Lifetime Management Starts with First Valve Choice

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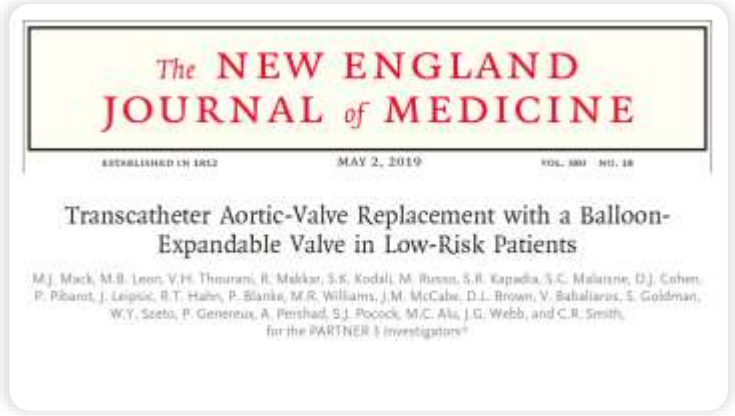
Lifetime Management of Low Risk Patients

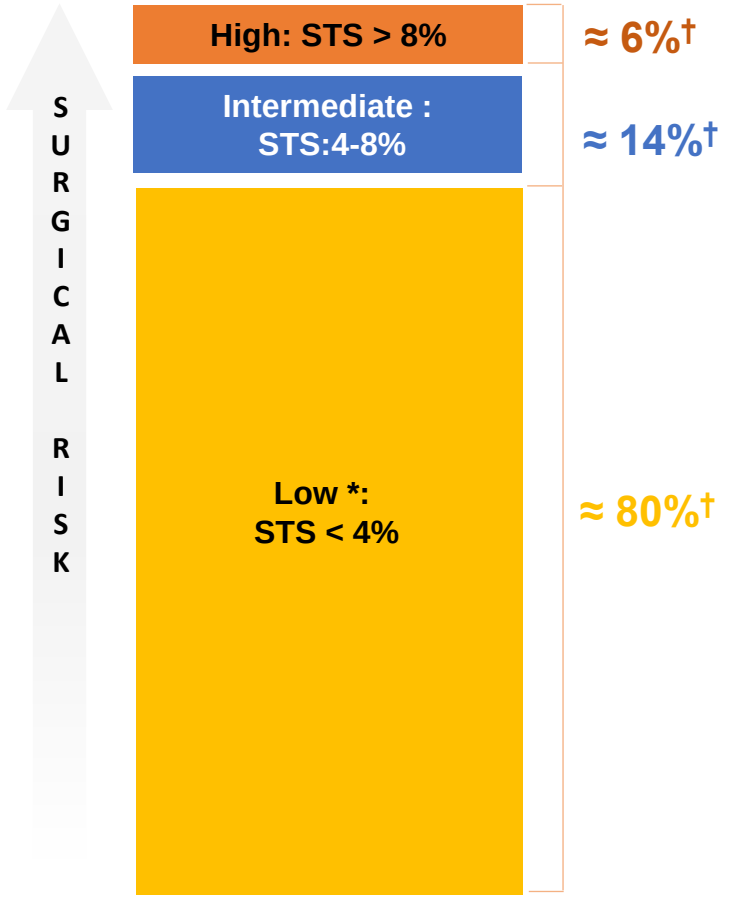
- **Lifetime Management TAVR vs SAVR: What Else Matters**
  - Mortality and Stroke: what is data telling us so far?
  - PVL: does mild leak matter?
  - LBBB or Pacemaker: benign?
  - Future Coronary Access (diagnostic, intervention for CAD): easy?
  - Other considerations:
    - What about bicuspid patients: do we have more data in TAVR
    - Reinterventions – is it feasible? If not what about re-do surgery or explant of THV?

- **Novel data to be mindful of to avoid unnecessary re-interventions**
  - Echo-Cath Discordance
    - How does this translate to gradients, PPM and Durability?
  - Evolution of Definitions in TAVR/SAVR
    - Need to be mindful of the differences

Evolution of TAVR

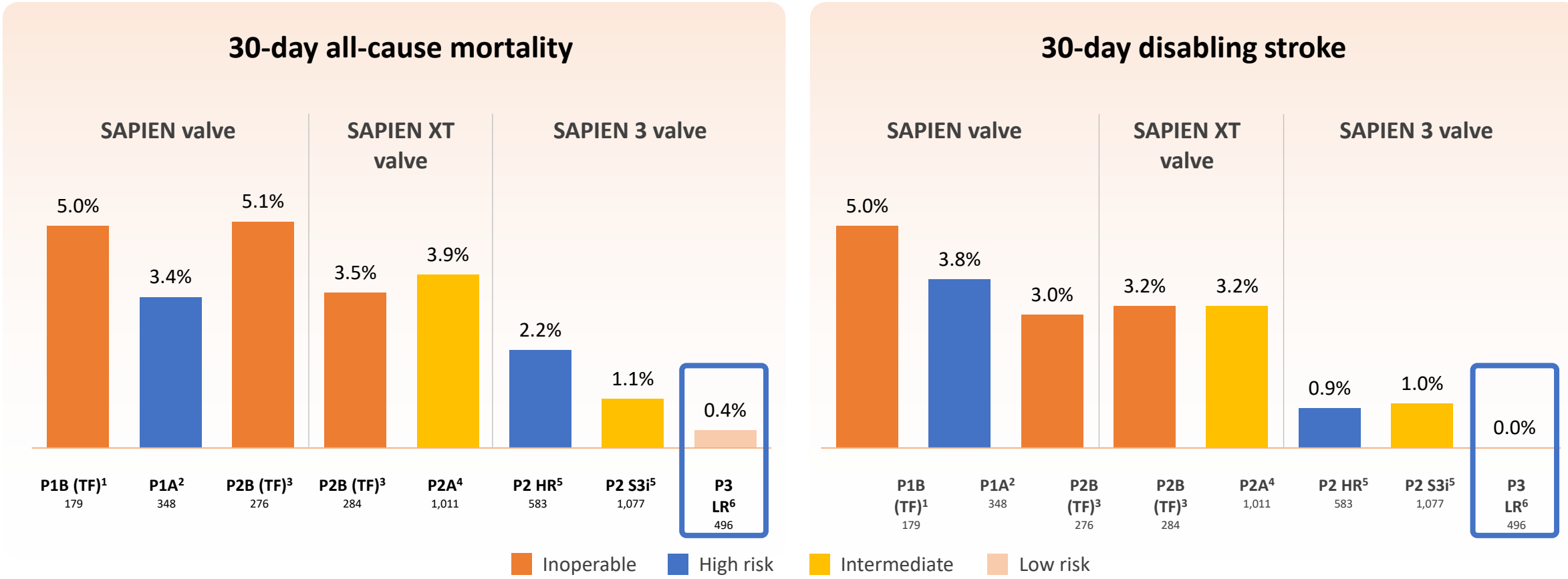
Outcomes from the PARTNER Trials have unlocked TAVI for patients with severe AS [1-5]





1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-1607. 2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-2198. 3. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374(17):1609-1620. 4. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380(18):1695-1705. 5. Thourani VH, Suri, RM, Dphil, et al. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg. 2015;99:55-61.

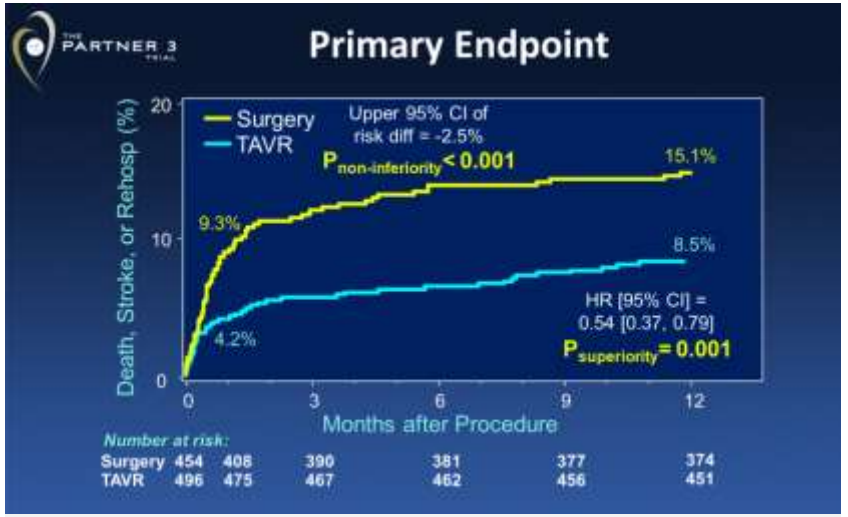
Improved TAVR Clinical Outcomes



1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597-1607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *N Engl J Med*. 2011;364:2187-2198.
3. Webb JG, Doshi D, Mack MJ, et al. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic stenosis who are not candidates for surgery. *JACC Cardiovasc Interv*. 2015;8(14):1797-1806.
4. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609-1620.
5. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J*. 2016;37(28):2252-2262.
6. Mack M, Leon M, Thourani R, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705.

