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Bioprosthetic valve fracture performed before versus after valve-in-valve intervention:

Insights from bench testing

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Short title: Impact of timing of bioprosthetic valve fracture

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Disclosures

Dr Allen has received research grants and speakers fees from Edwards Lifesciences, and

Medtronic. He is also a consultant to Abbott Vascular. Dr. Chhatriwalla is on the Speaker's

Bureau for Edwards Lifesciences, Medtronic Inc and Abbott Vascular and is a proctor for

Edwards Lifesciences and Medtronic Inc. Dr. Dasi reports having patent applications filed on

novel polymeric valves, vortex generators and superhydrophobic/omniphobic surfaces. Dr

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ABSTRACT

Aims:

Bioprosthetic valve fracture(BVF) may improve transvalvular gradients and transcatheter heart valve(THV) expansion during VIV interventions. However, the optimal timing of BVF is unknown. We assessed the impact of timing of BVF (before versus after) for valve-in-valve(VIV) intervention, on hydrodynamic function and THV expansion.

Methods and results:

Eurolni Three THV designs were assessed, a 23mm SAPIEN 3(S3), small ACURATE neo(ACn) and 23mm Evolut R, deployed into 21mm Mitroflow bioprosthetic surgical valves. We evaluated each THV in three groups: 1) No BVF, 2) BVF before VIV and 3) BVF after VIV. Hydrodynamic testing was performed using a pulse duplicator to ISO 5840:2013 standard. Transvalvular gradients were lower when BVF was performed after VIV for the S3(No BVF 15.5mmHg, BVF before VIV 8.0mmHg, BVF after VIV 5.6mmHg), and the ACn(No BVF 9.8mmHg, BVF before VIV 8.4mmHg, BVF after VIV 5.1mmHg). Transvalvular gradients were similar for the Evolut R, irrespective of performance of BVF or timing of BVF. BVF performed after VIV resulted in better expansion in all three THV designs. The ACn and Evolut R samples all had a mild degree of pinwheeling, and BVF timing did not impact pinwheeling severity. The S3 samples had severe

pinwheeling with no BVF, and significant improvement in pinwheeling when BVF was performed after VIV.

Conclusion:

BVF performed after VIV was associated with superior THV expansion in all three tested THVs designs, with lower residual transvalvular gradients in the S3 and ACn THVs. The Evolut R had similar hydrodynamic performance irrespective of BVF timing. Timing of BVF has potential Intervention implications on THV function.

CONDENSED ABSTRACT

The optimal timing of bioprosthetic valve fracture (BVF) is unknown. Transvalvular gradients were lower when BVF was performed after valve-in-valve (VIV) for the SAPIEN 3 (No BVF 15.5mmHg, BVF before-VIV 8.0mmHg, BVF after-VIV 5.6mmHg), and the ACURATE neo (No BVF 9.8mmHg, BVF before-VIV 8.4mmHg, BVF after-VIV 5.1mmHg). Gradients were <20mmHg for the Evolut R, irrespective of BVF performance or timing of BVF. BVF performed after VIV was associated with superior valve expansion in all three valve designs, with lower residual gradients with the SAPIEN 3 and ACURATE neo valves. The Evolut R had similar hydrodynamic performance irrespective of BVF timing.

ABBREVIATIONS AND ACRONYMS

ACn: ACURATE neo

BVF: Bioprosthetic valve fracture

S3: SAPIEN 3

THV: Transcatheter heart valve

VIV: Valve-in-valve

INTRODUCTION

Valve-in-valve (VIV) intervention with transcatheter heart valves (THV) is an established

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therapy for patients with failed surgical bioprothetic aortic valves(1). However, in small sized

surgical valves, high gradients and patient-prosthesis mismatch may persist and lead to poor

clinical outcomes(2). To address this issue, bioprosthetic valve fracture (BVF) has emerged as a

technique to optimize THV expansion, with subsequent reduction in transvalvular gradients and

an increase in effective orifice area(3,4). Early clinical experience has been favorable, but the

long-term clinical implications as well as the optimal timing of BVF are currently unknown(5).

BVF performed prior to VIV intervention has associated risks of acute aortic insufficiency and

hemodynamic compromise, whereas BVF performed after VIV intervention might damage THV

leaflets, affecting both short and long term THV function.

This study assessed the effect of BVF timing using three different THV designs, on acute hydrodynamic function and THV expansion, comparing BVF performed before versus after VIV intervention.

METHODS

Valves

VIV intervention was tested with a 23mm SAPIEN 3 (S3) (Edwards Lifesciences Inc., Irvine, CA), a small ACURATE neo (ACn) (Boston Scientific Corporation, Natick, MA) and a 23mm Evolut R (Medtronic Inc, St Paul, Minneapolis, MN) THVs.

