**Title:** **Impact of implant depth on hydrodynamic function with the ALLEGRA transcatheter heart valve following valve-in-valve intervention.**

**Authors:** Janarthanan Sathananthan, MBChB, MPH; Rob Fraser, MSc; Maximilian Kütting, PhD; Mark Hensey, MB, BCh, BAO; Uri Landes, M.D; Abdullah Alkhodair, M.D; Alexander Sedaghat, M.D; Philipp Blanke, M.D; Stefan Toggweiler, M.D; Jonathon Leipsic, M.D; Lars Søndergaard, M.D; David Wood, M.D; John G Webb, M.D

**DOI:** 10.4244/EIJ-D-19-00782

**Citation:** Sathananthan J, Fraser R, Kütting M, Hensey M, Landes U, Alkhodair A, Sedaghat A, Blanke P, Toggweiler S, Leipsic J, Søndergaard L, Wood D, Webb JG. Impact of implant depth on hydrodynamic function with the ALLEGRA transcatheter heart valve following valve-in-valve intervention. *EuroIntervention* 2019; Jaa-665 2019, doi: 10.4244/EIJ-D-19-00782

**Guest Editor:** Alec Vahanian, M.D, PhD

**Manuscript submission date:** 25 August 2019

**Revisions received:** 19v September 2019, 03 October 2019

**Accepted date:** 11 October 2019

**Online publication date:** 15 October 2019

**Impact of implant depth on hydrodynamic function with the ALLEGRA transcatheter heart valve following valve-in-valve intervention**

Janarthanan Sathananthan MBChB, MPH[1], Rob Fraser MSc[2], Maximilian Kütting PhD[3], Mark Hensey MB BCh BAO[1], Uri Landes MD[1], Abdullah Alkhodair MD[1], Alexander Sedaghat MD[4], Philipp Blanke MD[1], Stefan Toggweiler MD[5], Jonathon Leipsic MD[1], Lars Søndergaard MD[6], David Wood MD[1], John G Webb MD[1]

[1]Centre for Heart Valve Innovation, St Paul's Hospital, University of British Columbia, Vancouver, Canada

[2]ViVitro Labs Inc, Victoria, Canada

[3]New Valve Technology, Hechingen, Germany

[4]Med. Klinik und Poliklinik II, Herzzentrum, Universitätsklinikum Bonn, Germany

[5]Heart Center Lucerne, Luzerner Kantonsspital, Switzerland

[6]Rigshospitalet, Cardiology, Copenhagen, Denmark

**Correspondence**:

John Webb MD

St. Paul's Hospital, 1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6

Email: johngraydonwebb@gmail.com

**Financial disclosures**

Dr Blanke and Dr. Leipsic are consultants to Edwards Lifesciences and provide CT core lab services for Edwards Lifesciences, Medtronic, Neovasc, GDS, and Tendyne Holdings, for which no direct compensation is received. Dr. Leipsic has stock options in, is a consultant to, and receives institutional research support from HeartFlow. Dr. Leipsic is supported by a Canadian Research Chair in Advanced CardioPulmonary Imaging. Dr Sathananthan has received speaking fees and is a consultant to Edwards Lifesciences. Dr. Sedaghat has received travel grants from Abbott, Boston Scientific, Edwards Lifesciences, New Valve Technologies and Medtronic. Dr Lars Sondergaard has received consultant fees and institutional research grants from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, and Symetis. Dr Toggweiler is a consultant and proctor for Boston Scientific and NVT GmbH. He has also received an institutional research grant from Boston Scientific. Dr. Webb is a consultant to, and has received research funding from, Edwards Lifesciences, Abbott Vascular, and ViVitro Labs. Dr Wood is a consultant to Edwards Lifesciences.



**Key words**: valve-in-valve, prior cardiovascular surgery, aortic stenosis, valve restenosis, TAVI, degenerative valve

**Running title**: ALLEGRA valve-in-valve bench study

**ABSTRACT**

**Aims:**

We assessed the impact of implant depth on hydrodynamic function following valve-in-valve (VIV) intervention using the ALLEGRA (New Valve Technology, Hechingen, Germany) transcatheter heart valve (THV) in three different surgical valve designs.

**Methods and results:**

Multiple implantation depths (+2mm, -2mm and -6mm) were tested using a 23mm ALLEGRA THV for VIV intervention in 19mm, 21mm, 23mm, and 25mm Epic, Mitroflow and Magna Ease bioprosthetic valves. Multimodality imaging and hydrodynamic evaluation was performed at each implantation depth. The 23mm ALLEGRA valve had gradients <20mmHg in the Mitroflow and Epic valves sized ≥21mm, and in all sizes of the Magna Ease valve. Gradients did not increase significantly at lower implantation depths. The 19mm Epic (+2mm: 20.1±0.6mmHg, -2mm: 18.8±0.5mmHg, -6mm: 22.8±0.3mmHg) and 19mm Mitroflow (+2mm: 24.1±0.2mmHg, -2mm: 31.5±0.3mmHg, -6mm: 25.6±0.2mmHg) valves, had elevated mean gradients. In larger sized surgical valves (≥23mm) the regurgitant fraction was higher at low implantation depths. Pinwheeling was significantly worse in the smaller sized (≤21mm) surgical valves and also at low (<-2mm) implantation depth.

**Conclusion:**

The 23mm ALLEGRA valve had favourable (<20mmHg) gradients in all surgical valves sized ≥21mm, even when the THV was implanted low. In 19mm sized Mitroflow and Epic valves, gradients were elevated (>20mmHg). While there was no major difference in mean transvalvular gradients, leaflet pinwheeling was worse at lower implantation depths.

## CONDENSED ABSTRACT

We assessed the impact of implant depth on hydrodynamic function following valve-in-valve (VIV) intervention using the ALLEGRA (New Valve Technology, Hechingen, Germany) transcatheter heart valve (THV) in different surgical valves. Multiple implantation depths (+2mm, -2mm and -6mm) were tested using a 23mm ALLEGRA THV for VIV intervention in 19mm, 21mm, 23mm, and 25mm Epic, Mitroflow and Magna Ease bioprosthetic valves. The 23mm ALLEGRA valve had favourable (<20mmHg) gradients in all surgical valves sized ≥21mm, even when the THV was implanted low. While there was no major difference in mean transvalvular gradients, leaflet pinwheeling was worse at lower implantation depths.