PARTNER 3 Low Risk RCT

	30 days[1]		1 year[1]		
	TAVR	Surgery	TAVR	Surgery	P-Value[2]
All-cause mortality	**0.4%**	1.1%	**1.0%**	2.5%	<0.085
All-stroke	**0.6%**	2.4%	**1.2%**	3.1%	0.041
Rehospitalization	**3.4%**	6.5%	**7.3%**	11.0%	0.046
Life-threatening/disabling or major bleeding*	**3.6%**	24.5%	**7.7%**	25.9%	<0.0001
New-onset AFIB*	**5.0%**	39.5%	**7.0%**	40.9%	<0.0001
AKI*	**0.4%**	1.8%	**0.4%**	1.8%	0.0001



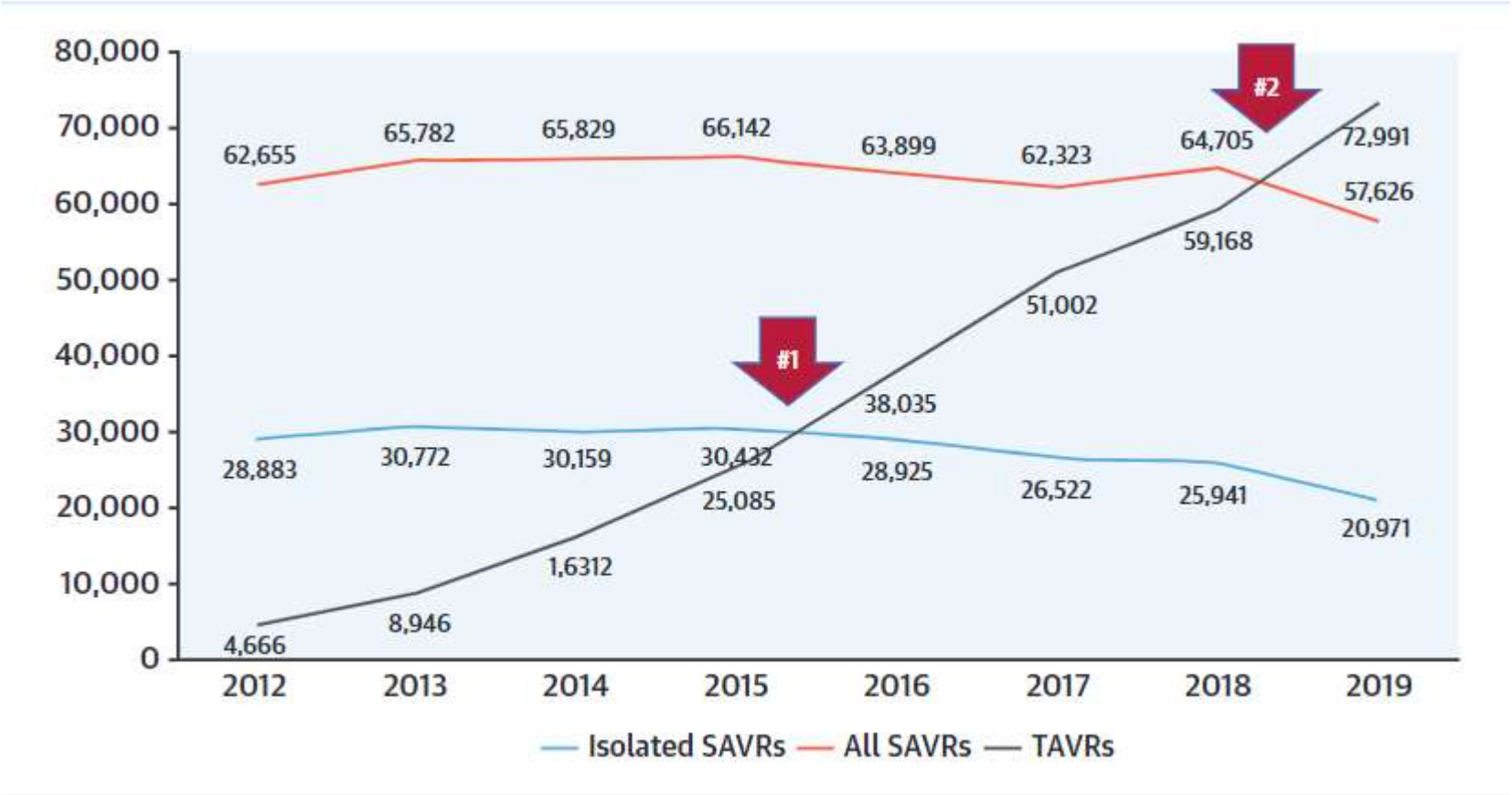
Delivering outcomes better than surgery in your low-risk patients:

- **Mortality**
- **Stroke**
- **Rehospitalization**
- **Bleeding**

*These endpoints were not subject to multiplicity adjustment.

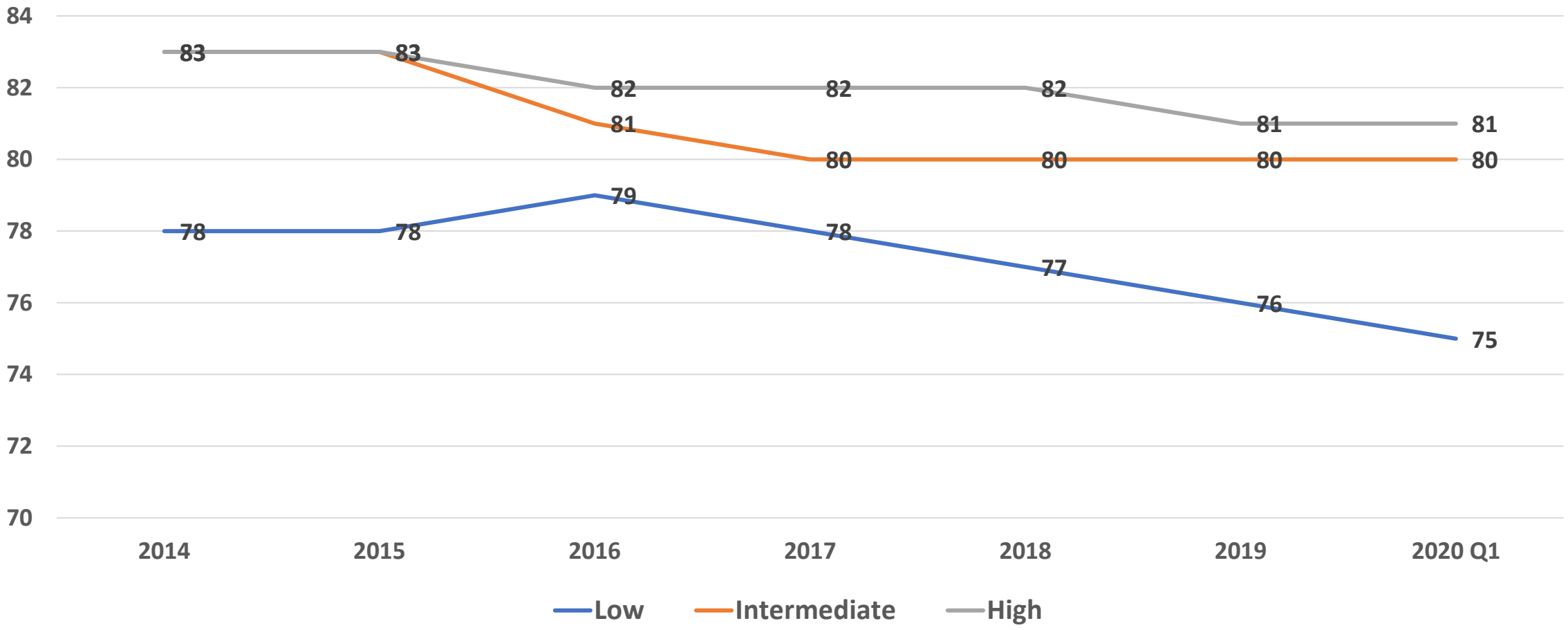
1. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med.* 2019;380(18):1695-1705.
2. The PARTNER 3 Trial, low-risk patients (N=496 TAVR, N=454 SAVR). Edwards Lifesciences clinical report on file.

TAVR Has Now Passed Isolated and All SAVRs in the US Market



Carroll J, et all. JACC 2020

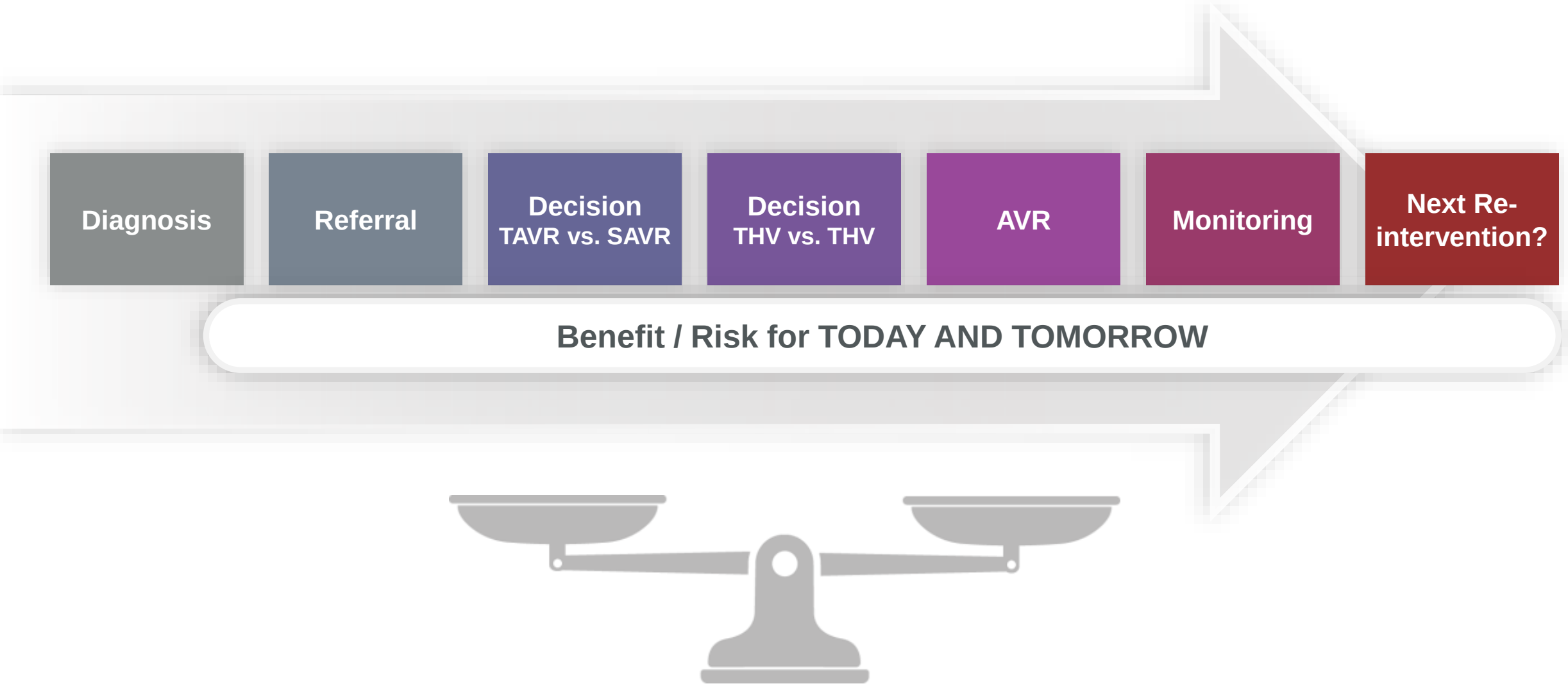
TAVR: Median Age



Considerations for the Young TAVR Patient

- Risk of Heart Block / need for Pacemaker
- Coronary Artery (Re)Access
- Valve Durability
- Lifetime Management – What is the next valve plan?
  - SAVR after TAVR
  - TAV-in-TAV
  - Valve-in-Valve TAVR