The S3 THV is a balloon expandable THV made of a cobalt-chromium alloy frame, bovine pericardial leaflets and internal and external polyethylene terephthalate fabric seals at the inflow level of the valve. The 23mm S3 valves has a stent frame height of 18mm when fully expanded as per manufacturer specifications(6). The ACn is a self-expanding THV with a nitinol frame and porcine pericardial leaflets positioned higher within the frame. There are inner and outer pericardial seals at the inflow level of the valve. There are three stabilization arches for axial alignment in the ascending aorta, an upper crown and a lower crown. The total height of the ACn ranges between 48-51mm with the stent body height being 18-19mm. Three sizes (small, medium and large) are currently available to accommodate an aortic annulus diameter between 21mm to 27mm. The Evolut R has similar features of its prior iterations with a radiopaque self-expanding nitinol frame, supra-annular trileaflet porcine pericardial leaflets,

and porcine pericardium fabric skirt. The 23mm Evolut R has a skirt height and frame height of 13mm and 45mm, respectively. The inflow diameter is 23mm and the outflow diameter is 34mm(7).

THVs were deployed into 21mm sized Mitroflow aortic bioprostheses (Sorin Group USA Inc, Arvada, CO). One mitroflow valve was utilized to assess each test condition and each THV design. A total of nine mitroflow valves were utilized. The Mitroflow bioprosthesis consists of an acetyl homopolymer stent frame with bovine pericardial sheets sutured externally to form the leaflets. The sewing ring covers the base of the frame and incorporates a non-rigid radiopaque silicone ring covered by a Dacron mesh(8). The 21mm Mitroflow valve has a true Eurolni internal diameter of 17mm(9).

Ex-vivo valve-in-valve procedure

The THVs were positioned in the surgical bioprosthetic valve with an aim to achieve a 'high' implant to maximize the effective orifice area, and lowest residual transvalvular gradient(10). The Mitroflow bioprosthesis has a visible radiopaque ring but the frame is radiolucent. Ex-vivo VIV using the S3 THV, was performed with the centre marker of the S3 THV positioned just above the level of the sewing ring of the Mitroflow valve. Ex-vivo VIV with the ACn THV was performed by positioning the upper crown just above the top of the acetyl stent frame. Ex-vivo VIV with the Evolut R was performed by positioning the THV at a depth of 2mm in relation to the sewing ring of the Mitroflow valve (Figure 1).

Ex-vivo bioprosthetic valve fracture

BVF was performed using a 23mm non-compliant True Dilatation balloon valvuloplasty catheter (Bard Vascular Inc, Tempe, AZ). A 23mm sized True Dilatation balloon was chosen based on a prior bench study from our group. This prior study demonstrated lower transvalvular gradients utilizing a 23mm True Dilatation balloon compared to smaller sized True balloons when performing BVF following VIV intervention in 21mm Mitroflow surgical valves, utilizing either a SAPIEN or ACn THV(11). Balloons were inflated using a set-up of a large syringe, indeflator and high pressure stopcock. The balloon was filled with a hand injection of the syringe first and then the stopcock was opened to the indeflator to pressurize the balloon. Eurolnie The inflation pressure when BVF was achieved was recorded.

Imaging

High resolution photography was performed at the same magnification and same fixed camera height. Fluoroscopy was performed using a standard adult cardiac catheterization laboratory (General Electric Healthcare, Chicago, IL). Radiograph images were made using a Nikon XT H 225 ST micro focus X-ray tomography system (Nikon Metrology, Cambridge, Canada). The THV valves were visually inspected for macroscopic damage after BVF was performed.

Measurements

Measurements were made using radiograph images for each sample. Diameter measurements were made using the centre of the THV strut as a marker. To account for potential elliptical THV deployment, two orthogonal measurements of diameter were made, and averaged.

SAPIEN 3 THVs had measurements at the inflow (IF), midvalve (MV), and outflow (OF) of the THV. ACn THV had measurements at the inflow (level of the adaptive polyethylene fabric seal) and nadir of the leaflets (at the level of the upper crown). Evolut R THV had measurements at the inflow and nadir of the leaflets (Figure 1).

Hydrodynamic assessment

Hydrodynamic testing was performed for each sample, using a commercially available pulse duplicator (ViVitro Labs Inc, Victoria, Canada) (Figure 1). Valves were tested in accordance with ISO 5840-3:2013 guidelines regarding in-vitro pulsatile flow testing for heart valve substitutes implanted by transcatheter techniques(12). Valves were placed in a holder fabricated from silicone with a durometer of scale Shore A hardness of 40±5. Justification for the selection of sample holder hardness was based on published data on acceptable tissue compliance matched with published data on the silicone material hardness scale(13-15). Test fluid used was 0.9±0.2 % Sodium Chloride test solution maintained at 37±2 °C (one drop of Cosmocil (preservative) per 1 L).

Valves were tested on the aortic side of the pulse duplicator with a spring-loaded disc valve (ViVitro Labs) on the mitral side of the pulse duplicator. Measurements were based on average results taken from 10 consecutive cycles. High speed video was captured at each step condition. Pulsatile forward flow performance was tested at nominal beat rate of 70±1 beats per minute, systolic duration of 35±5%, mean aortic pressure of 100±2 mmHg, and simulated

cardiac outputs of 5±0.1 liters per minute. Mean gradient (mmHg), regurgitant fraction (%) and effective orifice area (cm²) were assessed.

