasibility, safety, and efficacy endpoints (middle); and graphs for LV remodelling, NYHA Functional Class, and quality of life improvements (bottom) at 6 months after the implantation of the device in patients with at least moderate SMR and reduced ejection fraction. AE: adverse events; BACE: basal annuloplasty of the cardia externally; CABG: coronary artery bypass grafting; DSMB: Data Safety & Monitoring Board; LV: left ventricular; LVEDV: LV end-diastolic volume; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; SMR: secondary mitral regurgitation*

procedure. The procedure was performed off-pump in 20 (57%) patients, and the median number of grafts was 3 (2-4).

The primary safety endpoint was met in 70% of patients (31 of 44 patients implanted). Freedom from major device-related events was 100% and 98% at 6 and 12 months, respectively (i.e., compression of right ventricular inflow and outflow causing underfilling and reduced function in 1 patient who underwent surgical device removal). Two patients (5%) died before 30 days, and 6 patients died between 30 days and 6 months. None of these deaths were related to the device.

The primary efficacy endpoint was achieved in 82% of patients (SMR severity: 8 [24%] none or trace, 19 [58%] mild, 4 [12%] moderate and 2 [6%] severe; p-value vs baseline by Friedman test: $p<0.001$). In terms of secondary efficacy endpoints, 87% of patients had a reduction of at least one grade at 30 days, and 88% at 6 months. Echocardiographic parameters of left ventricular (LV) geometry/function and MV morphology (i.e., MV annulus diameter, tenting area, leaflet coaptation distance, indexed left atrial volume, LV end-diastolic volume, and LV end-systolic and end-diastolic diameters) significantly improved from baseline to 6 months **(Figure 1)** (all p-values by paired t-tests $\leq 0.003$).

At 6 months, patients experienced significant improvement in NYHA class ($p<0.001$ by Friedman test), with percentages decreasing from 34% in Class III-IV to 12%, and from 63% in Class II to 47% **(Figure 1)**. The MLHFQ score showed a marked improvement (i.e., reduction; paired t-tests: $p<0.001$) at 6 months **(Figure 1)**. MR reduction (i.e., ≤mild) persists at 12 and 24 months, respectively, in 83% (20/24) and 91% (21/23) of patients who underwent these subsequent FU.

## Discussion

The purpose of the BACE device is to achieve an extracardiac, indirect, and targeted restrictive mitral annuloplasty with the advantages of being less invasive than intracardiac downsized/restrictive annuloplasty and of offering the possibility of correcting persistent/recurrent MR by adjustment of the degree of annular restriction via the subcutaneous ports. Recurrent MR is believed to be the main reason for the lack of superiority of downsized annuloplasty versus mitral valve replacement for the treatment of ischaemic MR. The possibility of adjusting the degree of annular restriction achieved by the BACE device at any time during post-procedural follow-up may overcome this important limitation of standard intracardiac annuloplasty.

## Limitations

The main limitations of this study are the single-arm design and the high prevalence of concomitant CABG procedures, which implicate that we cannot ascertain the respective effects of extracardiac annuloplasty versus myocardial revascularisation on study endpoints.

## Conclusions

In summary, extracardiac basal annuloplasty with the BACE device appears to be safe and feasible and is associated with a significant reduction of SMR severity, positive LV remodelling, and improvement in the patient's quality of life and functional status. Future randomised controlled trials comparing BACE±CABG versus intracardiac annuloplasty±CABG are needed.

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## Conflict of interest statement

K. Talluri was the vice-president of clinical development at Phoenix Cardiac Devices. P. Pibarot received funding from Edwards Lifesciences, Medtronic and Phoenix Cardiac Devices for echocardiography core laboratory analyses, with no personal compensation. The other authors have no conflicts of interest to declare relevant to this study.

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# Outcomes of isolated tricuspid valve replacement: a systematic review and meta-analysis of 5,316 patients from 35 studies

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**KEYWORDS**

- miscellaneous
- tricuspid disease
- TTVR

## Abstract

**Background:** Transcatheter tricuspid valve replacement (TTVR) is rapidly emerging as a therapeutic option amongst patients with secondary tricuspid regurgitation. Historical data from surgical tricuspid valve replacement (TVR) studies may serve as a benchmark for the development of TTVR trials.

**Aims:** The aim of the study was to investigate the early and late outcomes following isolated surgical TVR.

**Methods:** Multiple electronic databases were searched to identify studies on isolated surgical TVR. The prespecified primary endpoint was operative mortality; secondary endpoints were early and late outcomes. Overall estimates of proportions and incidence rates with 95% confidence intervals (CI) were calculated using random-effects models. Multiple sensitivity analyses accounting for baseline characteristics, country and the operative period were applied.

**Results:** A total of 35 studies (5,316 patients) were included in this meta-analysis. The operative period ranged from 1974 to 2019. The overall rate of operative mortality was 12% (95% CI: 9-15), with higher mortality for patients who were operated on before 1995, who had prior cardiac surgeries, or who had liver disease. The most frequent clinical events were pacemaker implantation (10% [95% CI: 6-16]), bleeding (12% [95% CI: 8-17]), acute kidney injury (15% [95% CI: 9-24]) and respiratory complications (15% [95% CI: 12-20]). At follow-up analysis of the bioprosthetic TVR, there was an incidence rate per 100 person-years of 6 (95% CI: 2-13) for death and 8 (95% CI: 5-13) for recurrence of significant tricuspid regurgitation.

**Conclusions:** This meta-analysis provides an overview of the historical clinical outcomes following isolated surgical TVR. These findings can support the development of future clinical trials in the tricuspid space by providing thresholds for clinical outcomes.

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## Abbreviations

| | |
|---|---|
| **CI** | confidence interval |
| **HF** | heart failure |
| **TR** | tricuspid regurgitation |
| **TTVR** | transcatheter tricuspid valve replacement |
| **TV** | tricuspid valve |
| **TVR** | tricuspid valve replacement |

## Introduction

*"One of the most valuable things any person can learn is the art of using the knowledge and experience of others".*

Napoleon Hill

The presence of clinically significant tricuspid regurgitation (TR) is common and is independently associated with excess mortality[1,2]. Also, right-sided heart failure is an important public health problem, and several publications support its early treatment[3]. However, symptomatic TR continues to be undertreated in comparison to left-sided valvular diseases[4]. This has been mainly attributed to the high mortality and morbidity rates of tricuspid valve (TV) surgery.

The TV has challenging anatomical features that are known predictors of procedural failure and limit the broad application of repair techniques. In contrast to mitral valve surgery, the great majority of TV patients (59%) undergo surgical replacement[3,5]. Isolated tricuspid valve replacement (TVR) has been found to have an overall mortality risk of ~10%, and this figure has not significantly changed over time[5,6]. Considering the unwavering mortality risk associated with TV surgery, the sizeable gap between patients with TV disease and those undergoing definitive correction is unlikely to be filled by surgery; therefore, several transcatheter solutions are under investigation to address this unmet clinical need at a lower procedural risk[7,8].

Given the growing interest in transcatheter tricuspid valve replacement (TTVR), a more profound understanding of the historical surgical data is fundamental and may serve as a benchmark for developing future therapies[9]. To date, no randomised controlled trials or systematic literature analyses have examined this procedure. With this background, we performed an up-to-date comprehensive meta-analysis to provide a quantitative assessment of evidence regarding the outcomes after isolated surgical TVR.

## Methods

The protocol of this meta-analysis has been registered in PROSPERO (international prospective register of systematic reviews; CRD42021284309) and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines **(Supplementary Appendix 1, Supplementary Appendix 2)**[10,11]. Given the nature of the work, ethical approval was not required.

### SEARCH STRATEGY AND STUDY SELECTION

Randomised trials and observational studies on isolated surgical TVR were evaluated for inclusion in this meta-analysis. Prespecified criteria to consider the studies eligible for inclusion were: 1) they reported separate outcome data for patients undergoing isolated TVR; 2) they included at least 10 patients; 3) there were no overlapping populations; 4) there were no exclusively congenital TV diseases; 5) there were no paediatric populations. With the aim of investigating all the literature on isolated TVR as a benchmark for TTVR, we excluded the following from the analyses: 1) patients undergoing surgical tricuspid valve repair and 2) non-isolated TVR. No restriction on the publication date was applied.

A systematic search of the literature was performed in PubMed, EMBASE, Scopus, and Web of Science, from the database's inception up to the final search date of October 10th, 2021. In addition, the reference lists of prior systematic reviews and included articles were screened to find further potentially relevant studies (backward snowballing). The search strings are available in **Supplementary Appendix 3**. The data underlying this article will be shared upon reasonable request to the corresponding author.

### DATA EXTRACTION AND QUALITY ASSESSMENT

Two reviewers (A. Scotti, M. Sturla) independently searched the electronic bibliographic databases. After the removal of duplicates, the title and abstract were screened to exclude non-relevant studies; subsequently, the full text of the remaining results was retrieved for further appraisal. Discrepancies were discussed and resolved with a senior reviewer (A. Latib). A dedicated electronic database was used for data extraction and included: sample size, operative data, baseline patient characteristics, procedural complications and late outcomes.

Two independent reviewers (A.Scotti, M. Sturla) performed the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) assessment tool from the Cochrane handbook assessment for observational studies[12].

### OUTCOMES MEASURES

The prespecified primary endpoint was operative mortality, defined as any death that occurred within 30 days after TVR or during the index hospitalisation. Secondary endpoints were early events (stroke, acute kidney injury, renal replacement therapy, bleeding, respiratory complications, pacemaker implantation, and wound infection), late mortality, TV reintervention (surgical or percutaneous), valve thrombosis, structural valve deterioration, and recurrence of at least moderate TR at follow-up. The full list of characteristic and outcome definitions is available in the **Supplementary Appendix 4**.

### STATISTICAL ANALYSIS

Baseline characteristics were presented as pooled, weighted means or proportions and 95% confidence intervals (CI). Whenever applicable, the mean±standard deviation was calculated from the reported median and interquartile range according to Wan et al[13]. Study-level and pooled estimates were reported as proportions or incidence rates with 95% CI, for early and late outcomes, respectively. A random-effects model using the logit transformation with the "empirical

Bayes" (Paule-Mandel) estimator was applied for the meta-analysis of proportions[14,15]. A random-effects model using the log transformation and the maximum-likelihood estimator was used to calculate incidence rates. To account for heterogeneity in follow-up, overall incidence rates were estimated per 100 person-years. If available, the collection of the numbers of actual observations at follow-up was preferred over the whole sample size, avoiding assumptions about any participants for whom the outcome was not measured[16]. The indirect methods by Tierney and colleagues were adopted to retrieve missing data (i.e., events, time at risk) for incidence rate estimates; when the available information was insufficient, data were retrieved from Kaplan-Meier curves using follow-up time, estimated rates, and numbers at risk assuming random (non-informative) censoring[17]. A continuity correction of 0.5 has been applied for studies having either zero or all events (i.e., an event probability of either 0 or 1).

Statistical heterogeneity was assessed using Cochran's Q test and $I^2$ values. $I^2$ values of less than 25%, 25-50%, or more than 50% were regarded as being indicative of low, moderate or high heterogeneity, respectively[18]. Publication bias and small-study effect were assessed by visual inspection of funnel plots and using Begg's test. A Baujat plot, which is a scatter plot with the contribution of each study to the overall heterogeneity (as measured by Cochran's Q test) on the x-axis and the standardised difference of the overall treatment effect with and without each study on the y-axis, is provided[19].

As a sensitivity analysis, a random intercept logistic regression model was used for the meta-analysis of proportions[20,21]. The potential interaction among continents or operative periods (before 1995 versus after 1995, i.e., median operative time) and treatment effect was investigated with subgroup analyses for the primary endpoint. For this purpose, random-effects models were performed validating the confidence intervals by adjustment according to the Hartung-Knapp-Sidik-Jonkman method[22].

Meta-regressions were performed to evaluate the potential impact of several characteristics (year of publication, operative period, continent, estimated risk of bias, age, left ventricular (LV) ejection fraction, prevalence of females, diabetes mellitus, atrial fibrillation, hypertension, TVR with bioprostheses, endocarditis, secondary TR, liver disease, and previous cardiac surgery) on the outcomes of interest. Cumulative and leave-one-out sensitivity analyses were conducted to show how each study might affect the overall estimates. Further sensitivity analyses included the calculation of proportions and incidence rates with 95% CI using fixed-effects models with the Mantel-Haenszel method. Statistical significance was set at a p-value <0.05 (2-sided). All analyses were performed with R, version 4.0.2 (R Foundation for Statistical Computing), packages meta and metafor.