## ACRONYMS

EOA: Effective orifice area

RF: Regurgitant fraction

THV: Transcatheter heart valve

VIV: Valve-in-valve

## INTRODUCTION

Valve-in-valve (VIV) intervention is an alternative treatment to reoperation for patients with failed bioprosthetic surgical valves(1,2). However, in small sized surgical valves, high gradients may persist after VIV, which may lead to poor clinical outcomes(1). Different transcatheter heart valves (THV) can be utilized for VIV intervention, and some designs may result in superior performance following VIV intervention(3). The ALLEGRA valve (New Valve Technology, Hechingen, Germany) is a commercially available THV(4,5). However, there is less experience using this THV for VIV intervention compared to other commercially available THVs. Early in vitro and clinical experience have shown favourable hemodynamic performance using the ALLEGRA THV for VIV interventions(6,7). The optimum implantation depth and position of this THV relative to the surgical valve is poorly understood.

We assessed the impact of implant depth on hydrodynamic function using the ALLEGRA THV for VIV intervention in different surgical aortic bioprosthetic valves, of different sizes.

## METHODS

Testing was performed at the Centre for Heart Valve Innovation bench testing laboratory, and ViVitro Laboratories.

VIV intervention was assessed in 19mm, 21mm, 23mm and 25mm Mitroflow (Sorin Group Canada Inc, Burnaby, Canada), Epic (St Jude Medical, Minneapolis, MN, USA) and Magna Ease (Edwards Lifesciences, Irvine, CA, USA) aortic surgical bioprostheses, at three implantation depths (+2mm,-2mm,-6mm).



### Valves

The ALLEGRA THV is a self-expanding TAVI prosthesis which is a trileaflet, bovine pericardial bioprosthetic aortic heart valve attached to a nitinol stent frame. The THV leaflets are positioned in a supra-annular position with the base of the leaflets inserting 12mm above the inflow. By contrast the base of the leaflets of an Evolut R (Medtronic Inc, St Pauls, Minnesota, USA) and Edwards SAPIEN 3 (Edwards Lifesciences Inc, Irvine, CA), insert 13mm and 3mm above the inflow, respectively. The nitinol stent frame has a closed cell, diamond-shaped configuration with a variable cell size distribution. Six radiopaque gold markers are placed at the level of the valve plane to indicate the distal part of the semilunar valve. The ventricular inflow section of the prosthesis is covered by a bovine pericardial sealing skirt. The ALLEGRA transcatheter heart valve is available in three sizes (23, 27 and 31 mm) to match aortic annulus dimensions ranging from 19 to 28 mm(8). The 23mm ALLEGRA valve was utilized for this study, which has an inflow and outflow diameter of 23.8mm and 20.8mm, respectively. The commissural outflow diameter of a 23mm ALLEGRA is 24mm.The frame height is 37.3mm. (Figure 1).

The Mitroflow (Sorin Group Canada Inc, Burnaby, Canada) bioprosthesis consists of a polyester covered acetyl homopolymer stent frame. Bovine pericardial sheets sutured externally to form the leaflets. (9). The 19mm, 21mm, 23mm and 25mm Mitroflow valves have a true internal diameter of 15.4mm, 17mm, 19mm and 21mm, respectively(10).

The Epic (Abbott, Abbott Park, Illinois, USA) bioprosthesis consists of a dacron covered acetyl copolymer stent. Porcine leaflets are sutured within the stent frame(11). The 19mm, 21mm, 23mm and 25mm Epic valves have a true internal diameter of 17mm, 19mm, 21mm and 23mm, respectively(10).

The Magna Ease (Edwards Lifesciences, Irvine, CA, USA) valve is composed of a polytetrafluoroethylene cloth covered cobalt chromium stent. Bovine pericardial tissue are sutured within the stent frame. The 19mm, 21mm, 23mm and 25mm Magna Ease valves have a true internal diameter of 17mm, 19mm, 21mm and 23mm, respectively(10).



**Valve-in-valve procedure**

Three implantation depths (+2mm, -2mm and -6mm) were tested using a 23mm ALLEGRA THV for VIV intervention in the four sizes of Epic, Mitroflow and Magna Ease tested. In the VIV configuration using the Mitroflow valve, implantation depth was measured from the lower border of the radiopaque ring of the valve to the lowest point of the frame of the ALLEGRA THV. With the Epic and Magna Ease bioprostheses, implantation depth was measured from the lower border of the sewing ring to the lowest point of THV (Figure 1). Implantation depth was measured with both fluoroscopy and macroscopic measurements using digital scientific calipers.

**Imaging**

Imaging was performed at each tested implant depth by the utilization of high resolution photography. The latter was performed at the a prespecified magnification and fixed camera height. Fluoroscopic images were acquired using a standard adult cardiac catheterization laboratory (General Electric Healthcare, Chicago, Illinois).



**Hydrodynamic assessment**

Hydrodynamic testing was performed at each implant depth tested, 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 litres per minute. Mean gradient (mmHg), regurgitant fraction (%) and effective orifice area ($cm^2$) were assessed. The ISO standards for regurgitant fraction for a 23mm THV stipulate a minimum performance requirements of <10%. The effective orifice area was defined as the orifice area that has been derived from flow and pressure where $qv_{RMS}$ is the root mean square flow in ml/s, $\Delta$P is the mean pressure difference (measured over the positive differential pressure period of the forward flow phase) in mmHg, $\rho$ is the density of the test fluid in $g/cm^3$. This equation is derived from a simplified version of the Bernoulli equation.

$$\mathrm{EOA} = \frac{q_{V\ \mathrm{RMS}}}{51{,}6 * \sqrt{\frac{\Delta p}{\rho}}}$$



**Pinwheeling**

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). The degree of pinwheeling was based on high speed videos with backward pressure.

**Statistics**

Hydrodynamic variables are reported as mean $\pm$ SD.