Pin-wheeling index

Pin-wheeling, as defined by the International Standards Organization guideline for THV testing, refers to twisting of the leaflet free-edges resulting from excessive leaflet redundancy(12). A pin-wheeling index (PWI) as described by Midha et al was utilized(16). We quantified the degree of pin-wheeling by tracing the contour of the leaflet free edges and compare it to the unconstrained, ideal configuration. The following equation was used to Men calculate a pin-wheeling index:

Pin-wheeling index (%) = $[(L_{actual} - L_{ideal}) / L_{ideal}]*100$

Lactual denotes the length of the leaflet from the valve frame to the coaptation centre. Lideal denotes the straight line distance between the endpoints of the leaflet free edge(16). Determination of the pin-wheeling index was performed using a custom-made Matlab code after image calibration.

Statistical analysis

Hydrodynamic variables are reported as mean \pm standard deviation (SD).

RESULTS

Valve hydrodynamics

Mean Transvalvular Gradient

BVF timing and impact on mean transvalvular gradient are reported in Figure 2. Compared to VIV alone, transvalvular gradients were lower with BVF, with the lowest gradients achieved when BVF was performed after VIV for the S3 (No BVF: 15.5±0.1mmHg, BVF before VIV: 8.0±0.1mmHg, BVF after VIV: 5.6±0.1mmHg), and the ACn (No BVF: 9.8±0.2mmHg, BVF before VIV: 8.4±8.4mmHg, BVF after VIV: 5.1±0.1mmHg). Transvalvular gradients were similar for the Evolut R, irrespective of performance of BVF or timing of BVF (No BVF: 15.1±0.2mmHg, BVF before VIV: 13.8±0.2mmHg, BVF after VIV: 13.3±0.1mmHg).

Effective orifice area

BVF timing and impact on effective orifice area (EOA) are reported in Table 1. BVF resulted in an increase in EOA for the S3 (No BVF: 1.5±0.01cm², BVF before VIV: 2.2±0.01cm², BVF after VIV: 2.6±0.01cm²) and ACn (No BVF: 2.0±0.01cm², BVF before VIV: 2.2±0.01cm², BVF after VIV: 2.8±0.01cm²) samples, with a greater increase in EOA achieved when BVF was performed after VIV. The performance of BVF or its timing did not have a significant impact on EOA for the Evolut R samples (No BVF: 1.5±0.01cm², BVF before VIV: 1.6±0.01cm², BVF after VIV: 1.6±0.01cm²).

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Regurgitant fraction

BVF timing and impact on regurgitant fraction (RF) are reported in Figure 3. BVF resulted in a reduction in RF for the S3 (No BVF: 18.4%, BVF before VIV: 16.6%, BVF after VIV: 14.5%), with a great reduction in RF when BVF was performed after VIV. BVF resulted in an increased in RF for the ACn samples (No BVF: 14.1%, BVF before VIV: 16.5%, BVF after VIV: 22.0%), with a

greater increase in RF when BVF was performed after VIV. The performance of BVF or its timing did not have significant impact on RF for the Evolut R samples (No BVF: 10.7%, BVF before VIV: 8.4%, BVF after VIV: 9.1%).

THV expansion

BVF timing and impact on valve dimensions are reported in Table 2. Following VIV all three THV samples tested were under-expanded. Bioprosthetic valve fracture improved expansion in all three THV designs. BVF was achieved at an inflation pressure of 12 atmospheres. In the S3 sample there was better expansion at the mid-valve and inflow of the THV, particularly if BVF was performed after VIV. In the ACn samples BVF resulted in a similar degree of THV expansion at both the inflow and leaflet nadir, irrespective of timing. In the Evolut R sample there was better expansion at both the inflow and leaflet nadir level of the THV when BVF was performed after VIV. After BVF performed, there was no evidence of gross macroscopic damage to the three THV designs tested.

Pin-wheeling

BVF timing and the impact on pinwheeling index (PWI) in the three THV designs tested are reported in Figure 4 and Videos 1-9. BVF performed before VIV did not result in a significant reduction in PWI in all three THV designs tested. BVF resulted in a significant reduction in pinwheeling if BVF was performed after VIV intervention in all three THV designed, particularly in the S3 sample. The S3 had the highest degree of pinwheeling with VIV alone, and following

BVF after VIV there was no significant degree of pinwheeling (No BVF, PWI 8.8%; BVF before VIV, PWI 7.7%; BVF after VIV, PWI 0.8%).

DISCUSSION

This study demonstrates that BVF performed after VIV results in superior THV expansion and in the case of the S3 and ACn was associated with a better reduction in transvalvular gradients. BVF or its timing did not have a significant impact on transvalvular gradients with the Evolut R. The implications of timing and the impact on various THV designs is important to consider when performing BVF.