## Results

### SEARCH RESULTS

The search strategy results and study selection process are illustrated in **Figure 1** and **Supplementary Appendix 2**. Thirty-five

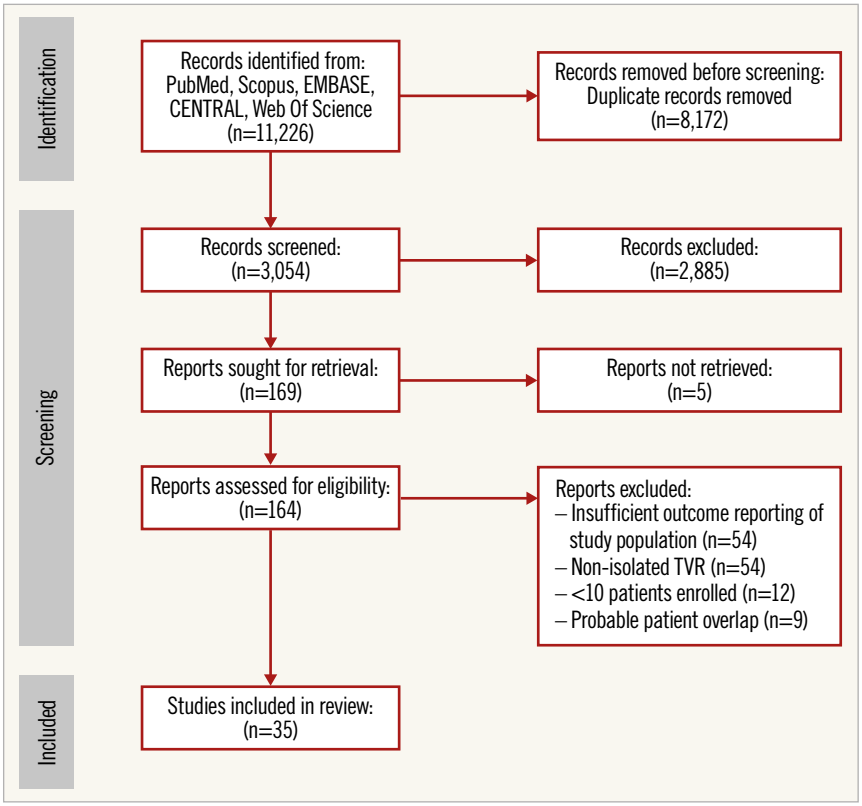


**Figure 1.** *Flowchart of the study selection progress. TVR: tricuspid valve replacement*

observational studies were found to be eligible for inclusion in this meta-analysis[3,23-54]. The main features of the included studies are presented in **Table 1**. The operative period was up to 2019, and the most represented countries were the USA and China. Apart from 6 studies that showed in-hospital outcomes, the others reported up to 14 years of mean follow-up time.

A total of 5,316 patients undergoing isolated TVR were analysed. The baseline characteristics of the study population are reported in **Supplementary Table 1**. The mean age was 53 (95% CI: 49-56) years, and the majority (63% [95% CI: 57-69]) were female. Six out of 10 patients (60% [95% CI: 27-85]) had previous cardiac surgery. The pooled mean LV ejection fraction was

**Table 1. Key study features.**

| Study | Year | Patients | Bioprosthetic valve (%) | Operative time | Country | Multicentre (n) | Follow-up§ (years) |
|---|---|---|---|---|---|---|---|
| Sanfelippo et al | 1976 | 15 | 0 (0) | Up to 1972 | USA | No | 4 |
| Glower et al* | 1995 | 35 | 35 (100) | 1974-1993 | USA | No | In-hospital |
| Ian Munro et al | 1995 | 30 | NR | 1975-1992 | Canada | No | 4 |
| Do et al | 2000 | 29 | 26 (90) | 1978-1998 | Canada | No | 6 |
| Mangoni et al | 2001 | 15 | 5 (33) | 1984-1994 | USA | No | 3 |
| Maleszka et al | 2004 | 20 | 5 (25) | 1985-2002 | Germany | No | 3 |
| Solomon et al | 2004 | 33 | 25 (76) | 1996-2002 | N. Zealand | No | 5 |
| Iscan et al | 2007 | 20 | NR | 1987-2004 | Turkey | No | 6 |
| Tokunaga et al* | 2008 | 31 | 27 (87) | 1975-2004 | Japan | No | 8 |
| Capoun et al | 2010 | 11 | 8 (73) | 1999-2009 | UK | No | 2 |
| Baraki et al* | 2013 | 18 | 14 (78) | 1996-2012 | Germany | No | 6 |
| Kim et al* | 2013 | 14 | 10 (71) | 1996-2010 | Republic of Korea | No | 3 |
| Bevan et al | 2014 | 29 | 23 (79) | 1995-2011 | N. Zealand | No | 14 |
| Buzzatti et al | 2014 | 61 | NR | 1997-2012 | Italy | No | 5 |
| Farag et al | 2017 | 68 | 36 (53) | 1995-2011 | Germany | No | NR |
| Hanedan et al* | 2017 | 30 | 10 (33) | 2004-2011 | Turkey | No | 2 |
| Rossello et al | 2017 | 25 | 0 (0) | 1996-2012 | Spain | No | 5 |
| Çakıcı et al | 2018 | 25 | 22 (88) | 2010-2016 | Turkey | No | 2 |
| Chen et al* | 2018 | 118 | 102 (86) | 2003-2016 | China | No | In-hospital |
| Fang et al* | 2018 | 90 | 74 (82) | 2007-2016 | China | No | 9 |
| Moutakiallah et al | 2018 | 11 | 5 (45) | 2000-2017 | Morocco | No | 6 |
| Di Mauro et al | 2019 | 80 | 54 (68) | 1979-2018 | Italy | Yes (21) | 19 |
| Kundi et al* | 2019 | 2,670 | 1,737 (65) | 2003-2014 | USA | Yes (841) | 1 |
| Liang et al* | 2019 | 76 | 43 (57) | 2010-2017 | China | No | 4 |
| Chen et al* | 2020 | 107 | 25 (23) | 2009-2017 | China | No | 5 |
| Dreyfus et al | 2020 | 273 | 264 (97) | 2007-2017 | France | Yes (12) | 3 |
| Sánchez-Espín G et al* | 2020 | 56 | 48 (86) | 1996-2017 | Spain | No | 4 |
| Wong et al | 2020 | 137 | NR | 2000-2013 | Taiwan | Yes (NA) | 4 |
| Yan et al* | 2020 | 49 | 49 (100) | 2012-2019 | China | No | 2 |
| Kawsara et al* | 2021 | 552 | 468 (85) | 2016-2017 | USA | Yes (NA) | In-hospital |
| Lee et al | 2021 | 216 | NR | 2000-2013 | Taiwan | Yes (NA) | 4 |
| Leviner et al | 2021 | 33 | 31 (94) | 2007-2018 | Israel | Yes (2) | 4 |
| Liu et al* | 2021 | 186 | 145 (78) | 1999-2018 | China | Yes (2) | 11 |
| Park et al | 2021 | 106 | 23 (22) | 1996-2018 | Republic of Korea | No | 4 |
| Tafti et al# | 2021 | 47 | 41 (87) | 2010-2018 | Iran | No | 5 |

§Mean follow-up. *Studies reporting outcome data for bioprosthetic valve group. #Reported data were clarified and confirmed upon contacting corresponding authors. NA: not applicable; NR: not reported

within normal limits (58% [95% CI: 54-61]). Comorbidities, such as diabetes, hypertension and liver disease, were present in less than one-third of patients.

## RISK OF BIAS AND PUBLICATION BIAS

The risk of bias was assessed for every observational study, as shown in **Supplementary Table 2**. The majority of included studies presented an overall moderate risk of bias. Possible concerns were raised for some studies in the domain of "bias due to confounding" because baseline prognostic characteristics were found to influence the choice of intervention (i.e., TVR).

Visual inspection of the funnel plot and the Begg's and Mazumdar's rank correlation tests indicated the absence of significant publication bias and small-study effects. The Baujat plot identified the studies by Tafti et al and Sanfelippo et al as introducing significative heterogeneity and the results of Kundi et al[45] as having a higher impact on the summary estimate **(Supplementary Figure 1)**.

## OUTCOMES

The overall random-effects rate of operative mortality, the primary endpoint, was 12% (95% CI: 9-15), with a high degree of heterogeneity ($I_2$: 68%) **(Figure 2)**.

Secondary endpoints were divided into early and late outcomes. Among the early outcomes, we found a 2% (95% CI: 1-4) rate of stroke, 15% (95% CI: 9-24) of acute kidney injury, 7% (95% CI: 3-15) of renal replacement therapy, 12% (95% CI: 8-17) of bleeding, 15% (95% CI: 12-20) of respiratory complications, 10% (95% CI: 6-16) of pacemaker implantation, and 3% (95% CI: 2-6) of wound infection **(Table 2)**. Late outcomes are reported as incidence rates per 100 person-years and are as follows: 6 (95% CI: 4-9) for mortality, 2 (95% CI: 1-3) for the need for percutaneous