**RESULTS**

Valve hydrodynamics

*Transvalvular gradient:*

Mean transvalvular gradients for the tested surgical valves at different implantation depths are reported in Table 1 and Figure 2. There was no major difference in mean transvalvular gradients with lower implantation depths. The 23mm ALLEGRA valve had <20mmHg gradients in all surgical valves sized ≥21mm at all implantation depths tested. The Magna Ease 19mm valve also had favourable gradients with mean transvalvular gradients of 10.5±0.mmHg, 12.9±0.1mmHg and 16.3±0.1mmHg, at an implantation depth of +2mm, -2mm and -6mm, respectively. In the 19mm Epic valve, the mean transvalvular gradient was 20.1±0.6mmHg, 18.8±0.5mmHg and 22.8±0.3mmHg, at an implantation depth of +2mm, -2mm and -6mm, respectively. In the 19mm Mitroflow valve, the mean transvalvular gradient was 24.1±0.2mmHg, 31.5±0.3mmHg and 25.6±0.2mmHg, at an implantation depth of +2mm, -2mm and -6mm, respectively.

*Effective orifice area:*

Effective orifice areas for the tested surgical valves at different implantation depths are reported in Table 2. For surgical valves sized ≥21mm, the EOAs remained similar irrespective of implantation depth of the 23mm ALLEGRA valve. In the 19mm Epic and Mitroflow surgical valves, EOAs remained similar irrespective of implantation depth. In the

19mm Magna Ease a lower implantation resulted in lower EOAs, with EOAs of 1.8±0.01cm$^2$, 1.6±0.01cm$^2$, and 1.4±0.01cm$^2$, at an implantation depth of +2mm, -2mm and -6mm, respectively.

*Regurgitant fraction:*

Regurgitant fractions for the tested surgical valves at different implantation depths are reported in Table 3. The ALLEGRA valve had favourable RF (<10%) in the Epic valve in all sizes and implantation depths. The Mitroflow valve had higher RF at an implant depth of +2mm for valves sized between 19mm (+2mm: 20.6±0.6%, -2mm: 8.4±0.6%, -6mm: 9.0±0.6%) 21mm (+2mm: 18.6±0.5%, -2mm: 14.3±0.5%, -6mm: 14.3±0.4%) and 23mm (+2mm: 16.9±0.7%, -2mm: 13.7±0.5%, -6mm: 13.9±0.5%). The 25mm Mitroflow had higher RF with lower implantation of the ALLEGRA THV (+2mm: 11.0±0.4%, -2mm: 21.3±0.4%, -6mm: 23.0±0.5%). The Magna Ease had higher RF in larger sized surgical valves and at lower implantation in the 23mm (+2mm: 16.5±0.5%, -2mm: 16.9±0.9%, -6mm: 20.7±0.6%) and 25mm (+2mm: 19.2±0.5%, -2mm: 11.5±0.6%, -6mm: 24.4±0.4%) sized valves.



Pin-wheeling

The degree of leaflet pinwheeling with maximum backward pressure are shown for the tested surgical valves at different implantation depths in Figures 3-5. Pinwheeling was significantly worse in the smaller sized surgical valves and also at lower implantation

## DISCUSSION

In this study, a unique finding with the ALLEGRA THV was that implantation depth did not significantly affect transvalvular gradients in all three tested surgical valves. By contrast, bench studies with the SAPIEN XT (Edwards Lifesciences Inc., Irvine, CA), CoreValve Evolut (Medtronic Inc, St Pauls, Minnesota, USA), Portico (Abbott, Abbott Park, Illinois, USA), and ACURATE neo (Boston Scientific Corporation, Natick, MA) THVs have all shown that lower implantation is associated with higher transvalvular gradients, compared to a high implant(16,17). Prior bench studies have shown that other self-expandable valves, the Portico and CoreValve Evolut THV, both had significantly lower mean gradients with a higher implantation. A lower implantation with these self-expandable valve has been shown to result in higher mean gradient(18).



In this study, the mean gradients remain generally consistent at all implantation depths, irrespective of surgical bioprosthetic valve type or size. Even with low implantation, the mean gradient did not vary significantly compared to a higher implant. Similarly the EOAs also remained similar, even with lower implantation depths. This may potentially be related to the supra-annular position of the THV leaflet. Of note, even at an implant depth of -6mm, the top of the THV leaflets, still extended above the surgical valve posts in THVs with supra-annular leaflet position. Valve implantation at depths >6mm, where the THV leaflets are at an intra-annular position, may potentially compromise EOAs and hydrodynamic function. Importantly, while mean gradients remained favourable, a low implantation with the ALLEGRA THV resulted in worse leaflet pinwheeling. Leaflet pinwheeling is a result of redundant leaflet tissue that can lead to increased strain and compromise THV durability(19). Therefore while gradients may be favourable, avoidance of a low implantation depth is still desirable to prevent leaflet pinwheeling. A low implantation in this study was also associated with higher RF in the larger sized (>23mm) valves tested in this study.

Based on prior bench studies, a higher implant is generally preferred to optimize hydrodynamic performance. However this does not necessarily apply to all THVs or surgical valve designs. In this study an implant depth of +2mm was desirable for the ALLEGRA THV in both Epic and Magna Ease surgical valves. However a +2mm depth in the Mitroflow valve was associated with higher RF, while an implant depth of -2mm resulted in the optimal hydrodynamic performance with the ALLEGRA THV. These differences are potentially related to design differences between the different surgical valves. At an implantation depth of +2mm, the base of the ALLEGRA THV was at the upper border of the sewing ring which may have led to higher regurgitant fraction. A potential lack of adequate sealing from the skirt of the ALLEGRA THV may have led to a high regurgitant fraction due to leak between the surgical valve and the ALLEGRA THV. Clinicians must be cognisant of the design features of each THV and its implications in different failed surgical valve types. In lieu of clinical evidence, bench testing can provide guidance on implantation depth to aid clinicians during clinical VIV interventions.

## Limitations

Bench testing may not entirely reflect how the THV will expand in a patient's native annulus, within a degenerated surgical bioprostheses, or valve deployment under physiological conditions. The findings of these study require correlation with clinical series. The long-term implications of implant depth and effect of pinwheeling would also be important to ascertain in future studies.

## CONCLUSION

The 23mm ALLEGRA valve had favourable (<20mmHg) gradients in all surgical valves sized ≥21mm, even when the THV was implanted low. In 19mm sized Mitroflow and Epic valves, gradients were elevated (>20mmHg). While there was no major difference in mean transvalvular gradients, leaflet pinwheeling was worse at lower implantation depths.