The results of our bench study are consistent with small clinical series that also demonstrate superior THV function when BVF was performed after VIV, in both balloon expandable and self-expandable THVs(17). Importantly this bench study also demonstrates that BVF and its timing impacts each THV design differently. The two self-expanding THVs assessed in this study both had a different response to BVF. This highlights the importance of assessing each THV design individually, rather than assuming there is a 'class effect' based on mode of THV deployment. The difference between the two self-expanding THVs may be related to differences in THV design. Prior bench studies have demonstrated that when the upper crown of the ACn is under-expanded, this leads to compromised THV function(18). Performance of BVF leads to better expansion of the upper crown which subsequently led to improvement in

transvalvular gradients with the ACn. In comparison, while there was better expansion at the inflow and leaflet nadir of the Evolut R with BVF, this did not impact the THV at the level of leaflet coaptation or hydrodynamic performance. While BVF after VIV intervention may be desirable, other considerations are also of importance. BVF requires high pressure balloon inflation with a non-compliant balloon, that might damage THV leaflets leading to both shortand long-term failure. There is a risk of acute leaflet dysfunction leading to aortic insufficiency and hemodynamic compromise(19). Crimping of transcatheter heart valves has been shown to cause damage to the surface layers of leaflets(20). High pressure inflations with non-compliant balloon during BVF may similarly cause leaflet damage that may lead to accelerated leaflet degeneration and failure. To avoid these concerns, BVF may be performed before VIV intervention. However, there are also risks of acute aortic insufficiency when BVF is performed first, due to damage of the surgical valve leaflet. This study also demonstrates that expansion and hydrodynamic function with BVF before VIV can be less favorable, which may compromise long term function.

The 23mm Evolut samples had gradients that were higher than the S3 and ACn samples. Importantly while the gradients were higher, they were still below <20mmHg which has been shown to be associated with favorable clinical outcomes following VIV intervention(2). However, this study analyzed hemodynamic data from VIV intervention in new, as opposed to degenerated, surgical valves, and how these results translate to the hemodynamic results of VIV intervention and BVF in degenerated bioprosthetic valves is unknown. Nevertheless, prior clinical series have demonstrated similar gradients following VIV intervention with the 23mm

Evolut R in 21mm Mitroflow valves(5,21-23). Typically, gradients using a THV design with supra-annular positioned leaflets would have lower gradients compared to an intra-annular leaflet design. Factors related to THV design and positioning can influence gradients. In this study the S3 THV was positioned high in the Mitroflow which may result in favorable gradients compared to a lower implant depth, where gradients may be higher(10). While the VIV app recommends a 20mm S3, a larger 23mm S3 was utilized in this study that may have led to more favorable gradients. Utilization of a larger 26mm Evolut may result in superior gradients compared to a 23mm Evolut.

Better THV expansion also resulted in less redundant leaflet tissue and pin-wheeling, which may improve durability(16). The degree of pinwheeling was minimal for the S3 when BVF was performed after VIV intervention. Importantly BVF had a different effect on the two self-expandable valves with supra-annular leaflets in this study. Prior bench studies, have demonstrated that optimum expansion of the ACn upper crown is important to facilitate favorable hydrodynamic function(18). BVF resulted in better expansion at the level of the leaflet nadir, with an associated reduction in transvalvular gradients. With better THV expansion with the ACn there was increasing regurgitant fraction. The mechanism for this is unclear. A potential reason for the increase in regurgitant fraction with the ACn and BVF may be related to the size of ACn used in this study. A small ACn was utilized in this study. While THV expansion was better after BVF, the small ACn may have been too small in a fractured 21mm Mitroflow surgical valve, that may have led to increased leak between the THV and the surgical

valve. A medium ACn may have resulted in better sealing in a fractured Mitroflow valve. Additionally, unlike the S3, the ACn does not have an outer sealing skirt which may have impacted regurgitant fraction.

In some test conditions, the regurgitant fraction was higher than expected. In this study the surgical valves were sealed to the silicon holders. Therefore the mechanism for regurgitant fraction in this study was not related to paravalvular leak. The mechanism for leak may be related to either inter-valvular (between the surgical valve and THV) leak or central. In VIV intervention, there may be leaflet pinwheeling that can lead to a central coaptation defect ref¹ leading to leak(11).

Limitations

Bench testing may not entirely reflect how a THV will expand in a patient's native annulus, within a degenerated surgical bioprosthesis, or valve deployment under physiological conditions. Future studies would need to assess the impact of BVF timing on long term durability and clinical outcomes. Testing of BVF timing in different surgical valve designs would also be desirable. Accelerated wear testing can assess the impact of BVF timing on leaflet mechanical wear, but this mode of testing cannot assess calcification or stenosis as a mode of failure. Ultimately large clinical series with long term follow-up are required to understand the short and long implications of BVF. Clinical series are also required to understand the impact of BVF timing on complications such as aortic root rupture. In this study VIV intervention with the ACn THV was performed by positioning the upper crown just above the top of the acetyl stent

frame. However this would be challenging to achieve clinically as the frame of the Mitroflow is radiolucent. Repetition of bench testing with more samples would be desirable.