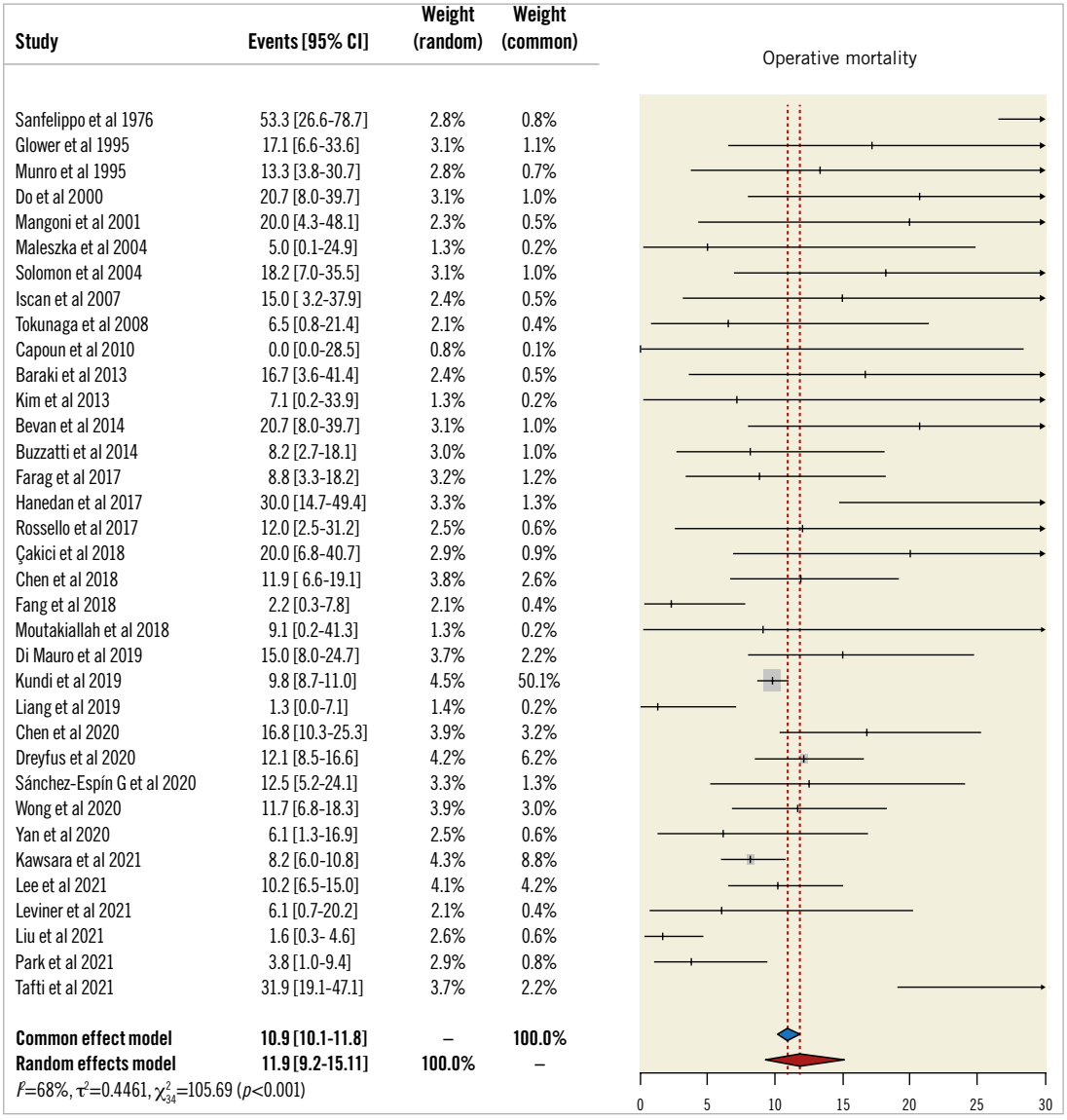


**Figure 2.** *Primary endpoint. Forest plot of operative mortality. CI: confidence interval*

**Table 2. Early and late outcomes – random effects models.**

| Outcome | Proportion/incidence rate % (95% CI) | $I^2$ % ($X^2$ *p*-value) | N. of studies |
|---|---|---|---|
| **Early outcomes** | | | |
| Bleeding | 12 (8-17) | 83 (<0.01) | 17 |
| Acute kidney injury | 15 (9-24) | 89 (<0.01) | 11 |
| Renal replacement therapy | 7 (3-15) | 63 (0.01) | 7 |
| Pacemaker implantation | 10 (6-16) | 75 (<0.01) | 13 |
| Respiratory complication | 15 (12-20) | 0 (0.56) | 7 |
| Stroke | 2 (1-4) | 74 (<0.01) | 9 |
| Wound infection | 3 (2-6) | 81 (<0.01) | 10 |
| **Late outcomes** | | | |
| Late mortality* | 6 (4-9) | 96 (<0.01) | 23 |
| Reintervention* | 2 (1-3) | 64 (<0.01) | 15 |
| Structural valve deterioration* | 3 (1-6) | 82 (<0.01) | 9 |
| Valve thrombosis* | 1 (0-2) | 49 (0.07) | 8 |
| Recurrence of TR ≥2* | 5 (2-13) | 85 (<0.01) | 4 |
| **Bioprostheses** | | | |
| Late mortality* | 6 (2-13) | 97 (<0.01) | 8 |
| Reintervention* | 1 (1-3) | 77 (<0.01) | 5 |
| Structural valve deterioration* | 3 (1-9) | 91 (<0.01) | 4 |
| Valve thrombosis* | 0 (0-1) | 68 (0.04) | 3 |
| Recurrence of TR ≥2* | 8 (5-13) | 33 (0.22) | 3 |

*per 100 person-years. CI: confidence interval; TR: tricuspid regurgitation

or surgical reinterventions, 3 (95% CI: 1-6) for structural valve deterioration, 1 (95% CI: 0-2) for valve thrombosis, and 5 (95% CI: 2-13) for the recurrence of moderate or greater TR **(Table 2)**.

## BIOPROSTHESES

A total of 14 studies reported outcome data for patients undergoing TVR with bioprostheses **(Supplementary Table 3)**. Late outcomes after bio-TVR differed from those observed in the overall cohort for a higher rate of significant TR recurrence (8 [95% CI: 5-13] per 100 person-years), with a similar incidence rate of mortality (6 [95% CI: 2-13] per 100 person-years) **(Table 2)**.

## SUBGROUP ANALYSIS AND META-REGRESSION

A subgroup analysis of the primary endpoint, stratifying for the operative period (i.e., before 1995 versus after 1995), found that the mortality rate of 18% (95% CI: 8-35) from the studies examining procedures performed before 1995 was greater than the 11% (95% CI: 8-14) obtained from operations carried out after that date **(Figure 3)**. However, the estimated mortality computed for the most recent studies was similar to the overall one. While investigating the influence of hospital locations (i.e., by continent) on operative mortality, the findings were consistent with the primary analysis, with no significant differences among the 3 subgroups (i.e., North America, Europe, Asia).

Meta-regression analysis detected a significant impact of previous cardiac surgery, liver disease, and the year of publication on the overall estimate of operative mortality **(Supplementary Table 4, Supplementary Figure 2)**. A trend for lower hospital mortality was apparent with increasing values of left ventricular ejection. Further meta-regression analyses found no significant interactions of baseline clinical and echocardiographic characteristics, risk of bias, endocarditis aetiology and the type of prosthetic valve with the primary endpoint rates.

## SENSITIVITY ANALYSES

The overall estimates of primary and secondary endpoints were computed excluding the studies with patients having an endocarditis aetiology of their tricuspid valve disease, and the results were consistent with the primary analysis for every investigated outcome **(Supplementary Table 5)**. Using fixed-effects models for the overall cohort, the only difference was in late mortality, whose estimate was mainly influenced by the study of Kundi et al[45] (19 [95% CI: 18-20] per 100 person-years) **(Supplementary Table 6)**. An alternative meta-analysis using a random intercept logistic-regression model was performed and resulted in similar results compared to the primary analysis **(Supplementary Figure 3)**. Leave-one-out random-effects meta-analyses were used to assess the absence of significant influential studies on the

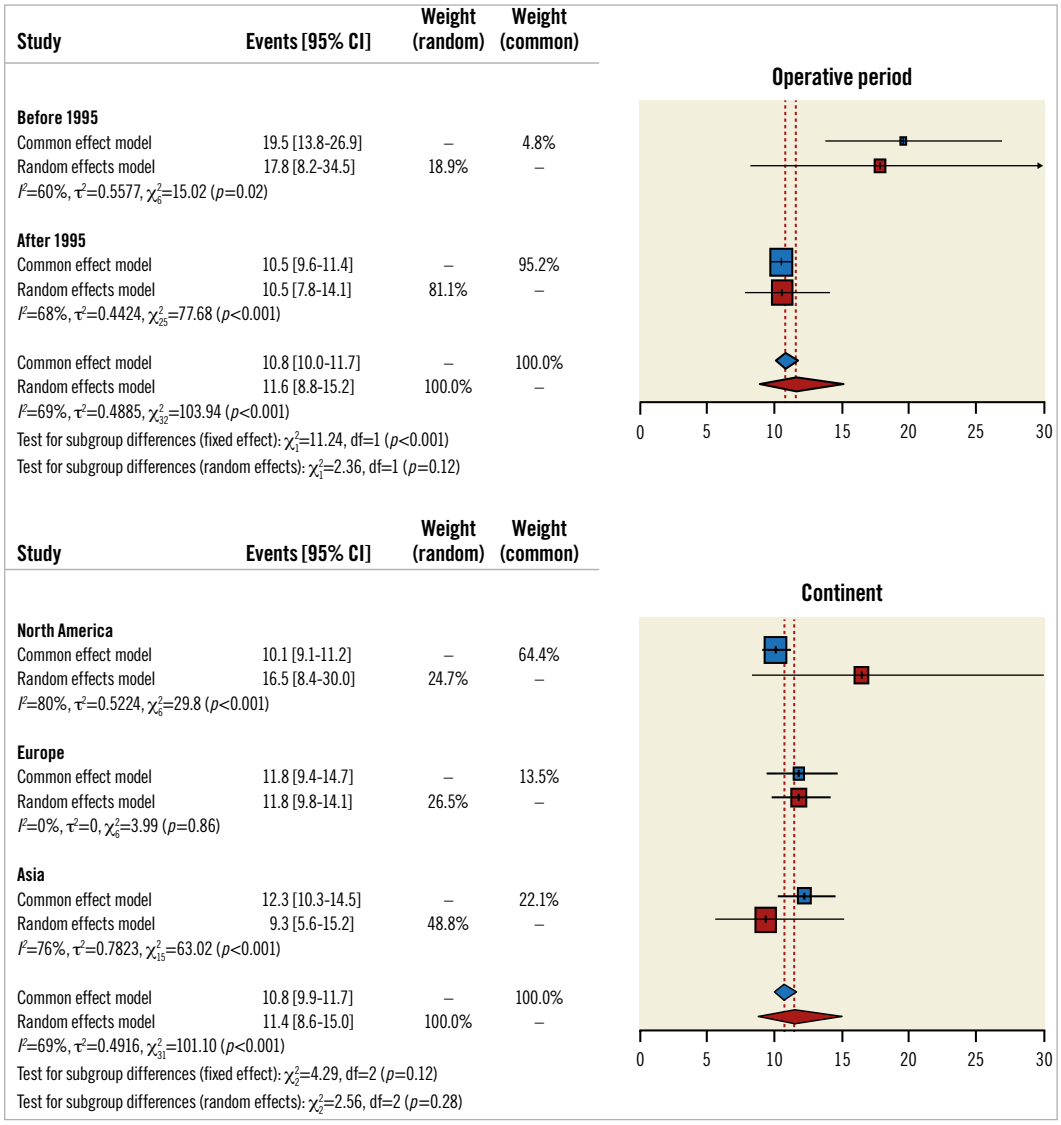


**Figure 3.** *Subgroup meta-analysis. Forest plot of subgroup meta-analysis investigating the impact of the operative period* and continent# on the primary endpoint. * The studies by Iscan et al and Di Mauro et al were excluded because of their operative period. #Africa (n=1) and Oceania (n=2) were excluded because of their underrepresentation. CI: confidence interval*

primary endpoint **(Supplementary Figure 4)**. A cumulative meta-analysis confirmed the higher rates of operative mortality for older studies **(Supplementary Figure 5)**.

## Discussion

This large systematic review and meta-analysis of 5,316 patients provides an overview of outcomes after isolated surgical TVR **(Central illustration)**. With the aim of guiding future perspectives in the development of transcatheter systems, there are several important takeaways from our study: 1) the overall operative mortality and the need for permanent pacemaker implantation in patients undergoing isolated TVR were 12% (95% CI: 9-15) and 10% (95% CI: 6-16), respectively; 2) long-term data concerning device durability deepen the knowledge regarding the extended efficacy of the bioprosthetic implantation on the TV; 3) providing the first systematic assessment of isolated TVR, this analysis gives critical insight and sets a benchmark for anticipated future TTVR trials.

Although no data restriction has been applied in the screening phase, a total of 35 studies throughout all the existing literature reported data on isolated surgical TVR. This limited amount of evidence is partially due to the considerable mortality rate of TV surgery[6]. The risk of treating these patients combined with the perception that TR has minimal prognostic impact are the reasons for the marked undertreatment of TR. However, recent evidence has demonstrated that untreated TR is associated with worse outcomes[1,2]. Moreover, the natural history of TV disease inexorably leads to progressive right heart failure (HF), resulting in excess mortality and recurrent hospitalisations. If we combine these adverse outcomes with the increasing prevalence of significant TR

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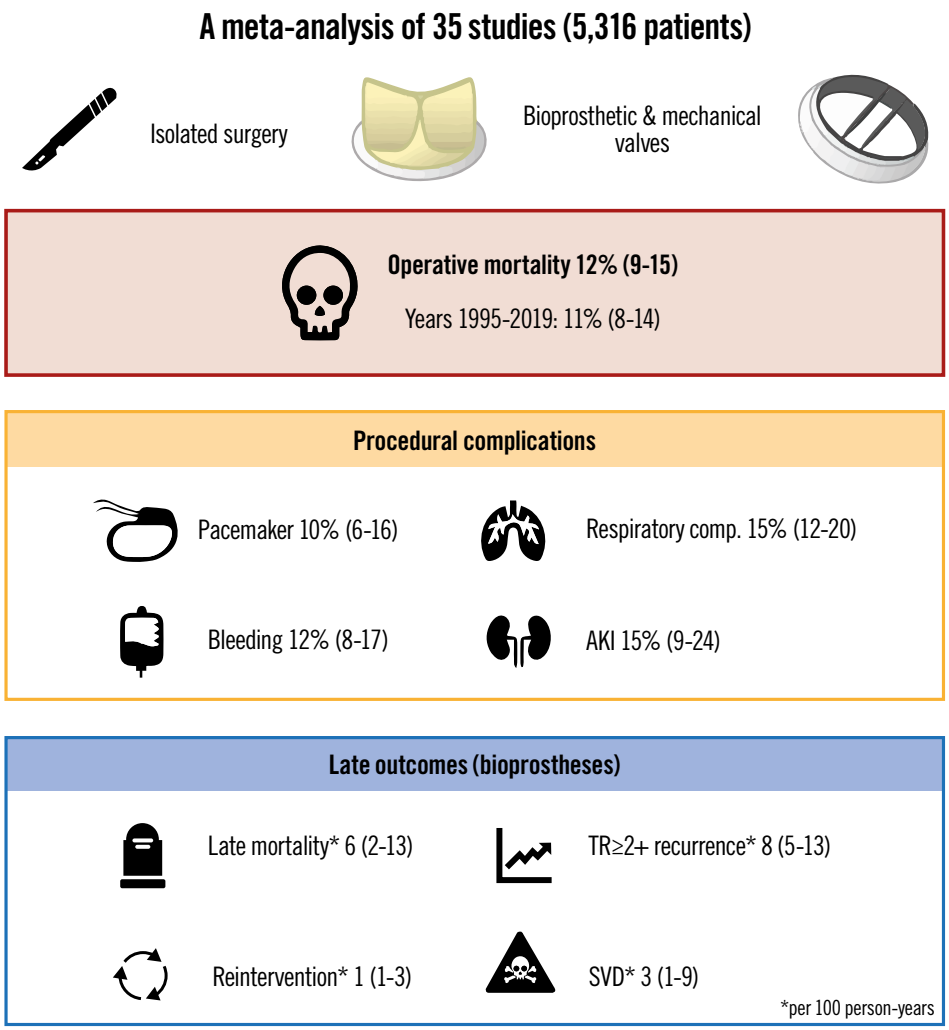
CENTRAL **ILLUSTRATION** Surgical outcomes of isolated tricuspid valve replacement.