## IMPACT ON DAILY PRACTICE

Clinical experience with the ALLEGRA THV is currently limited for VIV interventions. This study has shown that the ALLEGRA THV has favourable transvalvular gradients in multiple surgical valve designs sized ≥21mm. Importantly the gradients remained similar at all implantation depths, with no significant increase in gradients with lower implantation. While transvalvular gradients remained favourable even at low implantation depths, there was worse leaflet pinwheeling with a low implantation. This may have important implications for leaflet wear and durability. Bench testing can provide guidance to aid clinicians during VIV interventions with newer THV designs, where clinical evidence may be limited.

**REFERENCES**

1. 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.

2. 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-in-valve registry. Circulation. 2012 Nov 6;126(19):2335-44.

3. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, Schaefer U, Rodés-Cabau J, Treede H, Piazza N, Hildick-Smith D, Himbert D, Walther T, Hengstenberg C, Nissen H, Bekeredjian R, Presbitero P, Ferrari E, Segev A, de Weger A, Windecker S, Moat NE, Napodano M, Wilbring M, Cerillo AG, Brecker S, Tchetche D, Lefèvre T, De Marco F, Fiorina C, Petronio AS, Teles RC, Testa L, Laborde JC, Leon MB, Kornowski R; Valve-in-Valve International Data Registry Investigators. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA. 2014 Jul;312(2):162-70.

4. Kim WK, Möllmann H, Liebetrau C, Renker M, Rolf A, Simon P, Van Linden A, Arsalan M, Doss M, Hamm CW, Walther T. The ACURATE neo Transcatheter Heart Valve: A Comprehensive Analysis of Predictors of Procedural Outcome. JACC Cardiovasc Interv. 2018 Sep 10;11(17):1721-1729.

5. Kim WK, Hengstenberg C, Hilker M, Kerber S, Schäfer U, Rudolph T, Linke A, Franz N, Kuntze T, Nef H, Kappert U, Zembala MO, Toggweiler S, Walther T, Möllmann H. The SAVI-TF Registry: 1-Year Outcomes of the European Post-Market Registry Using the ACURATE neo Transcatheter Heart Valve Under Real-World Conditions in 1,000 Patients. JACC Cardiovasc Interv. 2018 Jul 23;11(14):1368-1374.

6. Schäfer U, Butter C, Landt M, Frerker C, Treede H, Schirmer J, Koban C, Allali A, Schmidt T, Charitos E, Conradi L. Thirty-day outcomes of a novel transcatheter heart valve to treat degenerated surgical valves - The "VIVALL" multi-center, single-arm, pilot study. EuroIntervention. 2019 Jul 30. pii: EIJ-D-19-00331.

7. Sedaghat A, Sinning JM, Werner N, Nickenig G, Conradi L, Toggweiler S, Schäfer U. In vitro hydrodynamic and acute clinical performance of a novel self-expanding transcatheter heart valve in various surgical bioprostheses. EuroIntervention. 2018 Apr 20;13(17):2014-2017.

8. Wenaweser P, Stortecky S, Schütz T, Praz F, Gloekler S, Windecker S, Elsässer A. Transcatheter aortic valve implantation with the NVT Allegra transcatheter heart valve system: first-in-human experience with a novel self-expanding transcatheter heart valve. EuroIntervention. 2016 May 17;12(1):71-7.

9. 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.

10. 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.

11. Jamieson WR, Lewis CT, Sakwa MP, Cooley DA, Kshettry VR, Jones KW, David TE, Sullivan JA, Fradet GJ, Bach DS. St Jude Medical Epic porcine bioprosthesis:results of the regulatory evaluation. J Thorac Cardiovasc Surg. 2011 Jun;141(6):1449-54.e2.

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. 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).

17. 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 <i>neo</i> 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.

18. Simonato M, Azadani AN, Webb J, Leipsic J, Kornowski R, Vahanian A, Wood D, Piazza N, Kodali S, Ye J, Whisenant B, Gaia D, Aziz M, Pasala T, Mehilli J, Wijeysundera HC, Tchetche D, Moat N, Teles R, Petronio AS, Hildick-Smith D, Landes U, Windecker S, Arbel Y, Mendiz O, Makkar R, Tseng E, Dvir D. In vitro evaluation of implantation depth in valve-in-valve using different transcatheter heart valves. EuroIntervention. 2016 Sep 18;12(7):909-17.

19. 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.

**FIGURES AND TABLES**

**Table 1:** Mean transvalvular gradient by implant depth for VIV intervention with the 23mm ALLEGRA

**Table 2:** Effective orifice area by implant depth for VIV intervention with the 23mm ALLEGRA

**Table 3:** Regurgitant fraction by implant depth for VIV intervention with the 23mm ALLEGRA

**Figure 1: Bench testing methodology**

Panel A: Example of an ALLEGRA THV; Panel B: Pulse duplicator used for hydrodynamic testing; Panel C: Implantation depth was measured from the lower border of the radiopaque ring of the Mitroflow valve to the lowest point of the frame of the ALLEGRA THV. With the Epic and Magna Ease bioprostheses, implantation depth was measured from the lower border of the sewing ring to the lowest point of THV.

**Figure 2: Photography, fluoroscopy and mean gradient by implant depth for VIV with the 23mm ALLEGRA THV in Epic, Mitroflow and Magna Ease bioprosthetic valves**

Panel A: VIV with ALLEGRA THV in 19mm Epic bioprosthetic valve; Panel B: VIV with ALLEGRA THV in 21mm Epic bioprosthetic valve; Panel C: VIV with ALLEGRA THV in 23mm Epic bioprosthetic valve; Panel D: VIV with ALLEGRA THV in 25mm Epic bioprosthetic valve. Panel E: VIV with ALLEGRA THV in 19mm Mitroflow bioprosthetic valve; Panel F: VIV with ALLEGRA THV in 21mm Mitroflow bioprosthetic valve; Panel G: VIV with ALLEGRA THV in 23mm Mitroflow bioprosthetic valve; Panel H: VIV with ALLEGRA THV in 25mm Mitroflow bioprosthetic valve.