AS Patient Journey: Lifetime Management of AS



AS Patient Journey – Lifetime Management of AS

Durability

Age/Life Expectancy

Bicuspid

Future Coronary Access

Annulus Size

Valve-in-Surgical Valve

Lifestyle

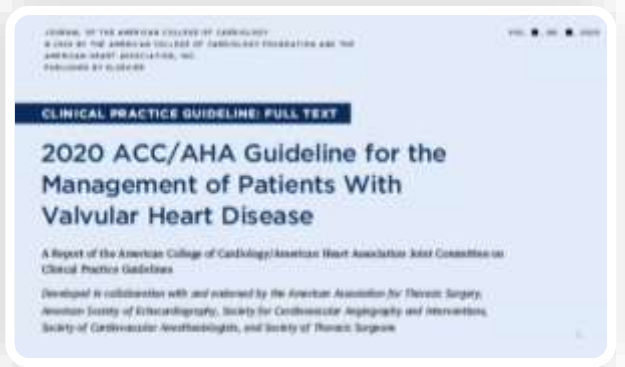
Coronary Heights

STJ Width/Height

Valve Explants

THV-in-THV

Sequence Planning:
1st Decision on AVR Impacts Others



AGE AT FIRST AVR Life Expectancy

Time after first AVR

~5

IMPLANT

1

15+

IMPLANT

1 — 2

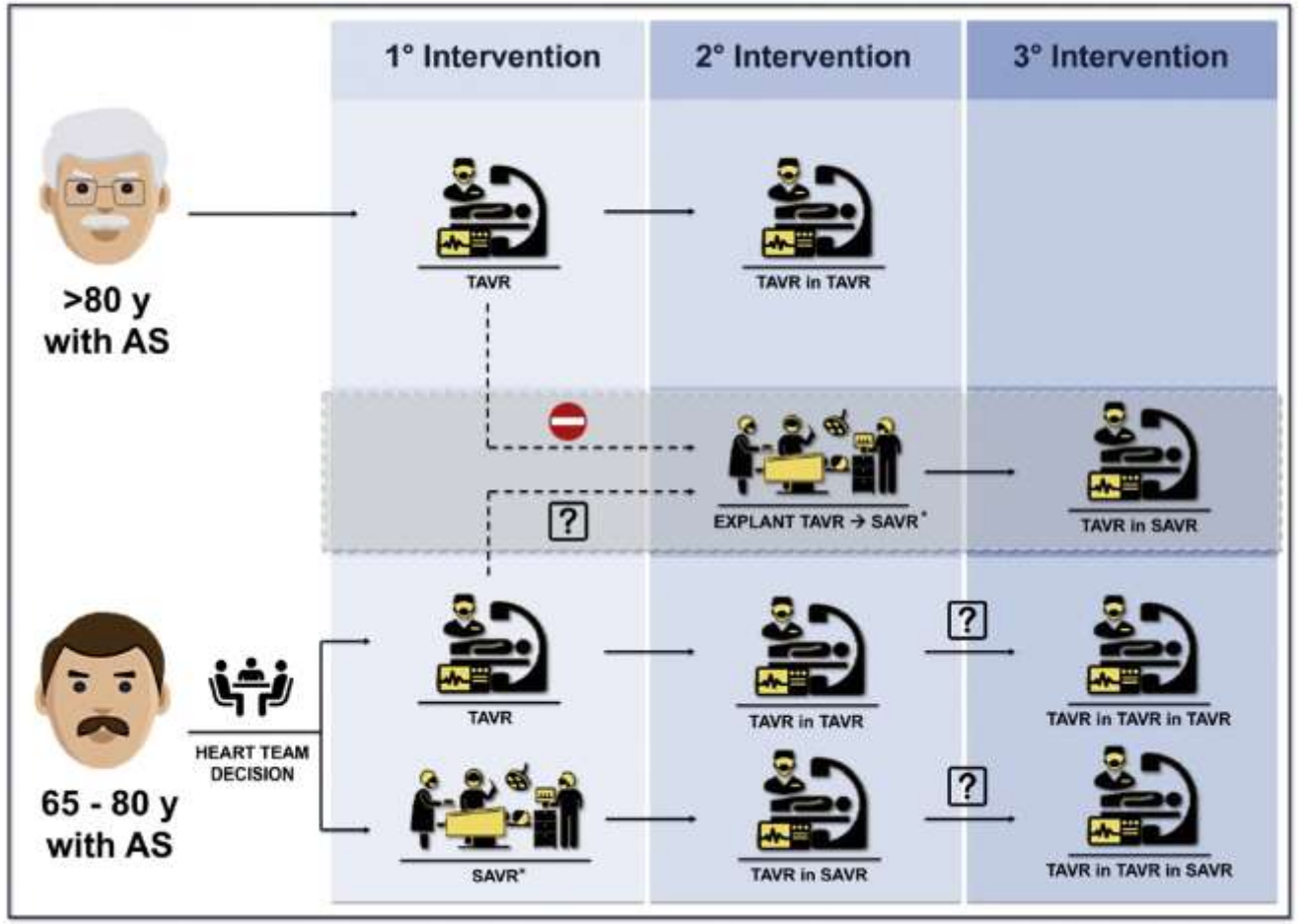
25+

IMPLANT

1 — 2 — 3

Decision for Today Impact Tomorrow Decisions

“[If] life expectancy exceeds the anticipated durability of valve… the Heart Team should envisage the impact of the first intervention on future therapeutic options”

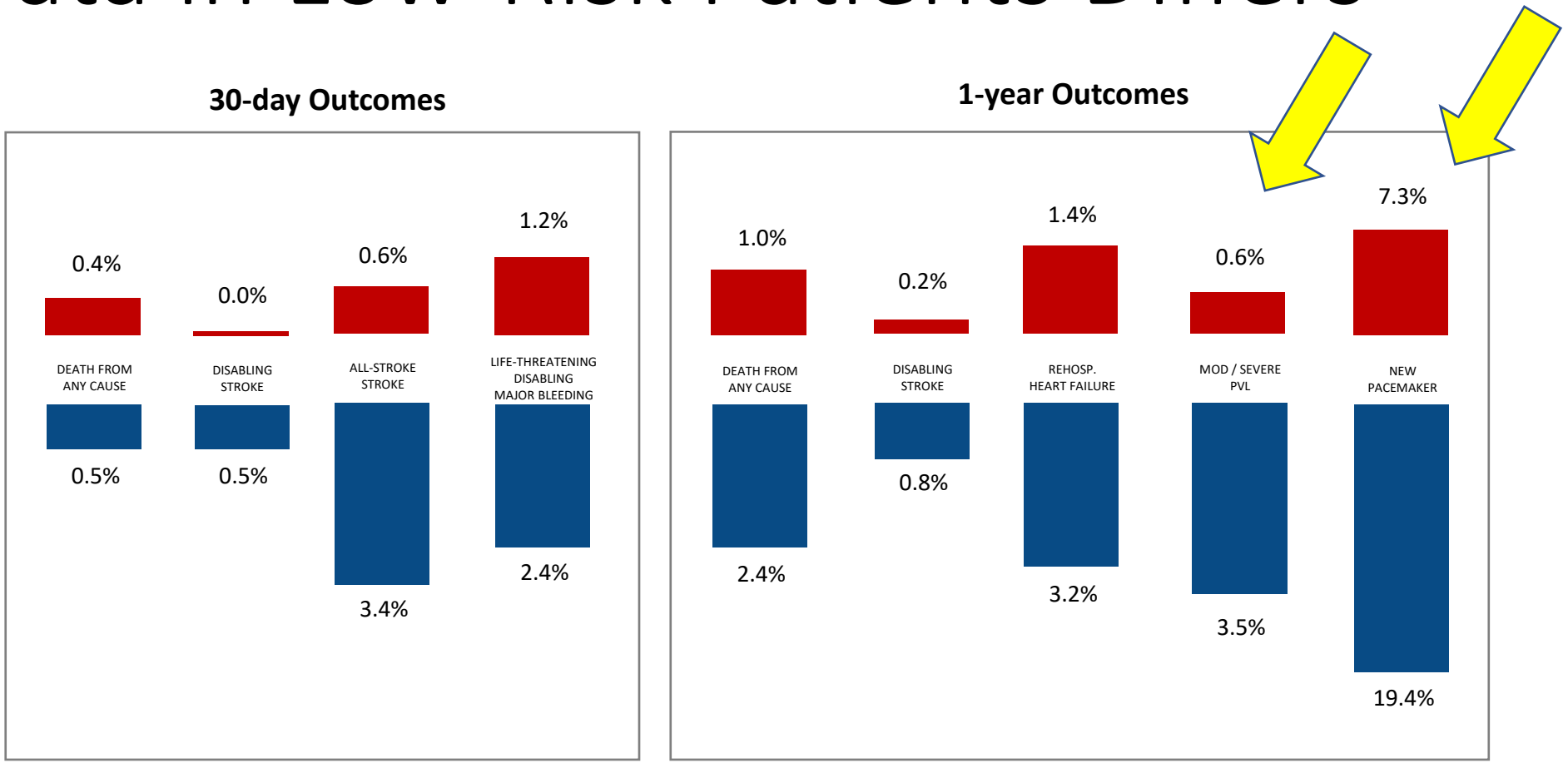


Tarantini, G., Fovino, LN. (2021). Lifetime Strategy of Patients With Aortic Stenosis The First Cut Is the Deepest. *JACC: Cardiovascular Interventions*, 14(15), 1727-30

THV Data in Low-Risk Patients Differs

PARTNER 3 Trial[1]