*The 35 included studies investigated isolated surgical tricuspid valve replacement. The pooled outcomes for 5,316 patients are reported as proportions and incidence rates (late) with confidence intervals. AKI: acute kidney injury; SVD: structural valve deterioration; TR: tricuspid regurgitation*

in an ageing population, it is clear that we are facing an important public health problem.

The absence of evidence-based trial data, the heterogeneous nature of TV disease and the unknown ideal timing for surgery makes it difficult to provide concrete recommendations for TV surgery. Indeed, guideline recommendations are currently based upon expert opinions, with the strongest classes of recommendation assigned to cases undergoing left-sided valve surgery. Isolated TV surgery is reserved for patients with primary TR who have signs and symptoms of right-sided HF (IIa) or progressive right ventricular dilation or systolic dysfunction (IIb), and for patients with severe secondary TR who have signs and symptoms of right-sided HF with a poor response to medical therapy and annular dilation (IIa), or prior left-sided valve surgery and the absence of severe pulmonary hypertension or severe right ventricular dysfunction (IIb)[55].

Therefore, the aim of this study was to fill this critical gap. The use of bioprostheses is currently the preferred approach, with a growing trend[3], and constitutes an option for emerging TTVR systems. Despite this, the choice to include trials investigating TVR with mechanical valves was made on the basis of several factors. First, there is no impact of prosthetic valve selection on the surgical technique or the periprocedural medical therapy, such as the anticoagulation regimen. Indeed, the incidences of early outcomes were consistent when comparing the bioprosthetic-only group with the overall one, and no effects of valve type were detected on the primary endpoint **(Table 2, Supplementary Table 4)**. Second, the inclusion of

studies which did not discriminate between bioprosthetic and mechanical valves allowed us to provide more robust results. This is observed by the addition of 21 studies and 2,529 patients (regarding primary endpoint data) to the overall population, making this analysis the largest and most comprehensive assessment on isolated TVR to date.

## OPERATIVE MORTALITY

The overall estimated operative mortality was 12%, with a CI ranging from 9 to 15%. After the exclusion of studies with an operative period prior to 1995, the estimated operative mortality for the most recent ones (i.e., after 1995) was in line with the overall one previously reported (11% [95% CI: 8-14]). This finding identifies isolated TVR as having a considerable surgical risk even in recent times, especially when compared to the replacement of other cardiac valves.

Since high-risk patients with aortic valve disease are nowadays treated with the transcatheter solution, data from clinical trials report operative mortality rates for isolated surgical aortic valve replacement of 0.9-1.3% and 1.7-4.1%, for low- and intermediate-risk, respectively[56-59]. On the other hand, isolated mitral valve replacement in ~150,000 patients in US hospitals was found to have an operative mortality rate as low as 4%[60].

The discrepancy between right- and left-sided surgery might be explained by several concomitant factors. First, patients with TV diseases, especially in the case of secondary TR, present with poor functional classes and significant comorbidities, such as a long history of atrial fibrillation and pulmonary hypertension. Second, isolated TVR is usually performed after previous interventions, particularly on left-sided valves. Third, the timing is usually too late: right ventricular function is already impaired and associated with signs of advanced right HF such as liver dysfunction[3]. Indeed, even if hypothesis-generating, the results of the meta-regression analysis found a history of prior cardiac surgery and the presence of liver disease as having a significant impact on the overall estimate of operative mortality. These findings support the insights derived from both surgical and transcatheter TV procedures[61,62].

## EARLY OUTCOMES

The procedural complication rates shown in **Table 2**, in addition to operative mortality, contribute to the reluctance to perform an isolated TVR. While most are common to all major invasive cardiac interventions, the risk of having to implant a permanent pacemaker is typical of this surgery. Since the atrioventricular node is in close proximity to the septal leaflet of the TV, its manipulation can lead to trauma of the surrounding area with subsequent heart block. On the contrary, the risk of stroke could be related to other concomitant factors. Prosthetic valves are associated with thromboembolism, but due to the position of the TV this phenomenon would result mostly in pulmonary emboli, unlike left-sided valve replacements which would lead to strokes.

## LATE OUTCOMES FOR BIOPROSTHETIC TVR

The incidence rate of mortality after a bioprosthetic TVR was found to be 6 per 100 person-years in the random-effects model, and 22 per 100 person-years in the fixed-effects model **(Table 2, Supplementary Table 5)**. This discrepancy is due to the great heterogeneity among the studies, which, as a result of being observational, included populations with different characteristics that might have influenced this outcome. This is reflected in the discordance of existing literature on the role of TVR on survival. While some studies report an improved survival rate after TV surgery, even in patients with TR and congestive HF[63], others found no difference in long-term survival regardless of whether patients with isolated severe TR underwent surgery or medical therapy alone, after accounting for immortal time bias[64].

The recurrence of at least moderate TR in the follow-up was not negligible (8 [95% CI: 5-13] per 100 person-years). However, this was accompanied by a much lower rate of reintervention (1 [95% CI: 1-3] per 100 person-years). This could reasonably be due to the growing risk of an already very compromised population having to undergo further major cardiac surgery.

## FUTURE PERSPECTIVES

Epidemiological data show that secondary TR is the most prevalent aetiology in patients undergoing surgical interventions (92.6%) and the one with the lowest indication rates for surgical correction (53.2%)[65]. As a matter of fact, isolated TV surgery was performed only in 5% of patients included in the EuroSCORE II database[66].

In this context, emerging percutaneous procedures appear to be an attractive solution for this substantial unmet clinical need. However, in order to advance TTVR technology, clinical researchers and regulatory bodies need comparative data from surgical isolated TVR. Our results provide a comprehensive extraction of published data surrounding isolated TVR. Results of either mechanical or bioprosthetic TVR are applicable to early outcomes, while results from only bioprosthetic TVR can be used for insight into TTVR durability studies. Among all TVR, the outcome data for operative mortality and permanent pacemaker implantation, critical outcomes of interest in the development of TTVR devices, should be set as the thresholds for outcomes to be utilised in prospective TTVR trials.

Of note, patients undergoing surgical TVR were relatively young (mean age 53 years), with good left ventricular function (mean ejection fraction 58%), and with few comorbidities, such as diabetes (13%), hypertension (23%), or liver disease (31%). These figures underline a selection bias in the surgical series, which include only patients deemed at an acceptable surgical risk and exclude the most advanced population. This warrants precaution when generalising the results of this meta-analysis to extreme-risk patients, such as those treated in compassionate-use studies of pioneering TTVR devices[7–9]. However, despite the baseline risk profile of patients and the absence of an appropriate learning curve, the outcomes observed in these studies are promising. As soon as

further data proves TTVR to be efficacious and acceptably safe, it will be possible to push even more in favour of this technology. For this purpose, having an in-depth knowledge of surgical TVR, with its results and pitfalls, is essential for a rigorous evaluation and to promote those developing percutaneous therapies by serving as the legitimate benchmark.

## Limitations

The results of the present meta-analysis have to be interpreted whilst acknowledging the following limitations. Since no randomised controlled trials investigated surgical TVR, all the included studies were observational and, thus, susceptible to error regarding patient selection and characteristics. As such, the results were affected by significant degrees of heterogeneity and should be interpreted according to their range distribution rather than point estimates. This is a study-level meta-analysis, and its findings are average pooled rates. The computation of person-years at risk was performed using study-level follow-up time when no data on the dropout date or number of days were available. Since a patient-level analysis for these 35 studies was not feasible, meta-regression analyses tested study-level characteristics, and their results should be considered as hypothesis-generating. The population was heterogeneous in terms of TV disease aetiologies, prior cardiac surgeries, and surgical experience or hospital operating volume. However, given the paucity of published evidence, the findings of this meta-analysis depict the full spectrum of patients undergoing isolated TVR.

## Conclusions

This systematic review and meta-analysis provides an overview of the early and late outcomes after isolated surgical TVR. The results can support patients and doctors in the clinical decision-making for TVR and may serve as a benchmark for developing percutaneous therapies.

## Impact on daily practice

Transcatheter tricuspid valve replacement (TTVR) is rapidly emerging as a therapeutic option amongst patients with secondary tricuspid regurgitation. The findings of this meta-analysis can support the clinical decision-making for tricuspid valve replacement (TVR) and may set the threshold for outcomes to be utilised in prospective TTVR trials. Surgical long-term TVR data may serve as a benchmark for developing TTVR systems. Late outcomes may inform on the bioprosthetic durability of the tricuspid valve.

## Conflict of interest statement

The authors have no conflicts of interest relevant to the contents of this paper to disclose.

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## Supplementary data

**Supplementary Appendix 1.** PRISMA checklist.
**Supplementary Appendix 2.** MOOSE reporting checklist.
**Supplementary Appendix 3.** Database search results.
**Supplementary Appendix 4.** Definitions.
**Supplementary Table 1.** Baseline characteristics of included patients.
**Supplementary Table 2.** Risk of bias assessment – observational studies.
**Supplementary Table 3.** Key study features – bioprosthetic tricuspid valve replacement.
**Supplementary Table 4.** Meta-regression analysis.
**Supplementary Table 5.** Early and late outcomes – no endocarditis.
**Supplementary Table 6.** Early and late outcomes – fixed effects models.
**Supplementary Figure 1.** Funnel plot and Baujat plot.
**Supplementary Figure 2.** Bubble plots for meta-regression analysis.
**Supplementary Figure 3.** Meta-analysis using a random intercept logistic regression model.
**Supplementary Figure 4.** Leave-one-out meta-analysis.
**Supplementary Figure 5.** Cumulative meta-analysis.

*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00442*

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# Impact of right ventricular-pulmonary arterial coupling on clinical outcomes of tricuspid regurgitation

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**KEYWORDS**

- mitral regurgitation
- mitral valve repair
- risk stratification
- tricuspid disease

## Abstract

**Background:** In terms of pathophysiology, tricuspid regurgitation (TR) and right ventricular (RV) function are linked to each other.

**Aims:** This study sought to evaluate RV-pulmonary artery (PA) coupling and its impact on clinical outcomes of TR in patients undergoing mitral transcatheter edge-to-edge repair (TEER).

**Methods:** We calculated RV-PA coupling ratios in patients undergoing mitral TEER from August 2010 to March 2019 by dividing the tricuspid annular plane systolic excursion (TAPSE) by the echocardiographic estimated PA systolic pressure (PASP). TR was graded as none/trace, mild, moderate, or severe. The primary outcome was all-cause mortality or rehospitalisation within 12 months.

**Results:** Among 744 patients analysed, severe TR was documented in 22.3% of patients and the mean TAPSE/PASP was 0.43±0.25. Technical success of TEER was achieved in 97.2% of participants. Severe TR vs TR ≤moderate (adjusted HR 1.92, 95% CI: 1.39-2.66) and TAPSE/PASP (adjusted HR 0.45, 95% CI: 0.22-0.93) were associated with the outcome. Patients were divided according to the TAPSE/PASP tertile. Compared to patients with TR ≤moderate, patients with severe TR had a higher event rate (TAPSE/PASP <0.30: 32.9% vs 45.1%; 0.30≤ TAPSE/PASP <0.44: 27.8% vs 41.8%; TAPSE/PASP ≥0.44: 16.0% vs 40.4%), whereas the prognostic significance of TR was attenuated in patients with reduced TAPSE/PASP (i.e., RV-PA uncoupling; interaction term p=0.03). The trends were consistent in the multivariable regression models, spline curves, and sensitivity analysis using post-interventional parameters.

**Conclusions:** RV-PA coupling affects the outcome correlation of TR in patients undergoing mitral TEER. The prognostic impact of TR is attenuated in patients with RV-PA uncoupling.