Panel I: VIV with ALLEGRA THV in 19mm Magna Ease bioprosthetic valve; Panel J: VIV with ALLEGRA THV in 21mm Magna Ease bioprosthetic valve; Panel K: VIV with ALLEGRA THV in 23mm Magna Ease bioprosthetic valve; Panel L: VIV with ALLEGRA THV in 25mm Magna Ease bioprosthetic valve.

**Figure 3:** High speed video images by implant depths for VIV intervention with the 23mm ALLEGRA THV in Epic bioprosthetic valve with backward pressure

**Figure 4:** High speed video images by implant depths for VIV intervention with the 23mm ALLEGRA THV in Mitroflow bioprosthetic valve with backward pressure

**Figure 5:** High speed video images by implant depths for VIV intervention with the 23mm ALLEGRA THV in Magna Ease bioprosthetic valve with backward pressure

Table 1

| Valve | Implant Depth | 19mm | 21mm | 23mm | 25mm |
|---|---|---|---|---|---|
| Epic | 2mm | 20.1±0.6mmHg | 13.4±0.4mmHg | 12.4±0.9mmHg | 13.2±0.2mmHg |
| | -2mm | 18.8±0.5mmHg | 13.1±1.7mmHg | 12.0±1.8mmHg | 13.2±0.9mmHg |
| | -6mm | 22.8±0.3mmHg | 11.7±0.6mmHg | 12.4±0.4mmHg | 13.9±0.9mmHg |
| Mitroflow | 2mm | 24.1±0.2mmHg | 12.4±0.2mmHg | 9.1±0.1mmHg | 6.8±0.0mmHg |
| | -2mm | 31.5±0.3mmHg | 15.2±0.2mmHg | 10.1±0.2mmHg | 6.8±0.0mmHg |
| | -6mm | 25.6±0.2mmHg | 14.7±0.1mmHg | 9.5±0.1mmHg | 6.8±0.2mmHg |
| Magna Ease | 2mm | 10.5±0.1mmHg | 9.6±0.1mmHg | 7.6±0.0mmHg | 6.7±0.0mmHg |
| | -2mm | 12.9±0.1mmHg | 9.3±0.1mmHg | 7.4±0.1mmHg | 6.3±0.1mmHg |
| | -6mm | 16.3±0.1mmHg | 10.5±0.1mmHg | 7.8±0.1mmHg | 6.9±0.0mmHg |

All values are mean±SD

Table 2

| Valve | Implant Depth | 19mm | 21mm | 23mm | 25mm |
|---|---|---|---|---|---|
| Epic | 2mm | 1.4±0.01cm$^2$ | 2.0±0.03cm$^2$ | 2.0±0.05cm$^2$ | 1.9±0.01cm$^2$ |
| | -2mm | 1.5±0.01cm$^2$ | 1.9±0.07cm$^2$ | 2.0±0.06cm$^2$ | 1.9±0.09cm$^2$ |
| | -6mm | 1.3±0.01cm$^2$ | 1.9±0.01cm$^2$ | 1.8±0.01cm$^2$ | 1.9±0.09cm$^2$ |
| Mitroflow | 2mm | 1.1±0.01cm$^2$ | 1.7±0.01cm$^2$ | 2.0±0.02cm$^2$ | 2.3±0.01cm$^2$ |
| | -2mm | 1.0±0.01cm$^2$ | 1.5±0.01cm$^2$ | 1.8±0.02cm$^2$ | 2.3±0.01cm$^2$ |
| | -6mm | 1.1±0.01cm$^2$ | 1.5±0.01cm$^2$ | 1.9±0.01cm$^2$ | 2.2±0.04cm$^2$ |
| Magna Ease | 2mm | 1.8±0.01cm$^2$ | 1.9±0.01cm$^2$ | 2.1±0.01cm$^2$ | 2.3±0.01cm$^2$ |
| | -2mm | 1.6±0.01cm$^2$ | 1.9±0.01cm$^2$ | 2.1±0.01cm$^2$ | 2.4±0.01cm$^2$ |
| | -6mm | 1.4±0.01cm$^2$ | 1.8±0.01cm$^2$ | 2.1±0.01cm$^2$ | 2.2±0.01cm$^2$ |