CONCLUSION

BVF performed after VIV is associated with superior THV expansion in all three tested THVs designs, and with lower residual transvalvular gradients with the SAPIEN 3 and ACURATE neo THVs. The Evolut R has similar hydrodynamic performance irrespective of BVF timing. ervention Timing of BVF has potential implications on THV function.

IMPACT ON DAILY PRACTICE

Early clinical experience with bioprosthetic valve fracture has been favorable with an improvement in transcatheter heart valve function for patients undergoing valve-in-valve interventions. Whether bioprosthetic valve fracture should be performed before or after valve intervention, and its implications are poorly understood. This study demonstrates that BVF performed after VIV is associated with superior THV expansion in all three tested THVs designs, and with lower residual transvalvular gradients with the SAPIEN 3 and ACURATE neo THVs. The Evolut R has similar hydrodynamic performance irrespective of BVF timing. Timing of BVF has potential implications on THV function. Larger clinical series are required to determine the impact of BVF timing on both short- and long-term THV function and durability.

REFERENCES

- 1. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, Descoutures F,
 Hengstenberg C, Moat NE, Bekeredjian R, Napodano M, Testa L, Lefevre T, Guetta V, Nissen H,
 Hernández JM, Roy D, Teles RC, Segev A, Dumonteil N, Fiorina C, Gotzmann M, Tchetche D,
 Abdel-Wahab M, De Marco F, Baumbach A, Laborde JC, Kornowski R. Transcatheter aortic valve
 replacement for degenerative bioprosthetic surgical valves: results from the global valve-invalve registry. Circulation. 2012 Nov 6;126(19):2335-44.
- 2. Webb JG, Mack MJ, White JM, Dvir D, Blanke P, Herrmann HC, Leipsic J, Kodali SK, Makkar R, Miller DC, Pibarot P, Pichard A, Satler LF, Svensson L, Alu MC, Suri RM, Leon MB. Transcatheter Aortic Valve Implantation Within Degenerated Aortic Surgical Bioprostheses: PARTNER 2 Valve-in-Valve Registry. J Am Coll Cardiol. 2017 May 9;69(18):2253-2262.
- 3. Allen KB, Chhatriwalla AK, Cohen DJ, Saxon JT, Aggarwal S, Hart A, Baron S, Davis JR, Pak AF, Dvir D, Borkon AM. Bioprosthetic Valve Fracture to Facilitate Transcatheter Valve-in-Valve Implantation. Ann Thorac Surg. 2017 Nov;104(5):1501-1508.
- 4. Nielsen-Kudsk JE, Christiansen EH, Terkelsen CJ, Nørgaard BL, Jensen KT, Krusell LR, Tang M, Terp K, Klaaborg KE, Andersen HR. Fracturing the Ring of Small Mitroflow Bioprostheses by High-Pressure Balloon Predilatation in Transcatheter Aortic Valve-in-Valve Implantation. Circ Cardiovasc Interv. 2015 Aug;8(8):e002667.
- 5. Chhatriwalla AK, Allen KB, Saxon JT, Cohen DJ, Aggarwal S, Hart AJ, Baron SJ, Dvir D, Borkon AM. Bioprosthetic Valve Fracture Improves the Hemodynamic Results of Valve-in-Valve Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv. 2017 Jul;10(7).

- 6. Webb J, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, Thielmann M, Treede H, Wendler O, Walther T. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol. 2014 Dec 2;64(21):2235-43.
- 7. Piazza N, Martucci G, Lachapelle K, de Varennes B, Bilodeau L, Buithieu J, Mylotte D. First-in-human experience with the Medtronic CoreValve Evolut R. EuroIntervention. 2014 Mar 20;9(11):1260-3.
- 8. Balsam LB, DeAnda A Jr. The Mitroflow aortic valve: A past, present, and future illuminated. J Thorac Cardiovasc Surg. 2017 Jan;153(1):40-42.
- 9. Bapat V. Valve-in-valve apps: why and how they were developed and how to use them. EuroIntervention. 2014 Sep;10 Suppl U:U44-51.
- 10. Simonato M, Webb J, Kornowski R, Vahanian A, Frerker C, Nissen H, Bleiziffer S, Duncan A, Rodés-Cabau J, Attizzani GF, Horlick E, Latib A, Bekeredjian R, Barbanti M, Lefevre T, Cerillo A, Hernández JM, Bruschi G, Spargias K, Iadanza A, Brecker S, Palma JH, Finkelstein A, Abdel-Wahab M, Lemos P, Petronio AS, Champagnac D, Sinning JM, Salizzoni S, Napodano M, Fiorina C, Marzocchi A, Leon M, Dvir D. Transcatheter Replacement of Failed Bioprosthetic Valves: Large Multicenter Assessment of the Effect of Implantation Depth on Hemodynamics After Aortic Valve-in-Valve. Circ Cardiovasc Interv. 2016 Jun;9(6).
- 11. Sathananthan J, Sellers S, Barlow AM, Stanová V, Fraser R, Toggweiler S, Allen KB, Chhatriwalla A, Murdoch DJ, Hensey M, Lau K, Alkhodair A, Dvir D, Asgar AW, Cheung A, Blanke P, Ye J, Rieu R, Pibarot P, Wood D, Leipsic J, Webb JG. Valve-in-Valve Transcatheter Aortic Valve Replacement and Bioprosthetic Valve Fracture Comparing Different Transcatheter Heart Valve Designs: An Ex Vivo Bench Study. JACC Cardiovasc Interv. 2019 Jan 14;12(1):65-75.