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## Abbreviations

| | |
|---|---|
| **CI** | confidence interval |
| **HR** | hazard ratio |
| **IQR** | interquartile range |
| **LV** | left ventricular |
| **MR** | mitral regurgitation |
| **PA** | pulmonary artery |
| **PASP** | pulmonary arterial systolic pressure |
| **RV** | right ventricular |
| **SD** | standard deviation |
| **TAPSE** | tricuspid annular plane systolic excursion |
| **TEER** | transcatheter edge-to-edge repair |
| **TR** | tricuspid regurgitation |

## Introduction

Tricuspid regurgitation (TR) is a highly prevalent disease in ageing societies[1]. TR commonly accompanies mitral regurgitation (MR), and functional TR is caused by pulmonary hypertension, right ventricular (RV) remodelling, and tricuspid annular dilatation[1]. Despite the development of therapeutic options for MR, previous studies collectively have shown that TR has a substantial impact on prognosis following transcatheter edge-to-edge repair (TEER) for MR[2,3]. In terms of pathophysiology, TR and RV function are tightly linked to each other. RV longitudinal elongation and spherical deformation lead to subsequent tricuspid leaflet tethering and the development of TR[4]. However, it remains uncertain whether TR contributes alone to the dismal outcome of TEER for MR or acts in conjunction with RV function. More specifically, RV function may interact with the prognostic impact of TR.

RV function can non-invasively be assessed by 2D Doppler echocardiography. Moreover, RV to pulmonary artery (RV-PA) coupling refers to the relationship between RV systolic function and RV afterload. Studies evaluating the RV-PA coupling in patients undergoing TEER for MR have shown that a lower tricuspid annular plane systolic excursion / pulmonary arterial systolic pressure (TAPSE/PASP), which reflects RV-PA uncoupling, was associated with adverse outcomes[5-7]. Despite the fact that TR and impaired RV systolic function often coexist[5], no published studies have examined the hypothesis that the clinical relevance of TR changes according to RV function, which would be fundamental in providing optimal therapeutic strategies for each individual. In the present study, we tested the hypothesis that the prognostic impact of TR may change according to RV-PA coupling.

## Methods

### STUDY SETTING AND DESIGN

The present analysis is based on data from the Rhineland registry, which is a prospective, multicentre, consecutive collection of patient information from three centres in Germany (Bonn, Cologne, Düsseldorf). We reviewed patients who underwent TEER with the MitraClip system (Abbott) to treat MR from August 2010 to March 2019. All patients suffered from symptomatic MR and were deemed either as ineligible or high risk for conventional surgery. For the purpose of the present analysis, patients were excluded if they had an absence of echocardiographic data within a time window of three months prior to TEER or if the baseline echocardiography was not adequate for the assessment of right ventricular function and tricuspid regurgitation. The study protocol was approved by the ethics committee of each centre. All patients provided written informed consent.

### ASSESSMENT OF TRICUSPID REGURGITATION

All study participants underwent transthoracic echocardiography. The acquired images were evaluated by board-certified cardiologists at each centre's echo laboratory. In the case of atrial fibrillation, three consecutive heartbeats were averaged to give an accurate measurement of the echocardiographic parameters. The assessment and grading of TR severity were based on both qualitative and quantitative parameters, as recommended in the guidelines[8,9]. The degree of TR was graded as follows: none/trace, mild, moderate, and severe. The vena contracta, effective regurgitant orifice area and regurgitant volume were also measured by proximal isovelocity surface area methods at baseline.

### ASSESSMENT OF RIGHT VENTRICULAR FUNCTION

We assessed RV-PA coupling by calculating the TAPSE/PASP ratio[10]. Both parameters were routinely recorded in the echocardiography studies at each centre. TAPSE was measured by using M-mode echocardiography with the cursor aligned on the tricuspid lateral annulus in the apical four-chamber view. TR pressure gradient was estimated from the peak velocity of the TR jet by utilising the simplified Bernoulli equation. The PASP was then calculated by adding the estimated right-atrial pressure according to the dimension of the inferior vena cava and its respiratory change. Additionally, RV fractional area change (RVFAC) <35% was calculated as [RV end-diastolic area – RV end-systolic area] / RV end-diastolic area ×100[8].

### CLINICAL OUTCOMES

The primary endpoint was a composite of mortality and heart failure rehospitalisation within 12 months after TEER. We also assessed each outcome separately. Clinical follow-up data were obtained through standardised interviews at scheduled hospital visits, telephone interviews with the patient's family, or documentation from the referring general practitioners. Acute technical success of TEER was defined according to the Mitral Valve Academic Research Consortium guidelines[11].

### STATISTICAL ANALYSIS

Continuous variables are reported as the mean±standard deviation (SD) or as medians and interquartile ranges (IQR), while categorical variables are reported as the number (percentage). The study population was divided into three groups according to tertiles of TAPSE/PASP. Continuous variables were compared using the one-way analysis of variance or Kruskal-Wallis tests. The chi-square test was applied to compare categorical variables. The Tukey's

honestly significant difference test was used to adjust for multiple testing between the groups. We also created receiver operating characteristic curves of TAPSE and TAPSE/PASP for predicting the primary endpoint.

To examine the study inference, we performed the following analyses. First, we fitted a Cox proportional hazard model to test the clinical significance of severe TR for the outcomes. The models were adjusted for age, sex, atrial fibrillation, coronary artery disease, estimated glomerular filtration rate, logistic EuroSCORE, New York Heart Association Functional Class, left ventricular (LV) ejection fraction, severity of MR, and TAPSE/PASP[5,10,12]. Hazard ratios (HR) and 95% confidence intervals (95% CI) were determined. Second, we depicted spline curves for the outcome correlation of TR across TAPSE/PASP. Third, an interaction term analysis was performed. Additionally, we conducted a mediation analysis using severe TR as an exposure and TAPSE/PASP as a mediator, which could elucidate the direct and indirect effects of TR.

To examine the robustness of our inference, we conducted several sensitivity analyses. We repeated these analyses for the post-procedural TR. Covariables for the adjustment were the aforementioned parameters measured after the procedure. Also, we applied RVFAC/PASP as RV function and depicted spline curves for the outcome correlation of TR across RVFAC/PASP.

Two-tailed p values <0.05 were considered statistically significant. All statistical analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing) and Stata 15.1 (StataCorp).

## Results

### POPULATION

A total of 744 patients were included in the analysis **(Table 1)**. The mean age was 77±9 years, and 414 (55.7%) were female. The participants exhibited a high logistic EuroSCORE (18.1% [IQR 10.1-31.1%]) and reduced LV ejection fraction (44.5±15.3%). Severe TR was documented in 166 (22.3%) patients. The mean TAPSE was 17.9±5.1 mm, PASP was 48.3±16.8 mmHg, and the TAPSE/PASP ratio was 0.43±0.25 **(Supplementary Figure 1)**. The median time from baseline echocardiography to TEER was 24 days (IQR 5-46 days) in the present analysis. Acute technical success was achieved in 97.2% of study participants.

### CLINICAL OUTCOMES

During a median follow-up of 18 months (IQR 8-30 months), 100 patients died and 121 patients were hospitalised due to heart failure, and the primary outcome occurred in 196 patients within 12 months. In the univariable Cox proportional hazard model, severe TR in comparison to TR ≤moderate was associated with an increased risk of the primary outcome (unadjusted HR 1.91, 95% CI: 1.41-2.59; p<0.001) **(Table 2)**. The association remained significant (adjusted HR 1.92, 95% CI: 1.39-2.66; p<0.001) after adjusting for the predefined covariates. As for the primary endpoint, severe TR was associated with the increased risk of mortality (adjusted HR 2.15, 95% CI: 1.37-3.38; p<0.001) and rehospitalisation due to heart failure (adjusted HR 1.66, 95% CI: 1.08-2.54; p=0.02) **(Table 2)**. Additionally, in the multivariable Cox proportional hazard model, the TAPSE/PASP ratio was independently associated with the primary endpoint (adjusted HR 0.45, 95% CI: 0.22-0.93; p=0.031) **(Figure 1, Supplementary Table 1)**. The receiver operating characteristics curve analyses of TAPSE and TAPSE/PASP for predicting outcomes are depicted in **Supplementary Figure 2**.

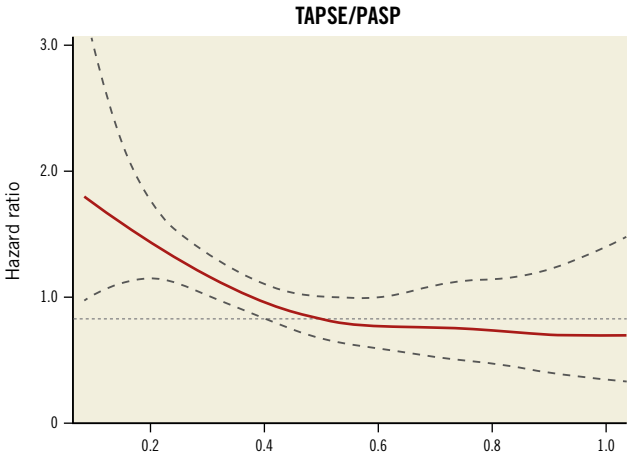


**Figure 1.** *Spline curve for the hazard ratio of TAPSE/PASP. A spline curve for the relationship between TAPSE/PASP and its hazard risk is shown. A linear association was observed: a reduced TAPSE/PASP (i.e., RV-PA uncoupling) was associated with an increased hazard for mortality or heart failure hospitalisation. The association was static if TAPSE/PASP was larger than approximately 0.5. PASP: pulmonary artery systolic pressure; RV-PA: right ventricular-pulmonary artery; TAPSE: tricuspid annular plane systolic excursion*

### BASELINE CHARACTERISTICS ACCORDING TO TAPSE/PASP TERTILE

Patients were divided according to TAPSE/PASP **(Table 1)**: tertile 1, TAPSE/PASP <0.30 (n=233); tertile 2, 0.30 ≤TAPSE/PASP <0.44 (n=244); tertile 3, TAPSE/PASP ≥0.44 (n=267). Patients in the first tertile were more likely to exhibit comorbidities (coronary artery disease, history of cardiac surgery, and higher NT-pro-BNP and logistic EuroSCORE values) compared with patients in the second or third tertile. Moreover, patients in the first tertile had a significantly reduced LV ejection fraction. The severity of TR differed significantly across the groups **(Supplementary Figure 3)**.

### CLINICAL IMPACT OF TRICUSPID REGURGITATION IN RELATION TO RV FUNCTION

Kaplan-Meier curves of each tertile are depicted in **Figure 2**. Compared to patients with TR ≤moderate, patients with severe TR showed a significantly higher outcome incidence in the second tertile (27.8% vs. 41.8%, p=0.03) and in the third tertile (16.0% vs. 40.4%, p<0.001), whereas the difference did not reach statistical