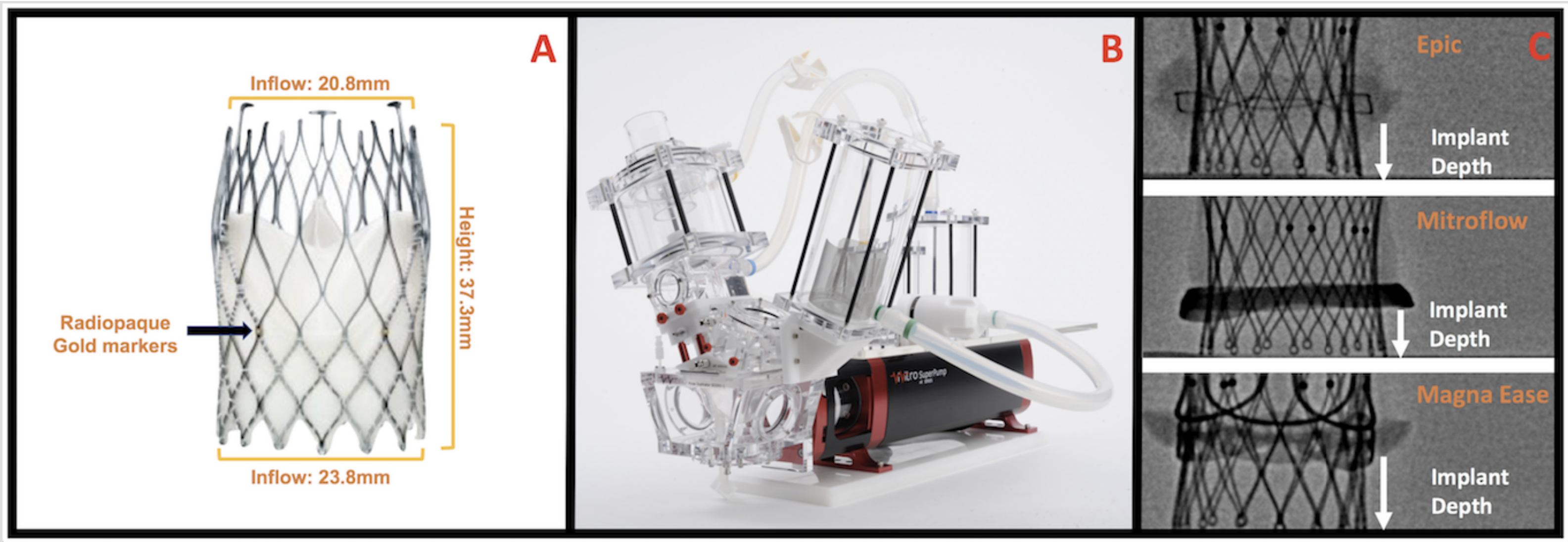
All values are mean±SD

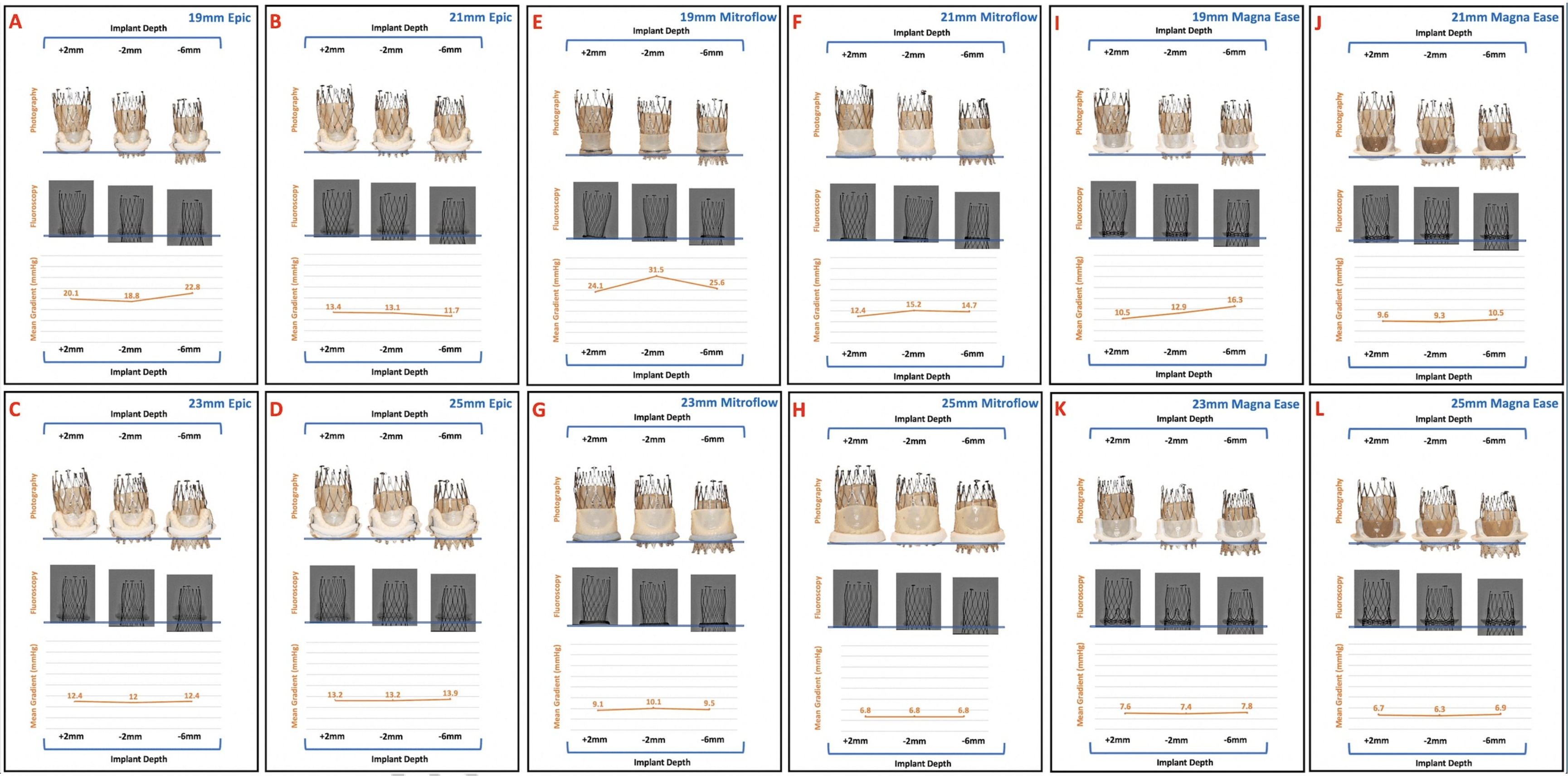


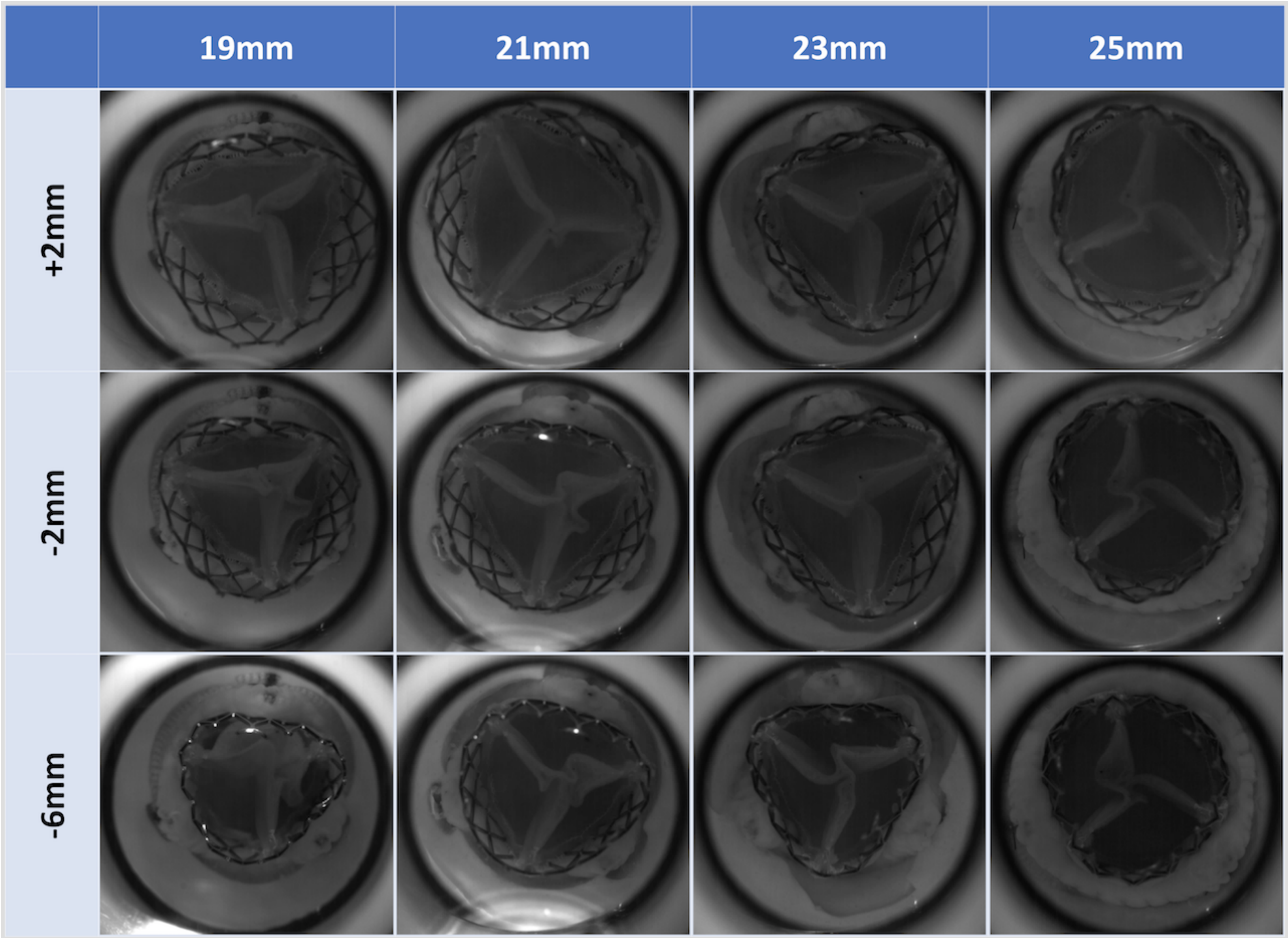
Table 3

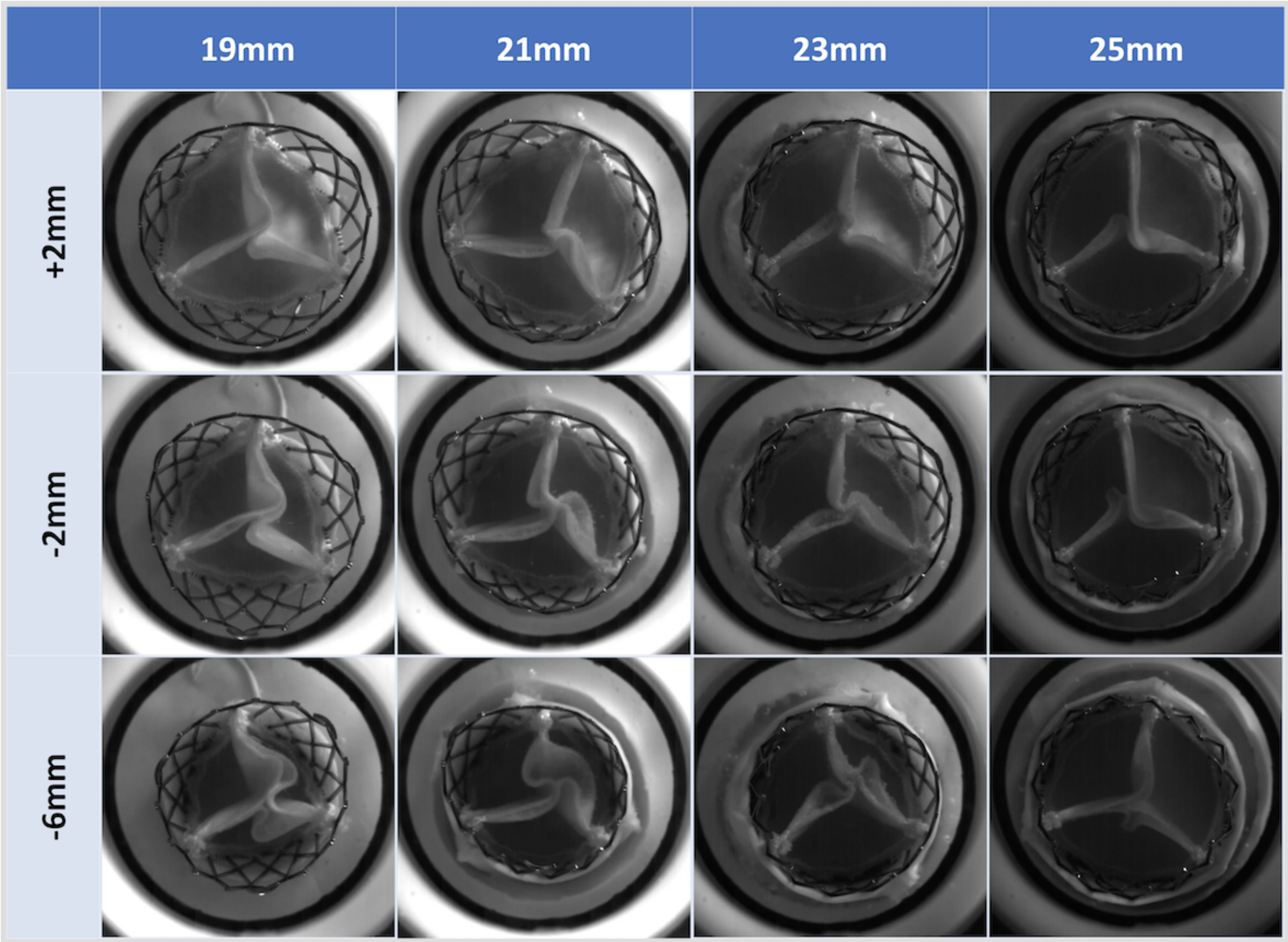
| Valve | Implant Depth | 19mm | 21mm | 23mm | 25mm |
|---|---|---|---|---|---|
| Epic | 2mm | 4.9±1.0% | 4.9±0.8% | 4.4±0.6% | 8.1±1.1% |
| | -2mm | 3.4±1.1% | 3.6±1.1% | 4.1±0.9% | 7.0±1.2% |
| | -6mm | 5.4±1.1% | 4.6±1.2% | 5.5±0.9% | 6.3±0.9% |
| Mitroflow | 2mm | 20.6±0.6% | 18.6±0.5% | 16.9±0.7% | 11.0±0.4% |
| | -2mm | 8.4±0.6% | 14.3±0.5% | 13.7±0.5% | 21.3±0.4% |
| | -6mm | 9.0±0.6% | 14.3±0.4% | 13.9±0.5% | 23.0±0.5% |
| Magna Ease | 2mm | 10.2±0.4% | 16.3±0.7% | 16.5±0.5% | 19.2±0.5% |
| | -2mm | 10.3±0.6% | 12.2±0.5% | 16.9±0.9% | 11.5±0.6% |
| | -6mm | 8.3±0.7% | 14.5±0.5% | 20.7±0.6% | 24.4±0.4% |