- 12. Cardiovascular implants cardiac valve prosthesis. Part 3: Heart valve substitutes implanted by trans catheter techniques. In: organization Is, editor. Geneva, Switzerland: International standard organization, 2013
- 13. Loree HM, Grodzinsky AJ, Park SY, Gibson LJ, Lee RT. Static circumferential tangential modulus of human atherosclerotic tissue. J Biomech. 1994 Feb;27(2):195-204.
- 14. Gnyaneshwar R, Kumar RK, Balakrishnan KR. Dynamic analysis of the aortic valve using a finite element model. Ann Thorac Surg. 2002 Apr;73(4):1122-9.
- 15. Meththananda IM, Parker S, Patel MP, Braden M. The relationship between Shore hardness of elastomeric dental materials and Young's modulus. Dent Mater. 2009 Aug;25(8):956-9.
- 16. Midha PA, Raghav V, Condado JF, Okafor IU, Lerakis S, Thourani VH, Babaliaros V, Yoganathan AP. Valve Type, Size, and Deployment Location Affect Hemodynamics in an In Vitro Valve-in-Valve Model. JACC Cardiovasc Interv. 2016 Aug 8;9(15):1618-28.
- 17. Allen KB, Chhatriwalla AK, Saxon JT, Cohen DJ, Nguyen TC, Webb J, Loyalka P, Bavry AA, Rovin JD, Whisenant B, Dvir D, Kennedy KF, Thourani V, Lee R; Bioprosthetic Valve Fracture Investigators. Bioprosthetic valve fracture: Technical insights from a multicenter study. J Thorac Cardiovasc Surg. 2019 Jan 31. pii: S0022-5223(19)30287-9.
- 18. Sathananthan J, Sellers SL, Fraser R, Dvir D, Hensey M, Murdoch DJ, Blanke P, Pibarot P, Toggweiler S, Wood D, Leipsic J, Webb JG. Impact of implant depth on hydrodynamic function with the ACURATE neo transcatheter heart valve following valve-in-valve transcatheter aortic valve replacement in Mitroflow bioprosthetic valves: an ex vivo bench study. EuroIntervention. 2019 May 20;15(1):78-87.

- 19. Saxon JT, Allen KB, Cohen DJ, Whisenant B, Ricci J, Barb I, Gafoor S, Harvey J, Dvir D, Chhatriwalla AK. Complications of Bioprosthetic Valve Fracture as an Adjunct to Valve-in-Valve TAVR. Structural Heart 2019.
- 20. Alavi SH, Groves EM, Kheradvar A. The effects of transcatheter valve crimping on pericardial leaflets. Ann Thorac Surg. 2014 Apr;97(4):1260-6.
- 21. Lopez S, Meyer P, Teboul J, Deharo P, Mihoubi A, Elbeze JP, Lena D, Camarasa P, Laborde JC, Drogoul L. Transcatheter valve-in-valve implantation in a degenerated very small Mitroflow prosthesis. Interact Cardiovasc Thorac Surg. 2018 Dec 1;27(6):850-855.
- 22. Jategaonkar SR, Scholtz W, Horstkotte D, Gummert J, Ensminger SM, Börgermann J. Transfemoral aortic valve-in-valve implantation with the CoreValve Evolut for small degenerated stented bioprosthesis. J Invasive Cardiol. 2014 Jun;26(6):291-4.
- 23. Scholtz S, Piper C, Horstkotte D, Gummert J, Ensminger SM, Börgermann J, Scholtz W. Valve-in-valve transcatheter aortic valve implantation with CoreValve/Evolut R(©) for degenerated small versus bigger bioprostheses. J Interv Cardiol. 2018 Jun;31(3):384-390.

FIGURE AND TABLE LEGEND

Figure 1: Bench testing methodology

Panel A: Pulse duplicator used for hydrodynamic testing; Panel B: Example radiograph image of a S3 THV with orange lines indicating measurement made at inflow, midvalve and outflow of valve; Panel C: Example radiograph image of an ACn THV with orange lines indicating measurements made at inflow and leaflet nadir of the valve; Panel D: Example radiograph image of an Evolut R THV with orange lines indicating measurements made at inflow and leaflet nadir of the valve; Panel E: TRUE dilatation balloon inflation technique. Set-up consisted of a large syringe, indeflator and a high pressure stop cock. The TD balloon was filled with the syringe first (1) and then the stop cock was turned to the indeflator (2) which pressurized the balloon to the desired pressure (3).