**Table 1. Baseline characteristics according to TAPSE/PASP.**

| | All n=744 | TAPSE/PASP | | | |
|---|---|---|---|---|---|
| | | Tertile 1 n=233 | Tertile 2 n=244 | Tertile 3 n=267 | *p*-value |
| **Demographic parameters** | | | | | |
| Age, years | 77±9 | 77±9 | 77±9 | 78±8 | 0.31 |
| Sex female, n (%) | 414 (55.7) | 141 (60.5) | 137 (55.9) | 136 (50.9) | 0.10 |
| Body surface area, $m^2$ | 1.87±0.22 | 1.84±0.24 | 1.88±0.22 | 1.86±0.29 | 0.30 |
| Hypertension, n (%) | 581 (78.1) | 179 (76.8) | 203 (83.2) | 199 (74.5) | 0.049 |
| Diabetes mellitus, n (%) | 222 (29.8) | 77 (33.0) | 80 (32.8) | 65 (24.3) | 0.048 |
| Coronary artery disease, n (%) | 61.4 (457) | 158 (67.8) | 153 (62.7) | 146 (54.7) | 0.009 |
| Atrial fibrillation, n (%) | 505 (67.9) | 154 (66.4) | 171 (70.1) | 181 (67.8) | 0.68 |
| Prior pacemaker/ICD/CRT, n (%) | 288 (38.7) | 98 (42.1) | 100 (41.0) | 90 (33.7) | 0.11 |
| Prior cardiac surgery, n (%) | 206 (27.7) | 90 (38.6) | 72 (29.5) | 44 (16.5) | <0.001 |
| NT-pro-BNP, pg/ml | 2971 [1525, 6345] | 4295* [2225, 8958] | 2932 [1773, 6115] | 1972 [949, 4517] | <0.001 |
| Estimated GFR, ml/min/$1.73m^2$ | 47.5±20.6 | 46.3±21.3 | 48.5±19.8 | 47.6±20.8 | 0.48 |
| Logistic EuroSCORE, % | 22.1 [10.1, 31.1] | 22.1* [13.3, 39.4] | 17.4* [10.6, 28.7] | 13.2* [8.1, 24.9] | <0.001 |
| NYHA III/IV, n (%) | 604 (81.2) | 193 (83.2) | 200 (82.0) | 211 (79.0) | 0.47 |
| **Echocardiographic parameters** | | | | | |
| LV ejection fraction, % | 44.5±15.3 | 40.1±15.2* | 44.7±15.3* | 48.2±14.4* | <0.001 |
| LV end-diastolic volume, ml | 143.8±69.3 | 150.7±66.4 | 141.0±60.0 | 142.7±76.5 | 0.26 |
| LV end-systolic volume, ml | 86.0±57.5 | 95.4±57.7$^{\$}$ | 84.2±52.1 | 79.4±61.4 | 0.007 |
| LA volume, ml | 107.8±61.3 | 118.1±75.6$^{\$}$ | 108.1±55.2 | 98.7±51.3 | 0.004 |
| Functional MR, n (%) | 430 (57.8) | 151 (64.8) | 144 (59.0) | 135 (50.6) | 0.005 |
| MR moderate-to-severe/severe, n (%) | 634 (85.2) | 192 (84.6) | 205 (84.7) | 237 (88.8) | 0.29 |
| TAPSE/PASP | 0.43±0.25 | 0.23±0.05* | 0.36±0.04* | 0.67±0.28* | <0.001 |
| PASP, mmHg | 48.3±16.8 | 63.3±15.3* | 48.6±10.6* | 34.8±10.3* | <0.001 |
| TAPSE, mm | 17.9±5.1 | 14.2±3.6* | 17.6±4.0* | 21.3±4.9* | <0.001 |
| RV fractional area change, % | 38.2±11.9 | 33.5±11.5* | 37.8±11.1* | 42.6±11.4* | <0.001 |
| RV end-diastolic area, $mm^2$ | 21.3±7.6 | 22.8±7.4$^{\$}$ | 21.5±7.2 | 20.0±7.8 | <0.001 |
| **Procedural parameters** | | | | | |
| Number of clips implanted | 1.5±0.6 | 1.5±0.6 | 1.4±0.6 | 1.5±0.7 | 0.15 |
| Post-procedural MR ≤moderate | 684 (91.9) | 215 (92.3) | 222 (91.0) | 247 (92.5) | 0.80 |
| Post-procedural transmitral pressure gradient, mmHg | 3.9±1.8 | 3.7±1.8 | 4.0±1.8 | 3.9±1.7 | 0.12 |

*$p<0.05$ vs All by Tukey's test. $^{\$}p<0.05$ vs Tertile 3 by Tukey's test. CI: confidence interval; CRT: cardiac resynchronisation therapy; GFR: glomerular filtration ratio; HR: hazard ratio; ICD: intracardiac defibrillator; LA: left atrial; LV: left ventricular; MR: mitral regurgitation; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation

significance in the first tertile (32.9% vs. 45.1%, p=0.11). **Table 2** lists the multivariable-adjusted HRs of severe TR in each tertile. The association of TR with the primary outcome was pronounced in the second tertile (adjusted HR 1.88, 95% CI: 1.05-3.36; p=0.033) and third tertile (adjusted HR 3.39, 95% CI: 1.79-6.43; p<0.001), while the association was attenuated in the first tertile (adjusted HR 1.58, 95% CI: 0.92-2.70; p=0.10; interaction term p=0.03). The trend was also observed in the fitting spline curves **(Figure 3)**. The prognostic impact of TR was attenuated in patients with reduced TAPSE/PASP, which was consistently observed regardless of the TR grade (i.e., moderate, severe). With a limited sample size, the trend was consistent for mortality and rehospitalisation due to heart failure **(Table 2)**. Furthermore, **Supplementary Figure 4** depicts the spline curve showing the outcome correlation of TR across RVFAC/PASP. Similar to the main analysis, the association of TR with outcome was attenuated with lower RVFAC/PASP.

Additionally, a summary of the mediation analysis is presented in **Supplementary Table 2**. There was a significant direct effect of TR on the outcome, whereas the indirect effect of TR mediated by TAPSE/PASP was not significant.

**Table 2. Association of severe TR with clinical outcomes after mitral TEER.**

| Severe TR vs moderate or less TR | Multivariable adjusted HR (95% CI) | | | |
|---|---|---|---|---|
| | All cohort | Tertile 1 | Tertile 2 | Tertile 3 |
| Primary endpoint | 1.92 (1.39-2.66) | 1.58 (0.92-2.70) | 1.88 (1.05-3.36) | 3.39 (1.79-6.43) |
| All-cause mortality | 2.15 (1.37-3.38) | 1.79 (0.76-4.18) | 2.69 (1.30-5.56) | 2.80 (1.18-6.64) |
| Rehospitalisation due to heart failure | 1.65 (1.08-2.54) | 1.49 (0.79-2.81) | 0.95 (0.36-2.48) | 3.82 (1.61-9.08) |

The models were adjusted for age, sex, atrial fibrillation, coronary artery disease, estimated glomerular filtration rate, logistic EuroSCORE, New York Heart Association Functional Class, LV ejection fraction, MR, and TAPSE/PASP. CI: confidence interval; HR: hazard ratio; LV: left ventricular; TEER: mitral transcatheter edge-to-edge repair; TR: tricuspid regurgitation

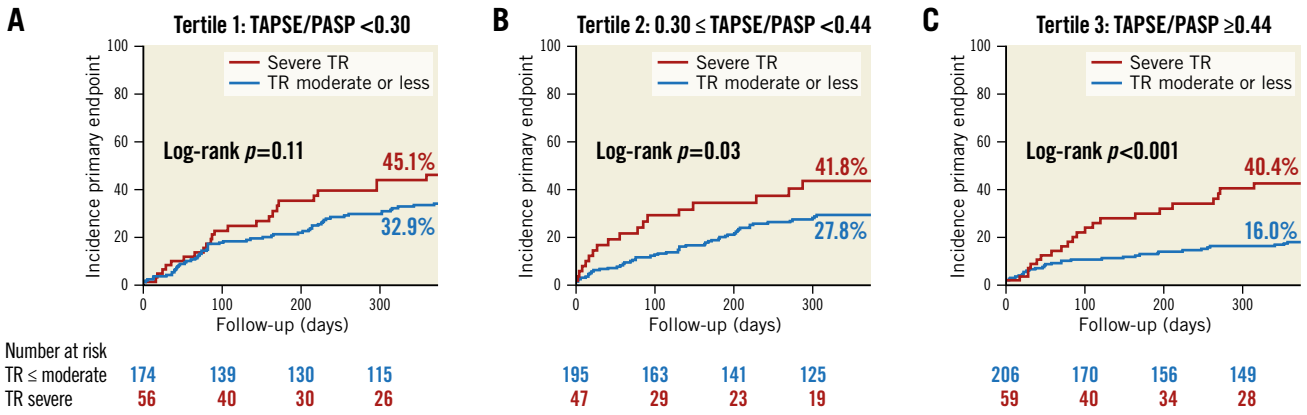


**Figure 2.** *Cumulative incidence of composite outcome between patients with severe TR and TR moderate or less. In the second and third tertile, patients with severe TR had a higher incidence of the primary endpoint than patients with TR moderate or less. Although the association was also observed in the first tertile, the difference did not reach statistical significance. PASP: pulmonary artery systolic pressure; RV-PA: right ventricular-pulmonary artery; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation*

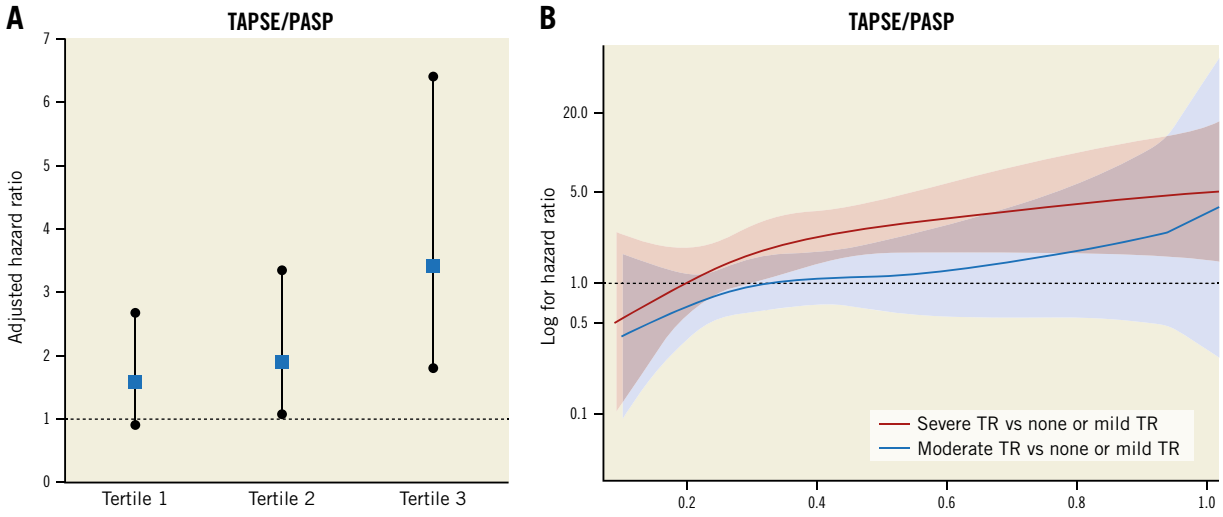


**Figure 3.** *Prognostic impact of TR according to TAPSE/PASP. Forest plot of adjusted HR for TR against the outcome in multivariable regression (A) revealed that the association of TR with outcomes was pronounced in the third tertile (i.e., patients with increased TAPSE/PASP) but attenuated in the first tertile (i.e., patients with decreased TAPSE/PASP). The interaction was also observed in the spline curves depicting the hazard risk of TR according to TAPSE/PASP (B). In addition, the HR of severe TR (red line) was greater than that of moderate TR (blue line), implying that the risk is higher with a higher grade of TR. HR: hazard ratio; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation*

### CORRELATION OF OUTCOME TO TRICUSPID REGURGITATION AFTER TEER

After the procedure, data from 637 patients (85.6%) were available to reassess TAPSE/PASP values. Mean TAPSE/PASP was 0.55±0.37, with a significant increase from baseline (p<0.001). Of these, 149 (23.4%) patients had post-procedural severe TR. MR reduction to moderate or less was achieved in 91.9% of patients, with 66.3% of patients having mild or less MR at discharge. In the multivariable model, after adjusting for the predefined baseline and post-procedural covariates **(Supplementary Table 3)**, post-procedural severe TR was associated with an increased risk of the primary endpoint (adjusted HR 1.86, 95% CI 1.25-2.77; p=0.002), which was mainly driven by all-cause mortality (adjusted HR 2.35, 95% CI: 1.38-3.99; p=0.002) **(Table 3)**. With a limited sample size, a similar association was observed for rehospitalisation due to heart failure (adjusted HR 1.56, 95% CI: 0.91-2.70; p=0.11). The association was also examined according to tertile of post-procedural TAPSE/PASP: tertile 1, TAPSE/PASP <0.37 (n=206); tertile 2, 0.37≤ TAPSE/PASP <0.56 (n=217); tertile 3, TAPSE/PASP ≥0.56 (n=214). Similar to the main analysis, the prognostic impact of TR was pronounced in patients with increased TAPSE/PASP but attenuated in those with decreased TAPSE/PASP (interaction term p=0.03) **(Table 3, Figure 4)**.

## Discussion

The present study investigated the prognostic impact of TR according to RV-PA coupling in patients undergoing mitral TEER. The main findings can be summarised as follows:

1. Severe TR was associated with mortality and rehospitalisation due to heart failure within 12 months after TEER for MR.
2. The prognostic impact of TR varied according to TAPSE/PASP: the association was pronounced in patients with a high TAPSE/PASP ratio but attenuated in patients with a low TAPSE/PASP (i.e., RV-PA uncoupling).
3. These findings were consistent across different statistic assumptions, including the analysis using the measurements after TEER.