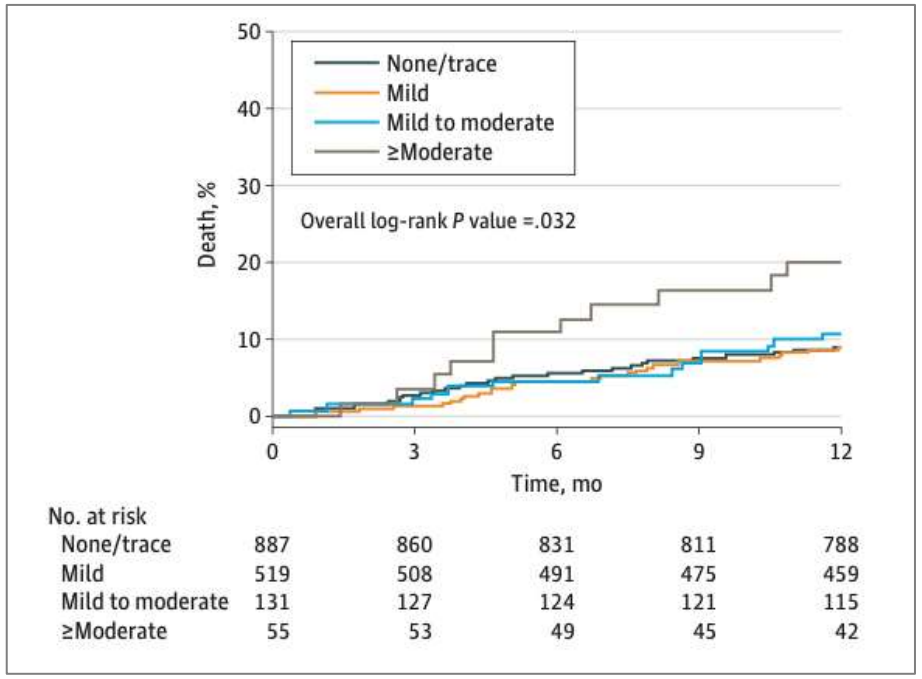
MDT Low-risk Trial[2]



1. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380(18):1695-1705.
2. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380(18):1706-1715.

Predictors of Mortality After TAVI: Perivalvular Regurgitation

Only patients with at least moderate PVR had higher 1-year mortality (hazard ratio [HR], 2.40; 95% CI, 1.30-4.43; P = .005)



Univariable and Multivariable Analyses of the Association Between at Least Moderate PVR and 1-Year Outcomes

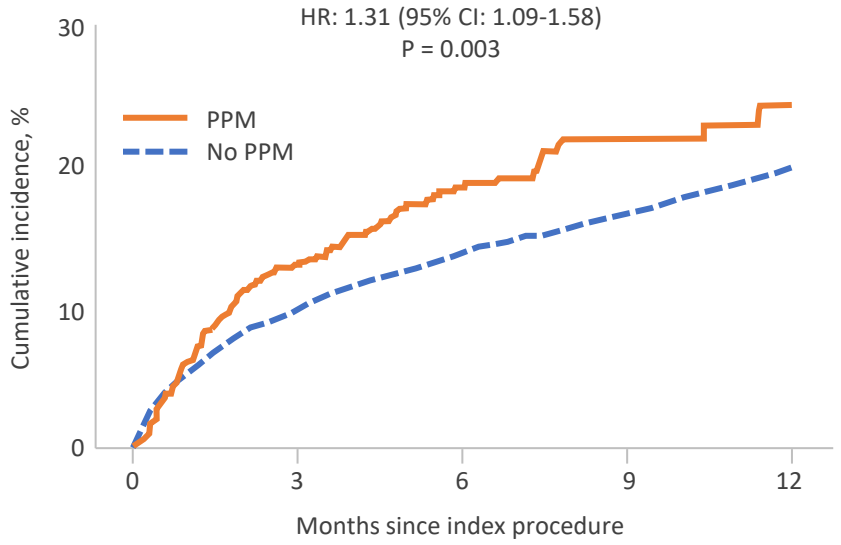
End Point	Univariable Analysis		Multivariable Analysis[a]	
	HR (95% CI)[b]	*P* Value	HR (95% CI)	*P* Value
All-cause mortality	2.40 (1.30-4.43)	.005	2.59 (1.39-4.85)	.003
Cardiovascular mortality	2.68 (1.24-5.81)	.01	2.87 (1.30-6.30)	.009
Rehospitalization	2.27 (1.34-3.83)	.002	2.27 (1.31-3.94)	.003
Composite of mortality and rehospitalization	2.35 (1.52-3.62)	.001	2.36 (1.50-3.69)	<.001
Aortic valve reintervention	13.14 (3.39-50.85)	<.001	NA	NA

"Given that patients with at least moderate PVR at 30 days harbor a 2.4-fold increase in 1-year mortality and that it is difficult to predict who among the survivors will exhibit a regression of PVR, it is essential to make every effort to avoid at least moderate PVR at the time of TAVR''. P Pibarot

Pibarot P, Hahn RT, Weissman NJ, et al. Association of Paravalvular Regurgitation With 1-Year Outcomes After Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve. *JAMA Cardiol.* 2017;2(11):1208–1216. doi:10.1001/jamacardio.2017.3425

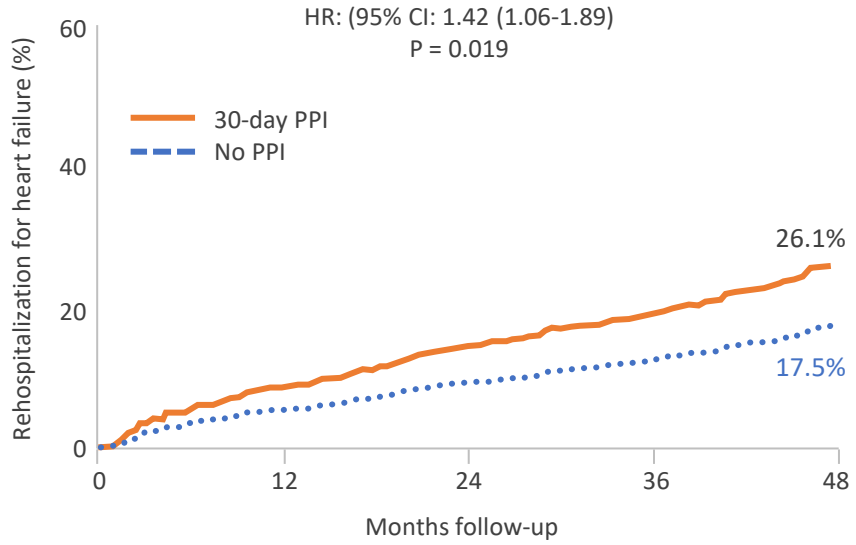
Low pacemaker rates mean better outcomes for patients

New pacemaker after TAVR is associated with a **31% increase in mortality** in the first year[1]



No. of events/No. at risk					
PPM	0/651	81/450	104/265	112/118	114/42
No PPM	0/9134	878/7489	1173/6071	1360/5086	1536/4276

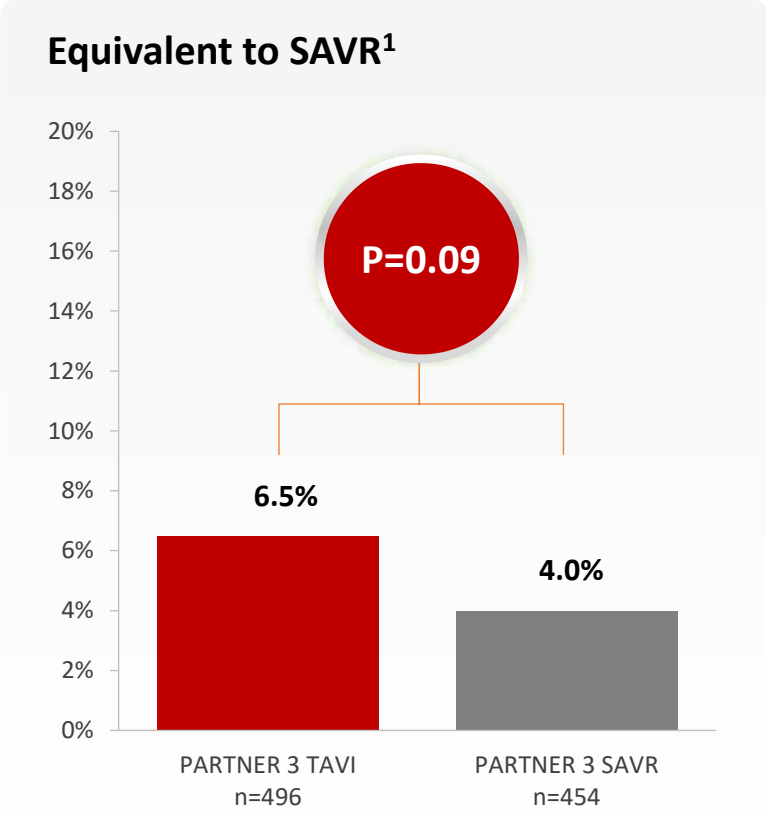
New pacemaker after TAVR is associated with a **42% increase in rehospitalization** at 4 years[2]