Figure 2/ Central Illustration: Multimodality imaging by BVF timing for VIV with the 23mm S3, small ACn and 23mm Evolut R in 21mm Mitroflow bioprostheses

The orange lines represent THV dimensions at the midpoint of the S3, the leaflet nadir of the ACn and the inflow of the Evolut R.

Figure 3: Regurgitant fraction by BVF timing for VIV with the 23mm S3, small ACn and 23mm Evolut R in 21mm Mitroflow bioprostheses

Figure 4: Pin-wheeling index (%) by BVF timing for VIV with the 23mm S3, small ACn and 23mm Evolut R in 21mm Mitroflow bioprostheses

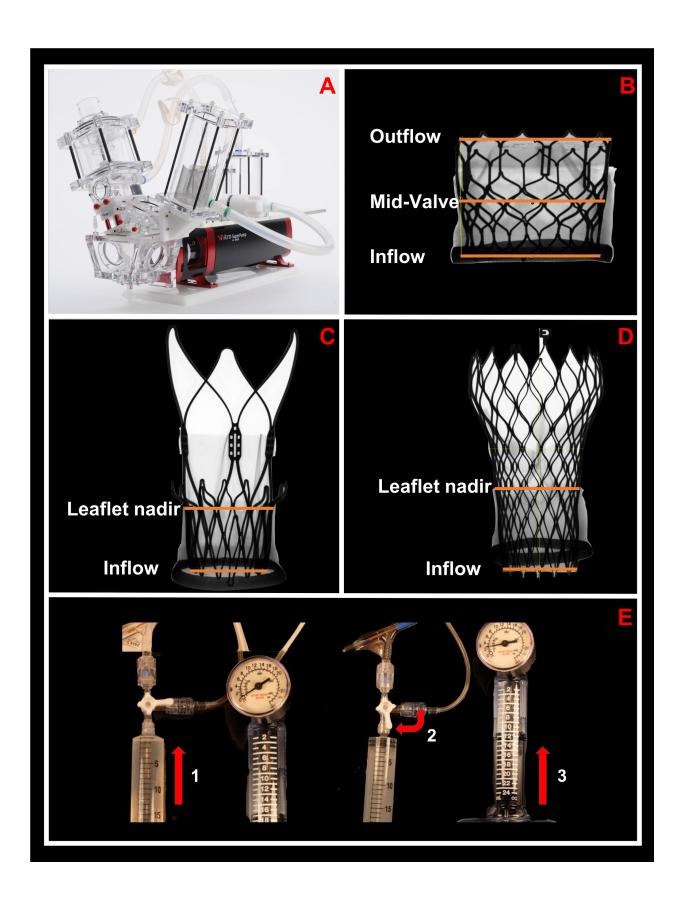
	NO BVF	BVF BEFORE VIV	BVF AFTER VIV	
SAPIEN 3	1.5±0.01	2.2±0.01	2.6±0.01	
ACURATE neo	2.0±0.01	2.2±0.01	2.8±0.01	
Evolut R		1.5±0.01	1.6±0.01	1.6±0.01

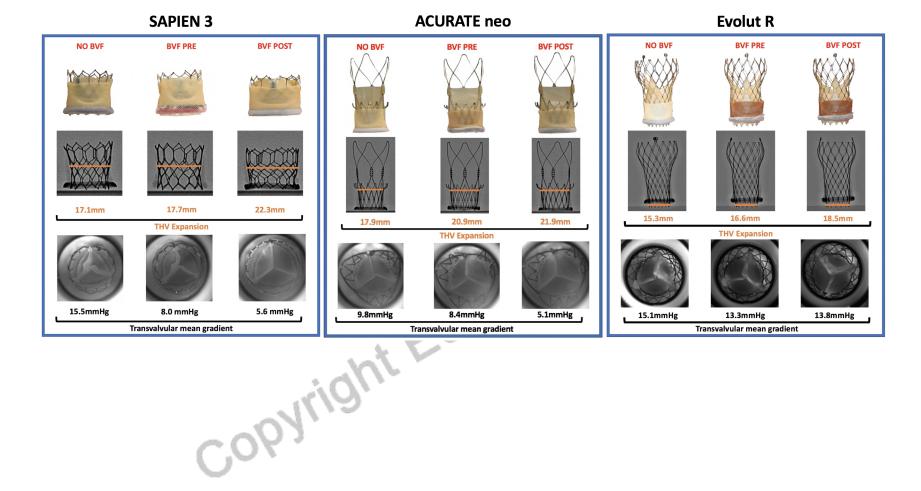
Table 1: All values represent effective orifice area (cm²)