TR is a common valvular heart disease, with 0.55% of the general population having moderate or severe TR[1]. In terms of pathophysiology, TR, RV dysfunction, and pulmonary hypertension are linked to each other. In patients with MR, longstanding elevated

**Table 3. Association of post-procedural severe TR with clinical outcomes after the procedure.**

| Postprocedural severe TR vs moderate or less TR | Multivariable adjusted HR (95% CI) | | | |
|---|---|---|---|---|
| | All cohort | Tertile 1 | Tertile 2 | Tertile 3 |
| Primary endpoint | 1.86 (1.25-2.77) | 1.47 (0.82-2.62) | 2.04 (0.83-4.99) | 2.68 (1.26-5.69) |
| All-cause mortality | 2.35 (1.38-3.99) | 1.89 (0.88-4.08) | 1.98 (0.59-6.64) | 3.58 (1.27-10.1) |
| Rehospitalisation due to heart failure | 1.56 (0.91-2.70) | 0.96 (0.42-2.22) | 1.82 (0.47-7.03) | 2.94 (1.19-7.29) |

The models were adjusted for age, sex, atrial fibrillation, coronary artery disease, estimated glomerular filtration rate, logistic EuroSCORE, New York Heart Association Functional Class, post-procedural LV ejection fraction, post-procedural MR, and post-procedural TAPSE/PASP.
CI: confidence interval; HR: hazard ratio; TR: tricuspid regurgitation

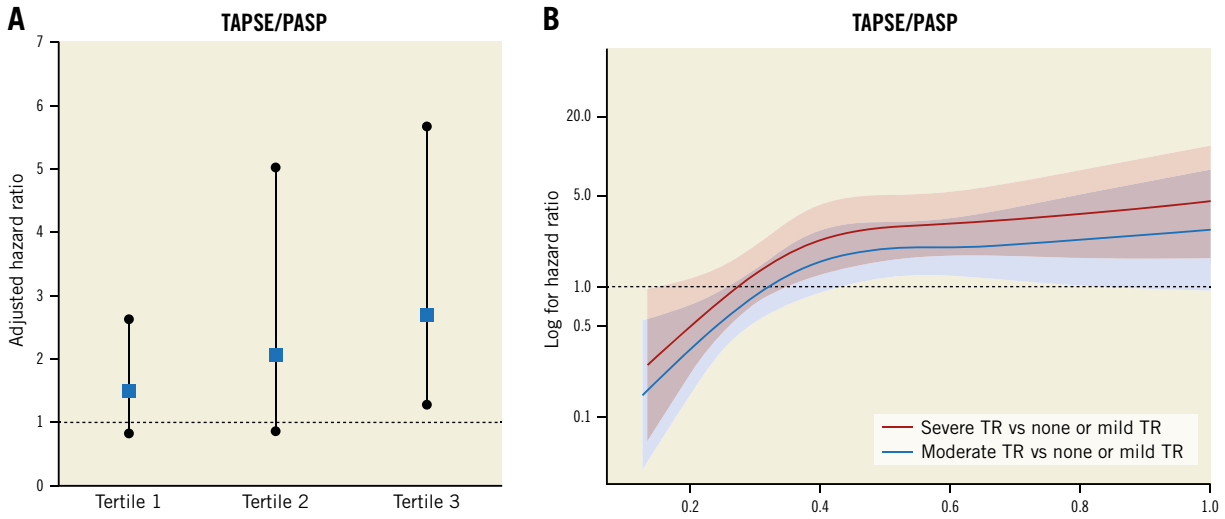


**Figure 4.** *Impact of post-procedural TR on outcomes according to TAPSE/PASP. Similar to the main analysis, there was a significant interaction between outcome of TR and TAPSE/PASP (A). The prognostic impact of TR was attenuated as TAPSE/PASP decreased. The trend was seen in the spline curve analysis, depicting the HR of severe TR (red line) and that of moderate TR (blue line) (B). HR: hazard ratio; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation*

pulmonary arterial pressure may result in RV longitudinal elongation and spherical deformation, which lead to subsequent tricuspid leaflet tethering and the development of TR[4]. Also, TR leads to a persistent volume overload for the RV and advances the impairment of RV function. However, it remains uncertain whether TR contributes alone to the dismal outcome or acts in conjunction with RV function.

Our study cohort consisted of patients undergoing TEER for MR, wherein 22.3% of the participants showed severe TR before the intervention. The prevalence of TR was comparable to earlier results (14.0% to 21.8%)[13,14]. Furthermore, a reduction in MR to moderate or less was achieved in 91.9% of patients, with 66.3% of patients having mild or less MR at discharge. This rate was comparable to earlier studies but slightly lower than what was reported in most recent investigations of the latest iteration of TEER devices[15-17]. Since the severity of MR may affect the study inference, a sensitivity analysis was conducted using the post-procedural covariables.

For the assessment of RV function, we used the concept of RV-PA coupling assessed by TAPSE/PASP. The concept has been initially valid for patients with pulmonary hypertension[18] but has also recently been applied to various patient cohorts[7,19-22]. The coupling of this measurement indicates that RV systolic function can compensate for an increased afterload (i.e., pulmonary artery pressure). In contrast, a decreased TAPSE/PASP, namely RV-PA uncoupling, suggests that RV systolic function cannot compensate for the afterload. More recently, Brener et al and Karam et al have collectively reported that RV-PA coupling was a strong predictor of outcomes in patients with heart failure and MR[5,7]. However, little is known about the interaction of the clinical impact of RV-PA coupling and TR, despite their pathophysiological interaction.

In the present study, TR was associated with the risk of mortality or hospitalisation due to heart failure, but the outcome correlation of TR changed according to RV-PA coupling assessed by TAPSE/PASP. The prognostic impact of TR was more pronounced in patients with increased TAPSE/PASP (i.e., RV-PA coupling) but attenuated in patients with reduced TAPSE/PASP (i.e., RV-PA uncoupling). The finding was consistent both at baseline and after the procedure. Also, a spline curve shows the interaction between the prognostic impact of TR and TAPSE/PASP. One of the contributing factors to the interaction between TR and TAPSE/PASP could be that a severely impaired RV function can worsen clinical prognosis[5]. Lurz et al reported that decreased TAPSE/PASP remained to be an independent factor associated with outcomes after a transcatheter treatment for TR[10], implying that severely impaired RV function might be a predominant prognostic factor in those populations. Another possible explanation for the interaction might be a mediation effect by RV function. Concomitant impaired RV function may mediate the prognostic impact of TR. However, our mediation analysis did not find a significant mediation effect of TR, through RV function, that was linked to the outcomes. Also, concomitant cardiac comorbidities (e.g., impaired LV systolic function or the presence of coronary artery disease) may play an essential role as risk indicators of the outcome[23], which might lower the clinical significance of TR.

Our findings do not entirely align with previous knowledge. A cohort study investigating patients with reduced LV ejection fraction reported that the outcome correlation with TR remained significant even after adjusting for RV dysfunction as a categorical variable[12]. Their study was conducted in the early 2000s, implying that the guideline-directed medical therapies differed from the current cohort. A large observational study reported that the prognostic impact of severe TR in patients with degenerative MR was irrespective of the presence of RV dysfunction ≥moderate[24]. We delved into the interaction by applying an afterload-corrected RV function (i.e., TAPSE/PASP) as a categorical and as a continuous variable, which could account for the differing results.

In clinical decision-making for TR, the principal issue is to determine if the TR should be treated to curb a dismal clinical prognosis. Identifying the subjects who would benefit from a tricuspid intervention is essential to obtain the optimal therapeutic strategy in each individual. We found that the clinical impact of TR changed according to RV-PA coupling. Notably, the spline curve of the severe TR was found to be left-upwards compared to moderate TR, implying that the risk is higher with a higher grade of TR. Thus, a novel conceptual framework could be suggested. The prognostic impact of TR is determined by two critical factors (i.e., the severity of TR and RV-PA coupling) **(Central illustration)**, as the severity of MR and LV function are on the mitral side. The impact of transcatheter TR treatment on outcomes might vary according to the severity of TR and RV function (e.g., RV-PA coupling). A multicentre cohort study reported that there was no outcome benefit of transcatheter tricuspid therapy over medical therapy alone in patients with TR and severely impaired RV function[25]. In contrast, patients with preserved RV function assessed by RV-PA coupling may be more likely to benefit from transcatheter tricuspid treatment[19].

## Limitations

Several limitations should be acknowledged. First, core lab adjudicated echocardiographic assessments are lacking. The assessment and grading of the TR severity are challenging in clinical practice. Although both qualitative and quantitative parameters were used to assess TR severity, as recommended in the guidelines[8,9], further investigations with a core lab analysis are needed to validate our preliminary findings. Second, TR and RV function might have changed in the interval between echocardiography and TEER. Nevertheless, the primary findings of the current study were consistent in the sensitivity analyses using post-procedural parameters, which would validate the study inference. Third, there was no haemodynamic data obtained by the right heart catheter. PASP might be underestimated in some patients due to a large coaptation gap and severe TR. Nonetheless, 2D echocardiography is the most widely used imaging technique to measure these parameters

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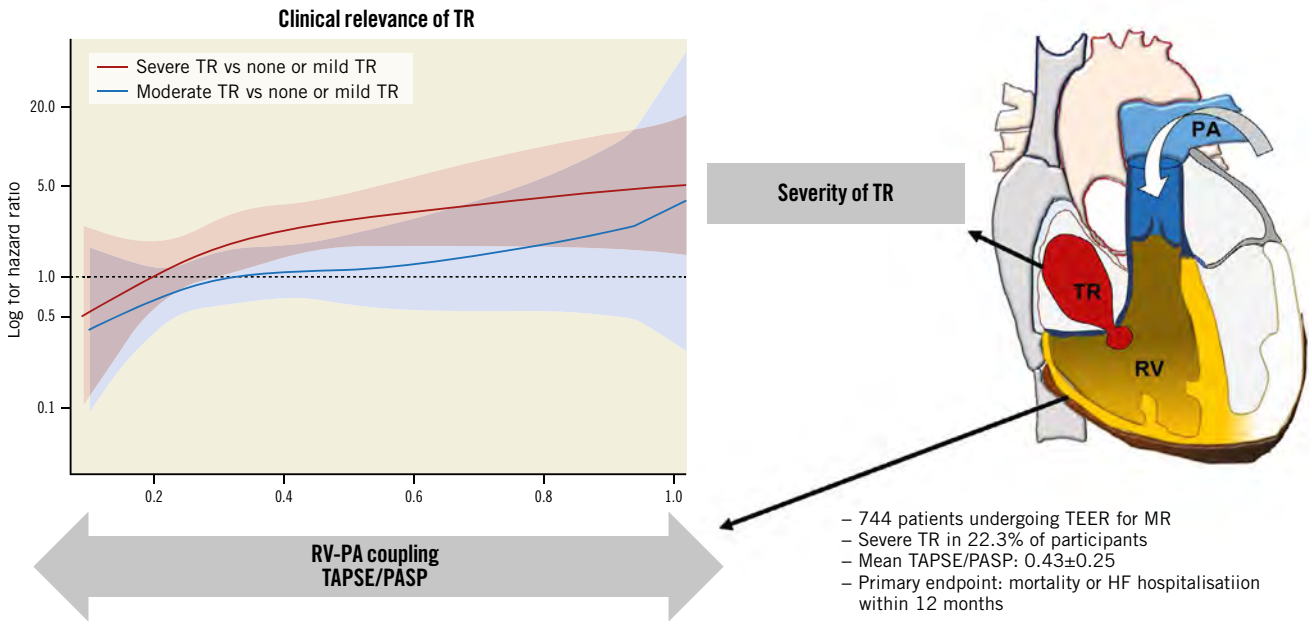
CENTRAL **ILLUSTRATION** **Impact of right ventricular-pulmonary arterial coupling on outcomes of TR.**




*TR is a strong predictor of all-cause mortality and rehospitalisation due to heart failure in patients undergoing mitral TEER. The risk is higher with a higher grade of TR. Besides, RV-PA coupling is also associated with the outcome. Moreover, RV-PA coupling affects the outcome correlation of TR. The prognostic impact of TR is pronounced in patients with a high TAPSE/PASP ratio but attenuated in patients with a low TAPSE/PASP (i.e., RV-PA uncoupling). HF: heart failure; HR: hazard risk; MR: mitral regurgitation; PASP: pulmonary artery systolic pressure; RV-PA: right ventricular pulmonary artery; TAPSE: tricuspid annular plane systolic excursion; TEER: mitral transcatheter edge-to-edge repair; TR: tricuspid regurgitation*

in clinical practice. Still, our preliminary findings need to be validated in large-scale studies with invasively measured PASP. Finally, we did not assess additional interventions to treat TR during the follow-up period. Our findings could serve as a basis in further investigations to look at the prognostic impact of treating TR with regard to the two parameters (i.e., the severity of TR, RV-PA coupling).