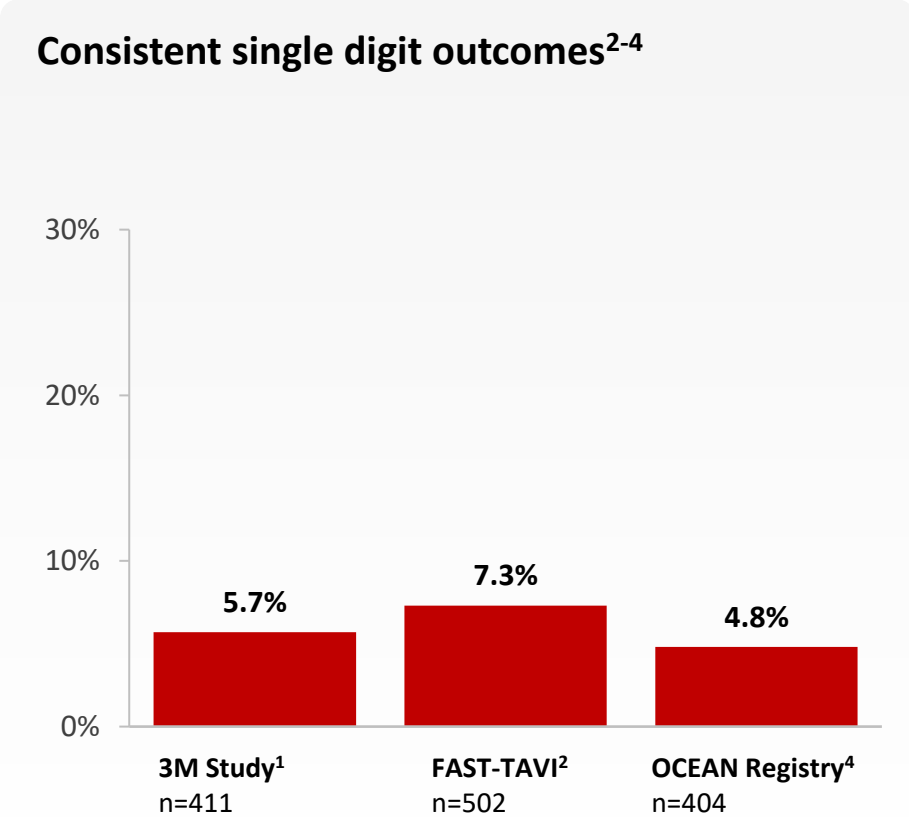


Patients at risk					
30-day PPI	322	246	197	127	89
No PPI	1307	1064	923	624	397

1. Fadahunsi OO, Olowoyeye A, Ukaigwe A, et al. Incidence, predictors, and outcomes of permanent pacemaker implantation following transcatheter aortic valve replacement – Analysis from the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry. *JACC: Cardiovasc Interv.* 2016;9(21):2189-2199.
2. Chamandi, C, Barbanti M, Munoz-Garcia A, et al. Long-term outcomes in patients with new permanent pacemaker implantation following transcatheter aortic valve replacement. *JACC: Cardiovasc Interv.* 2018;11(3):301-310.

BEV Platform Demonstrates Single Digit Rates of new Pacemaker

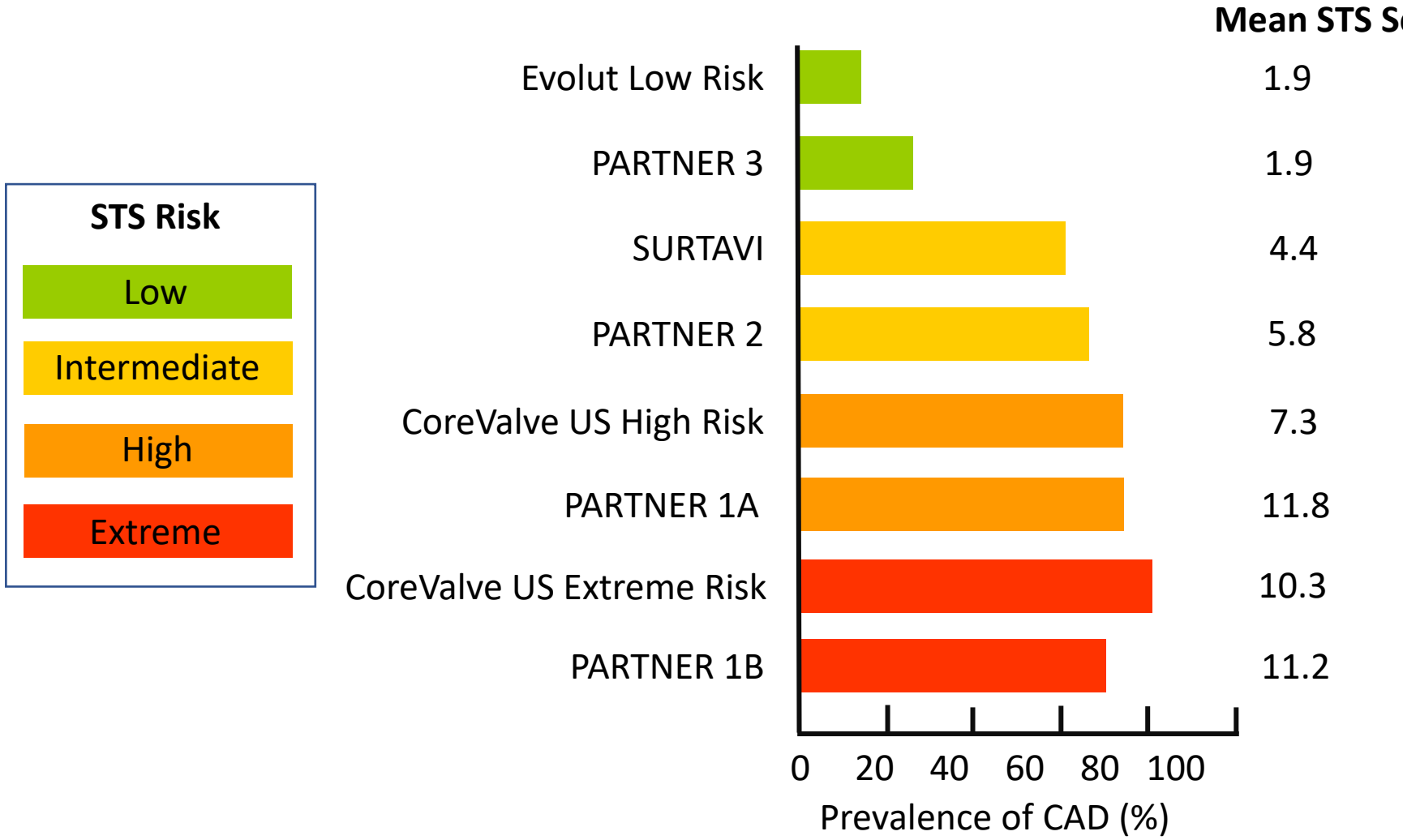




30-day outcomes

1. Mack M, Leon M, Thourani R, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705.
2. Wood et al. The Vancouver 3M Clinical Pathway Facilitates Safe Next-Day Discharge Home at Low, Medium and High Volume TAVR Centers JACC. Published on Mar, 2019.
3. Saia F, et al. In-hospital and thirty day outcomes of the SAPINE 3 Ultra balloon-expandable TAVR: the S3U registry. Eurointervention 2020.
4. Yamamoto M, et al. TAVR Outcomes in Japan: OCEAN Japanese Multicenter Registry. Cardiovascular Revascularization Medicine. 2019

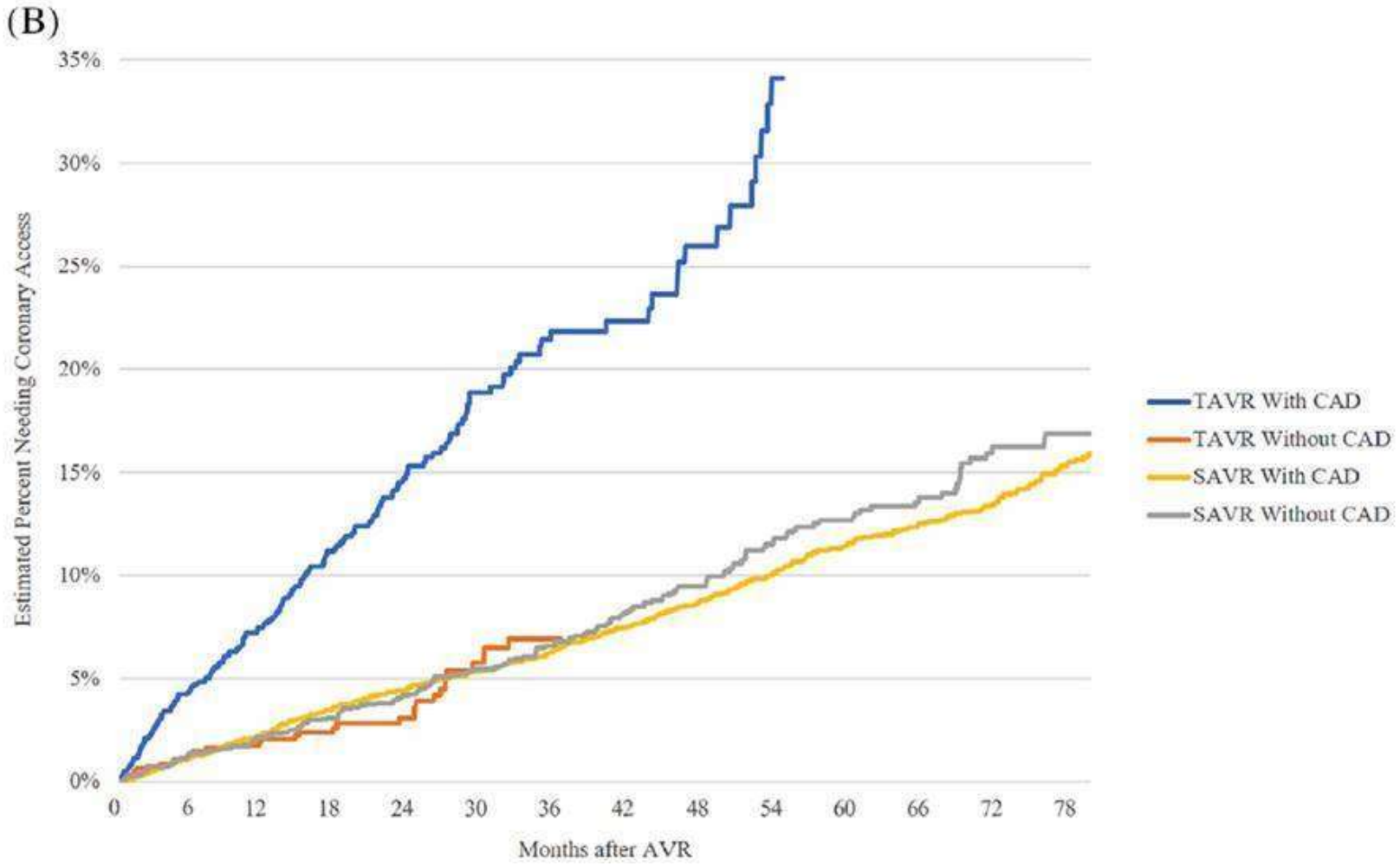
Coronary artery disease is very common in the TAVR population even among those at low surgical risk



CAD was seen in 60% to 80% of TAVR patients in the intermediate-, high-, and extreme-risk trials

Faroux L, et al. *J Am Coll Cardiol*. 2019;74(3):362-372.