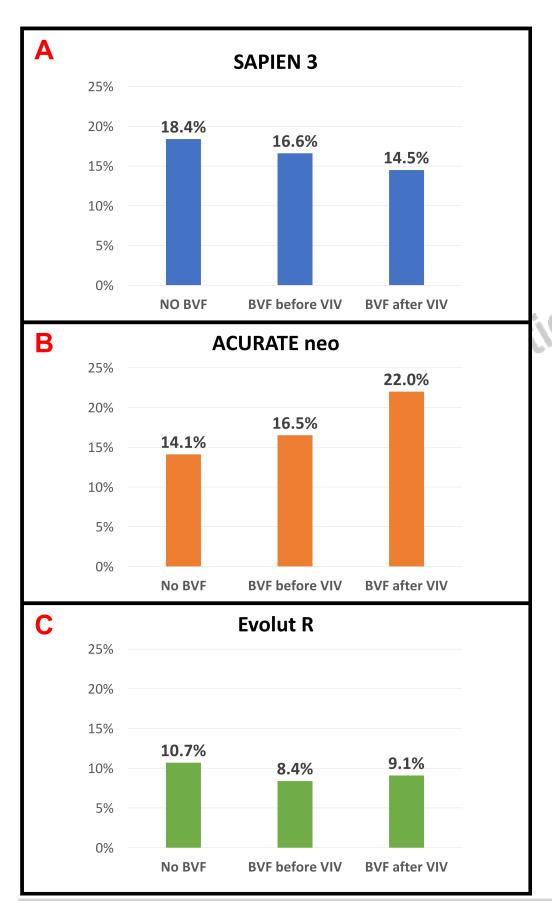


SAPIEN 3	NO BVF	BVF BEFORE VIV	BVF AFTER VIV		
Inflow	16.8mm	18.4mm	21.8mm		
Mid-valve	17.1mm	17.7mm	22.3mm		
Outflow	21.5mm	20.7mm	22.8mm		
ACURATE neo	NO BVF	BVF BEFORE VIV	BVF AFTER VIV		
Inflow	15.5mm	17.2mm	17.6mm		
Leaflet nadir	17.9mm	20.9mm	21.9mm		
Evolut R	NO BVF	BVF BEFORE VIV	BVF AFTER VIV		
Inflow	15.3mm	16.6mm	18.5mm		
Leaflet nadir	18.3mm	18.2mm	19.7mm		
Table 2					

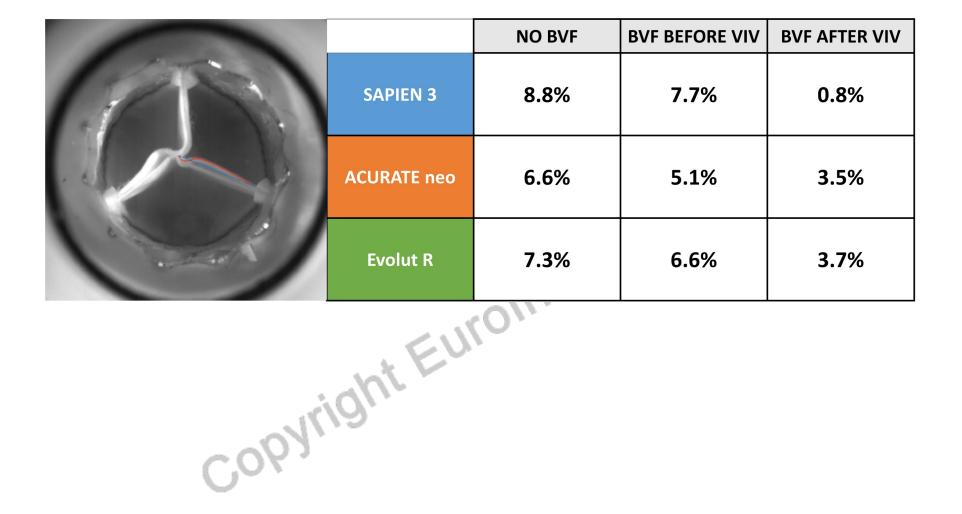
Table 2







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Supplementary Material

Video 1: VIV with a 21mm S3 in a 21mm Mitroflow, and no BVF

Video 2: VIV with a 21mm S3 in a 21mm Mitroflow, and BVF before VIV

Video 3: VIV with a 21mm S3 in a 21mm Mitroflow, and BVF after VIV

Video 4: VIV with a small ACn in a 21mm Mitroflow, and no BVF

Video 5: VIV with a small ACn in a 21mm Mitroflow, and BVF before VIV

Video 6: VIV with a small ACn in a 21mm Mitroflow, and BVF after VIV

Video 7: VIV with a 23mm Evolut R in a 21mm Mitroflow, and no BVF

Video 8: VIV with a 23mm Evolut R in a 21mm Mitroflow, and BVF before VIV

Video 9: VIV with a 23mm Evolut R in a 21mm Mitroflow, and BVF after VIV