## Conclusions

TR is a strong predictor of all-cause mortality and rehospitalisation due to heart failure in patients undergoing mitral TEER. The risk is higher with a higher grade of TR. Besides, RV-PA coupling is also associated with the outcome. Moreover, RV-PA coupling affects the outcome correlation of TR. The prognostic impact of TR is pronounced in patients with a high TAPSE/PASP ratio but attenuated in patients with a low TAPSE/PASP (i.e., RV-PA uncoupling). Our findings propose a novel conceptual framework: the clinical relevance of TR will be determined according to its severity and concomitant RV-PA coupling ratio. Further investigations are needed to investigate the prognostic impact of transcatheter TR treatment with regard to these two parameters.

## Impact on daily practice

TR is a strong predictor of all-cause mortality and rehospitalisation due to heart failure in patients undergoing mitral TEER. Besides, RV-PA coupling is also associated with the outcome. Moreover, RV-PA coupling affects the outcome correlation of TR. The prognostic impact of TR is pronounced in patients with a high TAPSE/PASP ratio but attenuated in patients with a low TAPSE/PASP (i.e., RV-PA uncoupling). Our findings propose a novel conceptual framework: the clinical relevance of TR will be determined according to its severity and concomitant RV-PA coupling ratio.

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## Conflict of interest statement

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## Supplementary data

**Supplementary Table 1.** Association of adjusted variables for the primary endpoint.

**Supplementary Table 2.** Summarised output of mediation analysis.

**Supplementary Table 3.** Association of post-procedural variables in the Cox proportional hazard model.

**Supplementary Figure 1.** Distribution of TAPSE/PASP.

**Supplementary Figure 3.** Receiver operating characteristics curve analysis for predicting all-cause mortality or rehospitalisation due to heart failure.

**Supplementary Figure 3.** Severity of TR by TAPSE/PASP tertile.

**Supplementary Figure 4.** Fitting spline curve of the outcome correlation of TR according to RVFAC/PASP.

*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00045*

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# First-in-human implantation of the Topaz transcatheter tricuspid valve replacement system

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## Introduction

Severe tricuspid regurgitation (TR) is frequent and associated with poor outcomes[1]. Nevertheless, many patients are declined for surgery because of prohibitive surgical risks. In this setting, transcatheter tricuspid valve (TV) intervention may be a less invasive option. Transcatheter edge-to-edge repair (TEER) has been the most used approach so far[2]; however, transcatheter tricuspid valve replacement (TTVR) might be a more attractive strategy. Indeed, besides providing an alternative for patients whose anatomies are not suitable for TEER (due to large coaptation gaps or short/retracted septal leaflets), TTVR procedures are likely to be less challenging and more reproducible, as demonstrated in the first-in-human trials[3].

## Methods

The Topaz transfemoral tricuspid heart valve replacement system (TRiCares) is a novel orthotopic self-expanding TTVR system designed with a two-stent frame made of nitinol. The outer stent provides a sealed anchoring into the native tricuspid apparatus while protecting the inner stent, which contains the valve, from any deformation caused by the contraction of the right ventricle (RV). The stiffer inner stent houses the three-leaflet valve made from porcine pericardium, which acts independently of the outer stent, thus allowing it to maintain a circular shape and full valve integrity. The system is delivered via the femoral vein through a 29 Fr steerable introducer, currently with no possibility of recapture. The steerable introducer is first brought into the right atrium and oriented toward the tricuspid annulus. The crimped valve is then advanced to the apex of the RV and deployed in a two-step procedure, first the ventricular part of the valve and then the atrial part. The anchoring mechanism does not rely on radial force but on a layer of anchors located below the annulus level. Therefore, no oversizing of the valve is needed. To date, only one size of the valve is available, which allows treatment of an annulus diameter <45 mm based on diastolic computed tomography (CT) scan measurements.

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We herein report the first two cases of compassionate use of the TRiCares Topaz transfemoral tricuspid heart valve replacement system for the treatment of TR. These two cases were approved by the French authorities (Agence nationale de sécurité du médicament et des produits de santé [ANSM]; Ref. No. 2100459) **(Figure 1)**.

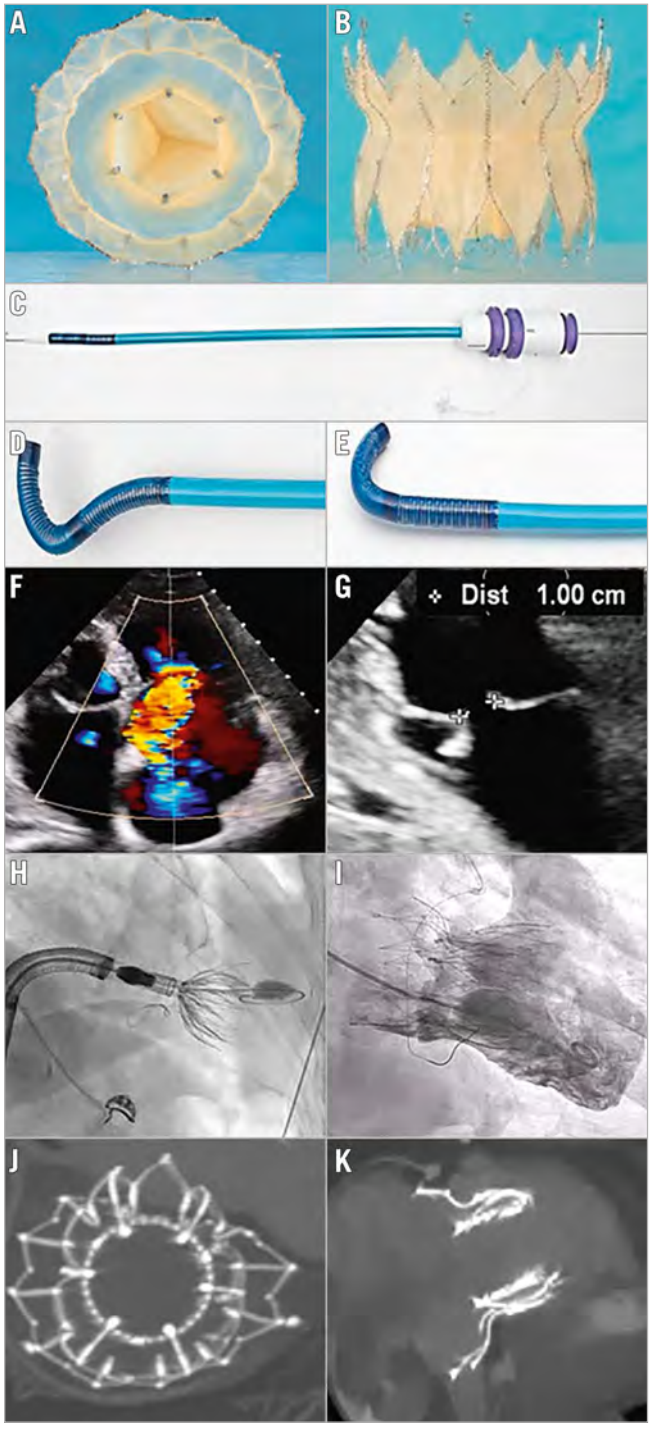


**Figure 1.** *Topaz orthotopic transcatheter tricuspid valve replacement for severe TR. Topaz system: a two-stent design, self-expanding prothesis with 3 porcine pericardium leaflets; the outer stent adapts to the anatomy while the inner stent is more rigid, thus maintaining a circular shape. A) En face view; B) side view. C, D & E) Double-curve steerable sheet for transvenous femoral access. F) Colour Doppler view of the preprocedural torrential tricuspid regurgitation of patient 2 (all the following images are also for patient 2). G) Two-dimensional echographic view of the tricuspid valve coaptation defect. H) Fluoroscopic view of valve deployment. I) Right ventricular angiography immediately after valve deployment. J & K) Post-procedural CT showing the round inner stent linked to the outer stent that conforms to the patient's anatomy. CT: computed tomography; TR: tricuspid regurgitation*

## Results

The two procedures were performed in June 2021. The patients were 70-year-old (patient 1) and 86-year-old (patient 2) females. They presented with massive and torrential functional TR[1] due to tricuspid annulus dilatation related to chronic atrial fibrillation. However, both were declined for surgery by the local Heart Teams because of prohibitive surgical risks with TRI-SCOREs of 5 (intermediate risk) and 6 (high risk), respectively[4], and were not considered suitable for TEER owing to excessive coaptation gaps[5].

Interventions were performed under general anaesthesia, using a transvenous femoral approach and guided by fluoroscopy and transoesophageal echocardiography. Procedural success (defined as implantation of the valve at the intended position without migration or significant paravalvular leak) was achieved in both cases, with a short procedure time (18 and 12 minutes, respectively, from delivery system in to delivery system out) and with no adverse events. Immediate haemodynamic results were excellent, with good valve deployment at the intended annular position, a mean transvalvular gradient of 2 mmHg in both patients, no residual TR and no paravalvular regurgitation. The two patients were discharged on day four and, given the setting of atrial fibrillation, remained on a non-vitamin K oral anticoagulant.

## Discussion

No death or complication and, notably, no rehospitalisation for heart failure occurred before the post-procedure 3-month follow-up. Transthoracic echocardiography at 3 months showed sustained haemodynamics with no residual TR and an unchanged mean transvalvular gradient (2 mmHg for both patients). However, while there was complete resolution of TR, RV function decreased at three months in both patients (tricuspid annular plane systolic excursion [TAPSE]: 18 mm to 11 mm in patient 1 and 14 mm to 11 mm in patient 2). The three-month CT scan did not reveal any valve thrombosis. Clinical improvement was significant, with an improvement in New York Heart Association (NYHA) functional status from Class III to Class I in both patients. Moreover, in patient 1, the furosemide dose was decreased from 500 mg to none, and the right heart failure symptoms (oedema and jugular congestion) present at baseline were not present at 3 months. Finally, no conduction abnormalities were observed during follow-up.

## Limitations

As further investigations are needed, the TRICURE first-in-human trial is planned to start soon.

## Conclusions

This first-in-human experience with the Topaz TTVR confirms feasibility and safety, abolishing TR with an effective associated short-term clinical improvement.

## Conflict of interest statement

T. Ruf is a consultant and proctor for TRiCares, Abbott Laboratories, and Edwards Lifesciences. P. Blanke is a shareholder of TRiCares. U. Schäfer is a shareholder of TRiCares. H. Treede is a shareholder of TRiCares. R. Gallet is a shareholder of TRiCares. P. Lim is the founder and a shareholder of TRiCares. The other authors have no conflicts of interest to declare.

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Onyx Frontier™ DES

# Great just got better

Onyx Frontier DES inherits the same stent platform, clinical data, and indications you've come to rely on with Resolute Onyx™ DES.

What makes it even better is its delivery system enhancements,† resulting in best-in-class deliverability[1] with a lower crossing profile.[2]

Most deliverable DES[1]

See more at **medtronic.eu/ OnyxFrontier**

†Stent delivery system updates were implemented on the 2.0–4.0 mm Onyx Frontier DES diameters.

[1] Based on bench test data on file at Medtronic. [D00339634 - Test Report for DES Competitive Comparison with Frontier test methods, Rev C, 05-May-2022] May not be indicative of clinical performance. N = 7 DES of each tested: Onyx Frontier DES, Resolute Onyx DES, Orsiro®* Mission DES, XIENCE Sierra™* DES, XIENCE Skypoint™* DES, SYNERGY™* DES, SYNERGY™* XD DES, Ultimaster™* Tansei™* DES.

[2] Based on bench test data on file at Medtronic. [D00339634 - Test Report for DES Competitive Comparison with Frontier test methods, Rev C, 05-May-2022] May not be indicative of clinical performance. N = 5 DES of each tested: Onyx Frontier DES, Orsiro Mission DES, Resolute Onyx DES, XIENCE Skypoint DES, SYNERGY DES, Ultimaster Tansei DES.

See the device manual for information regarding the instructions for use, indications, contraindications, warnings, precautions, and potential adverse events. For further information, contact your local Medtronic representative and/ or consult the Medtronic website at www.medtronic.eu.

For applicable products, consult instructions for use on manuals.medtronic.com. Manuals can be viewed using a current version of any major internet browser. For best results, use Adobe Acrobat® Reader with the browser.

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# THE FIRST CHOICE
# TO RESTORE THE TRICUSPID VALVE

99%

Highest implant success rate and lowest device times – despite more massive/torrential TR at baseline[3]

TR reduced to moderate or less in >70% of real-world patients and in a broad range of anatomies[2]

Significant NYHA functional class and quality of life improvement[1,2,3]

<1% MAE

Excellent safety profile[1,2,3]

**SCAN HERE TO** FIND OUT MORE


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