For TAVR patients with CAD, the need for coronary access will be up to 8% at 1 year, and **34% at 4.5 years**

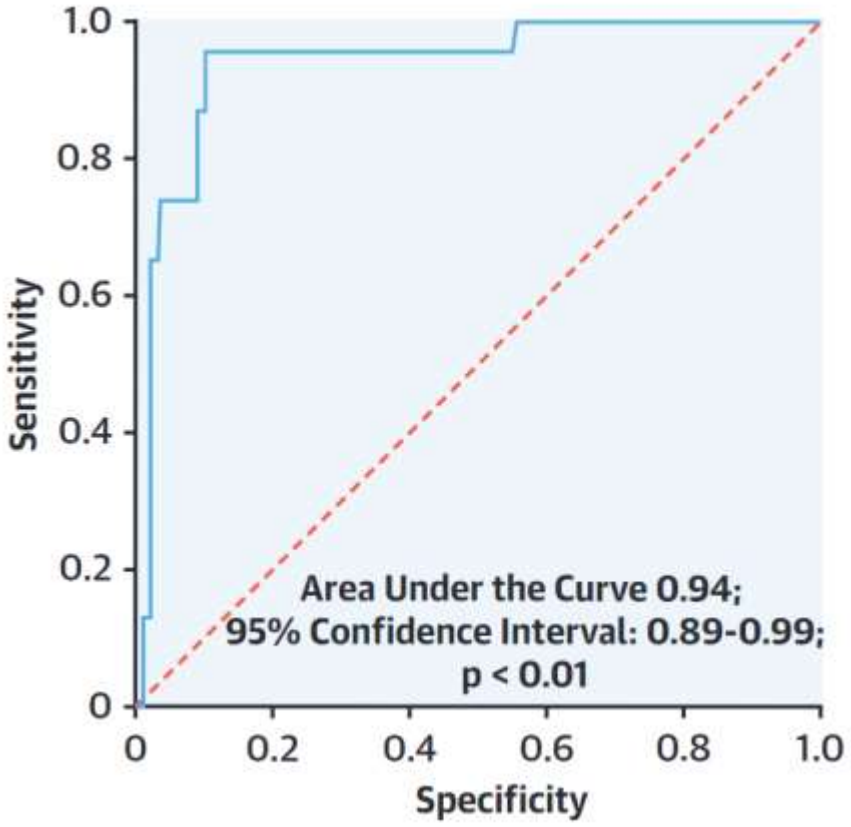


Hermiller JB Jr, Gunnarsson CL, Ryan MP, Moore KA, Clancy SJ, Irish W. The need for future coronary access following surgical or transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2021;1–7. https://doi.org/10.1002/ccd.29841

Coronary Cannulation After Transcatheter Aortic Valve Replacement

The RE-ACCESS Study

Predictors of Unsuccessful Coronary Cannulation After Transcatheter Aortic Valve Replacement and Receiver-Operating Characteristic Curve Analysis Applied to Logistic Regression Model



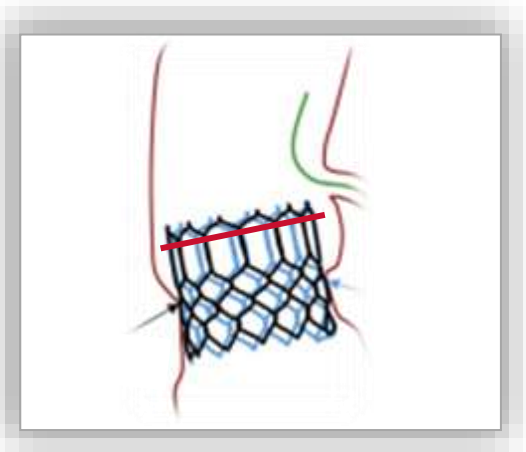
Transcatheter Aortic Valve/ Sinuses of Valsalva Relation
Odds Ratio 1.1;
95% CI: 1.0-1.2; p < 0.01

Transcatheter Aortic Valve Implant Depth
Odds Ratio 1.7;
95% CI: 1.3-2.3; p < 0.01

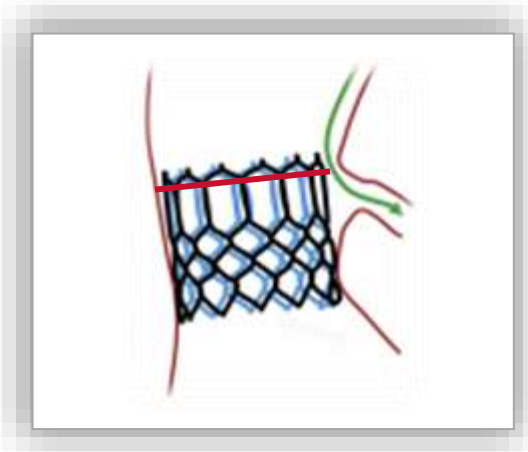
Evolut Transcatheter Aortic Valve
Odds Ratio 29.6;
95% CI: 2.6-335.0; p < 0.01

Barbanti M, et al. *JACC Invt* 2020;13:2542-55.

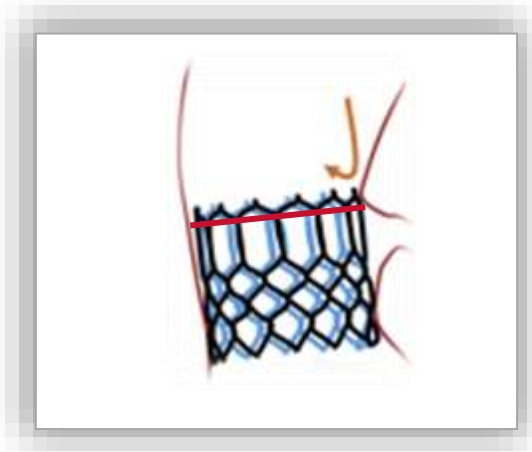
Considerations for coronary re-access and future TAV-in-TAV



Risk Plane (RP)



VTA (Valve to Aorta distance) between RP and coronaries

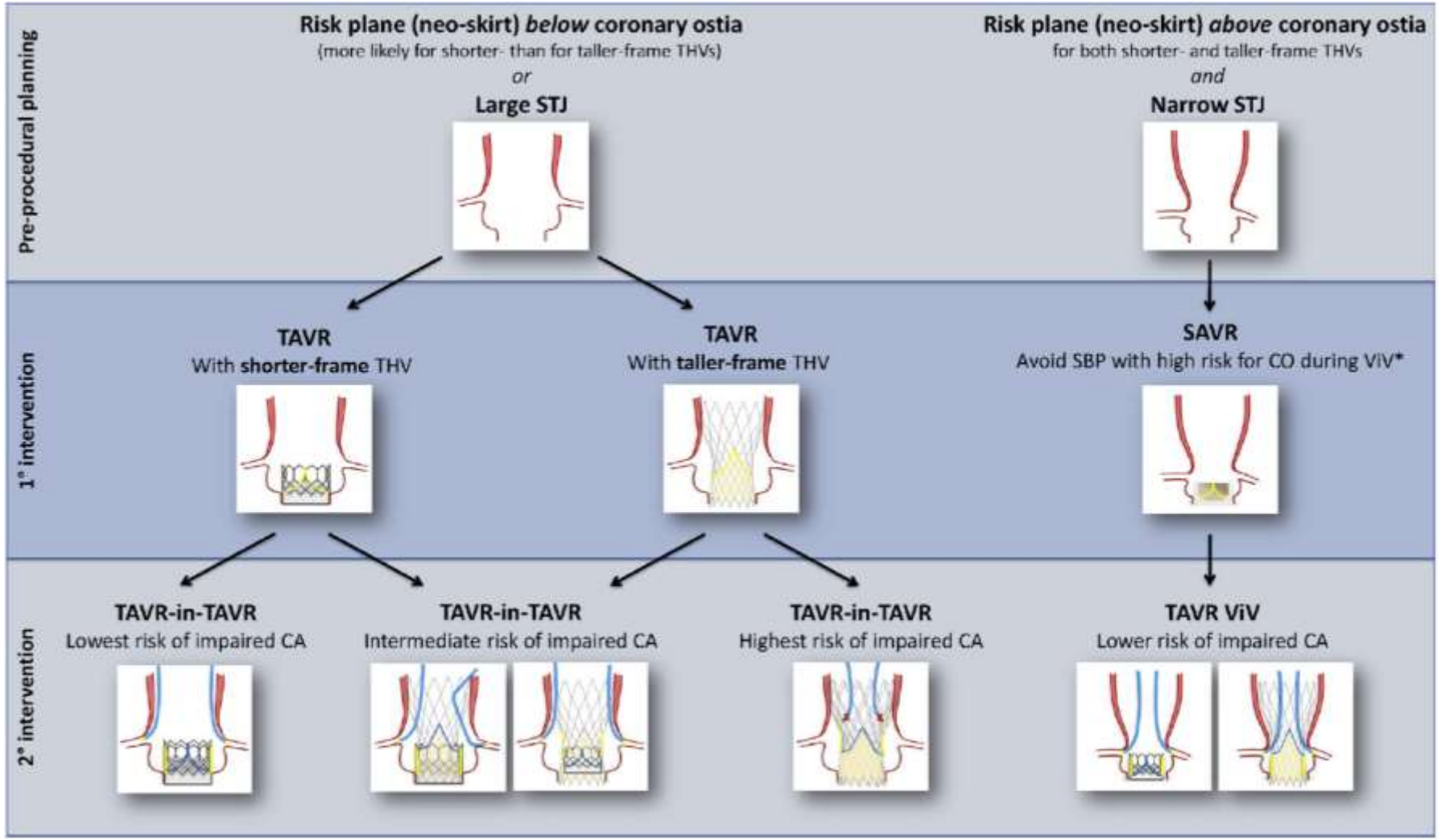


Sinus Sequestration = if the first TAV commissure is above STJ and its stent frame is close to or directly contacting the STJ, coronary flow can be impaired after the second TAV implantation.[1]