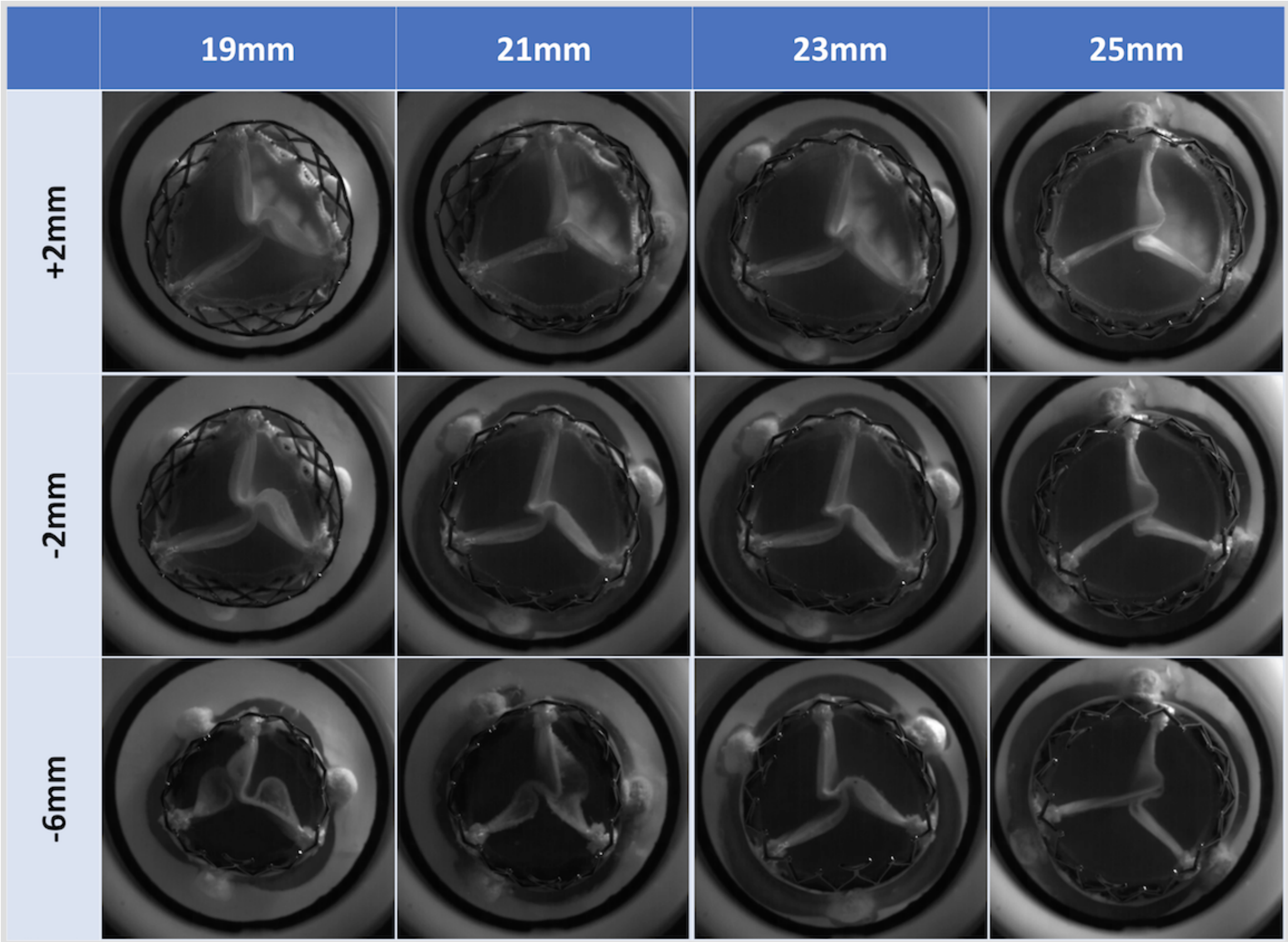
All values are mean±SD


A
Inflow: 20.8mm
Height: 37.3mm
Radiopaque
Gold markers
Inflow: 23.8mm
B
C
Epic
Implant
Depth
Mitroflow
Implant
Depth
Magna Ease
Implant
Depth


A
19mm Epic
B
21mm Epic
E
19mm Mitroflow
F
21mm Mitroflow
I
19mm Magna Ease
J
21mm Magna Ease
C
23mm Epic
D
25mm Epic
G
23mm Mitroflow
H
25mm Mitroflow
K
23mm Magna Ease
L
25mm Magna Ease
Implant Depth
+2mm
-2mm
-6mm
Photography
Fluoroscopy
Mean Gradient (mmHg)
20.1
18.8
22.8
13.4
13.1
11.7
24.1
31.5
25.6
12.4
15.2
14.7
10.5
12.9
16.3
9.6
9.3
10.5
12.4
12
12.4
13.2
13.2
13.9
9.1
10.1
9.5
6.8
6.8
6.8
7.6
7.4
7.8
6.7
6.3
6.9


19mm
21mm
23mm
25mm
+2mm
-2mm
-6mm


19mm
21mm
23mm
25mm
+2mm
-2mm
-6mm


19mm
21mm
23mm
25mm
+2mm
-2mm
-6mm