Adapted from Rogers, T., Greenspun, BC., Weissman, G., et al. (2020). Feasibility of Coronary Access and Aortic Valve Reintervention in Low-Risk TAVR Patients, *JACC: Cardiovascular Interventions*, 13(6), 726-35

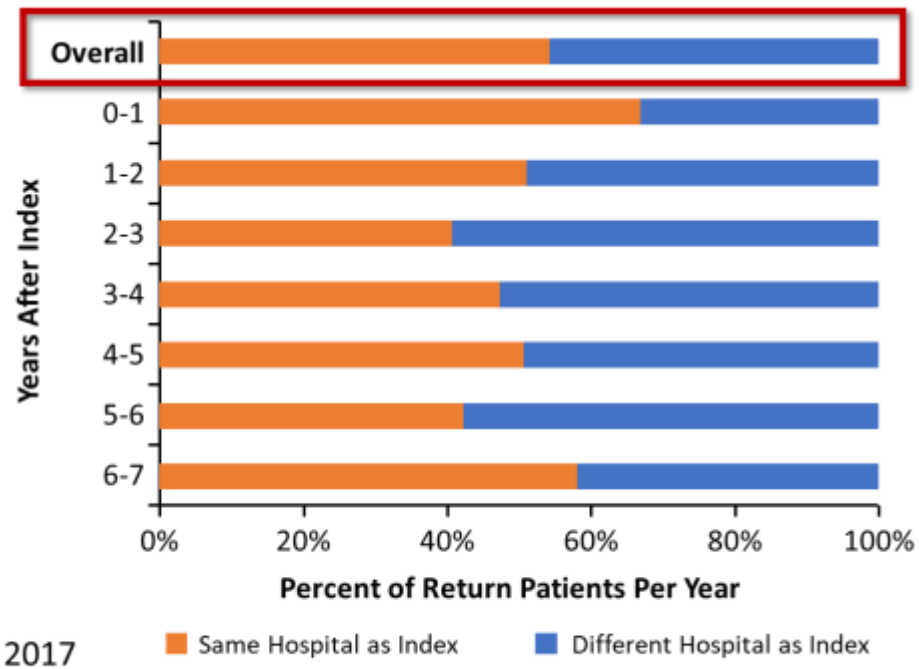
1. Ochiai, T., Oakley, L., Sekhon, N., et al. (2020). Risk of Coronary Obstruction Due to Sinus Sequestration in Redo Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions,* 13(22), 2617-27

Use of a shorter frame offers the lowest risk of impaired coronary access in TAV-in-TAV and TAV-in-SAV



Tarantini G, et al. *JACC Cardiovasc Interv*. 2020;13(21):2539-2541.

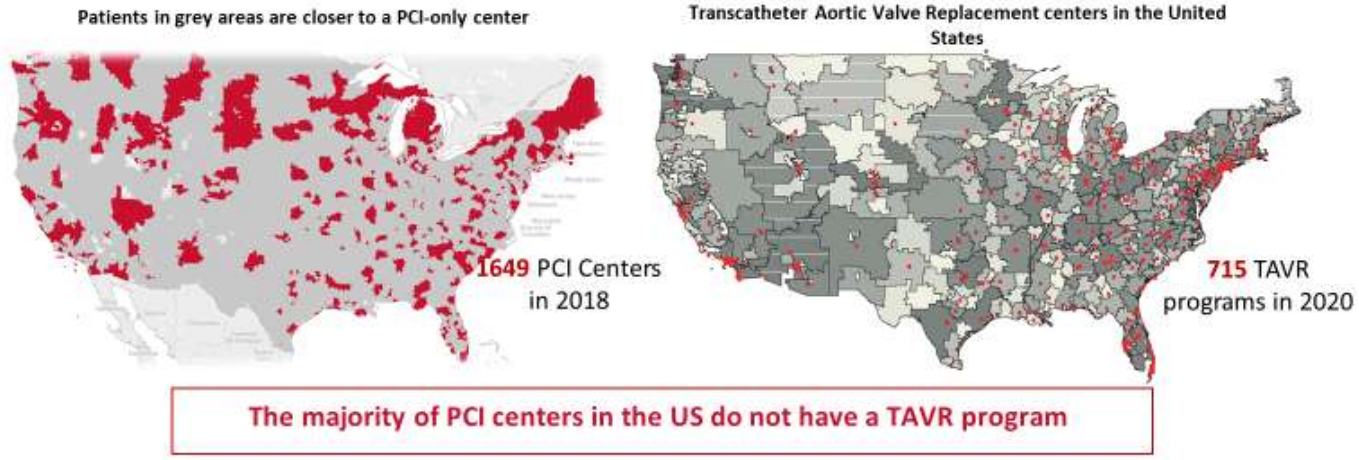
47% of patients that undergo TAVR have their PCI or angiogram performed at a different hospital



2011 to 2017
N=11,466

The majority of PCI centers do not have a TAVR program

>60% of the population over the age of 65 live closer to a PCI-only center



The majority of PCI centers in the US do not have a TAVR program

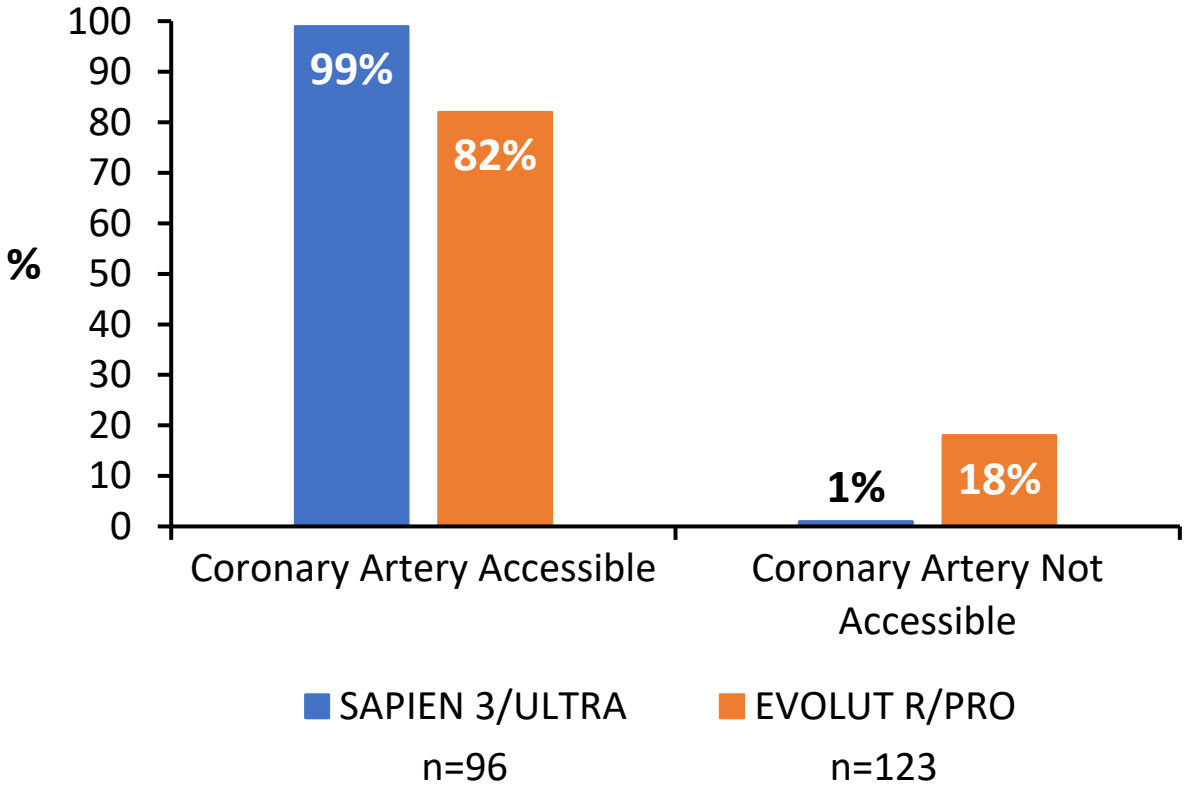
2017 ACS Census Data, Medicare Quarterly SAF; 2018. Khera R, et al. *JAMA Intern Med*. 2020;180(10):1317-1327.
Marquis-Gravel G, et al. *JAMA Cardiol*. 2020;5(9):1006-1010; Carroll JD, et al. *J Am Coll Cardiol*. 2020;76(21):2492-2516.

Hermiller JB Jr, Gunnarsson CL, Ryan MP, Moore KA, Clancy SJ, Irish W. The need for future coronary access following surgical or transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2021;1–7. https://doi.org/10.1002/ccd.29841

Nearly all SAPIEN 3 patients had accessible coronary arteries

RE-ACCESS

Coronary artery accessibility



Predictors of unsuccessful cannulation

	Odds Ratio	95% Confidence Interval
EVOLUT R/PRO	29.6	2.6–335.0 *P*<0.01
Transcatheter Aortic Valve implant depth	1.7	1.3–2.3 *P*<0.01
Transcatheter Aortic Valve/Sinuses of Valsalva relation	1.1	1.0–1.2 *P*<0.01

N=300

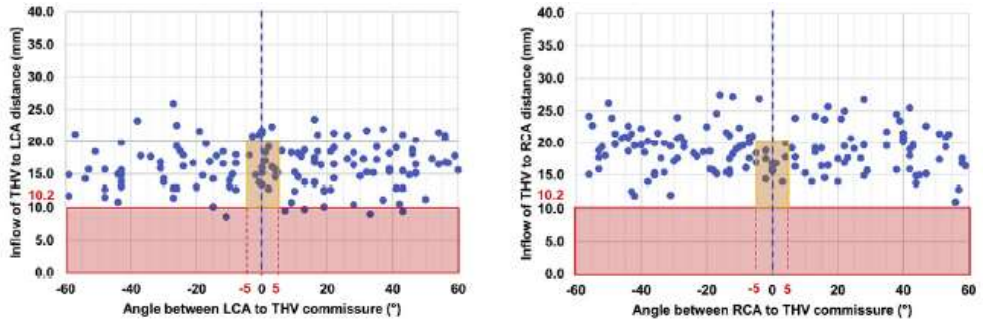
Barbanti M, et al. *JACC Cardiovasc Interv*. 2020;13(21):2542-2555.

SAPIEN 3 has low rates of CT-assessed unfavorable coronary access post-TAVR

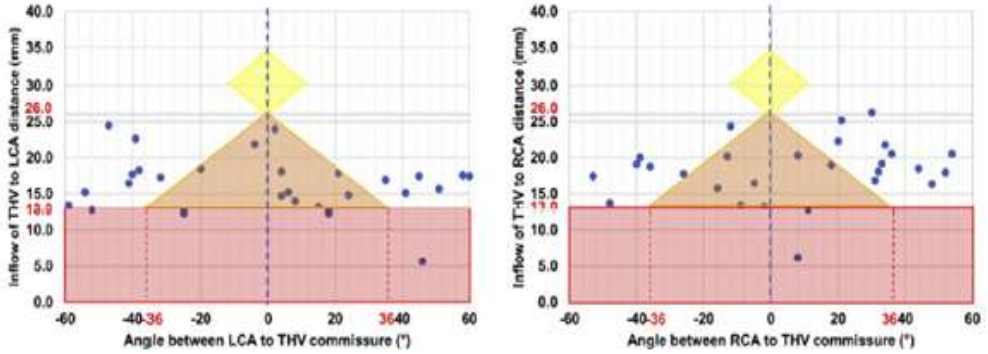
RESOLVE

CT-identified coronary ostia/TAVR alignment

SAPIEN 3: 26 mm

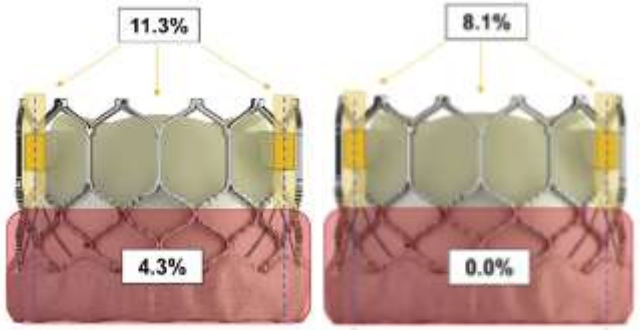


EVOLUT R/PRO: 26 mm



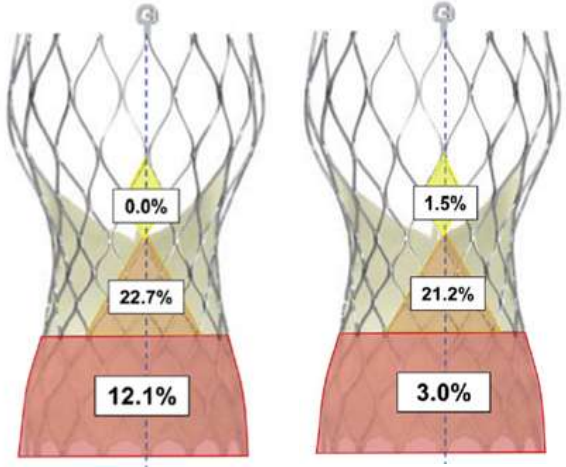
Unfavorable coronary access

SAPIEN 3



LCA 15.7% **RCA 8.1%**

EVOLUT R/PRO



LCA 34.8% **RCA 25.8%**

Unfavorable coronary access post-EVO R/PRO was primarily due to the three commissural triangles

Ochiai T, et al. *JACC Cardiovasc Interv*. 2020;13(6):693-705.

SAPIEN 3 provided the highest predicted rate of coronary access post-TAV-in-TAV

University of Padua Medical School

Coronary angiography was performed prospectively in 137 consecutive patients post-TAVR

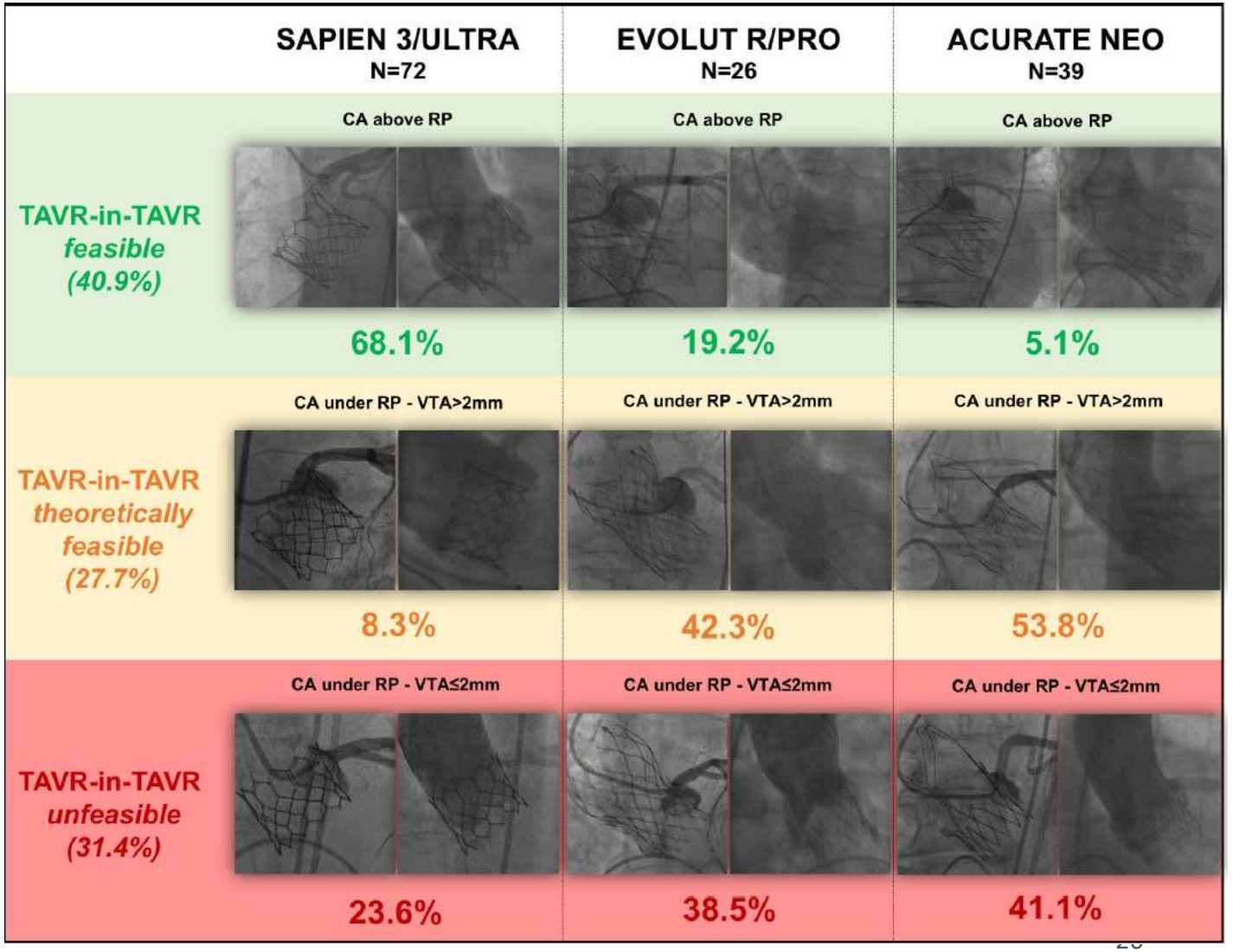
Unfeasible CA after TAV-in-TAV

23.6% for SAPIEN 3

38.5% for Evolut R/PRO

41.1% for ACURATE NEO

SAPIEN 3 (n=17/72)
Evolut R/PRO (n=10/26)
ACURATE *neo* (n=16/39)



Fovino LN, et al. *J Am Heart Assoc*. 2020;9(13):e016446.

Surgical Explantation After TAVR Failure

Mid-Term Outcomes From the EXPLANT-TAVR International Registry

269 patients

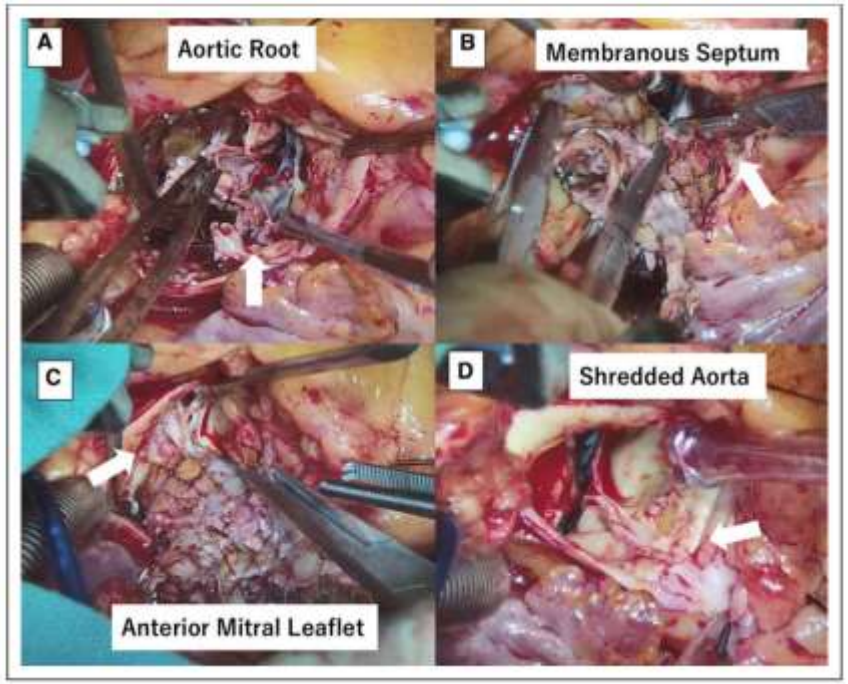
Mean age 72.7 ± 10.4 years

Mean time to failure 11.5 mo

STS score 3.2% at TAVR

STS score 5.0% at explant

11.9% in-hospital mortality



Short- and Mid-Term Outcomes After Transcatheter Aortic Valve Replacement Explantation (N = 269)

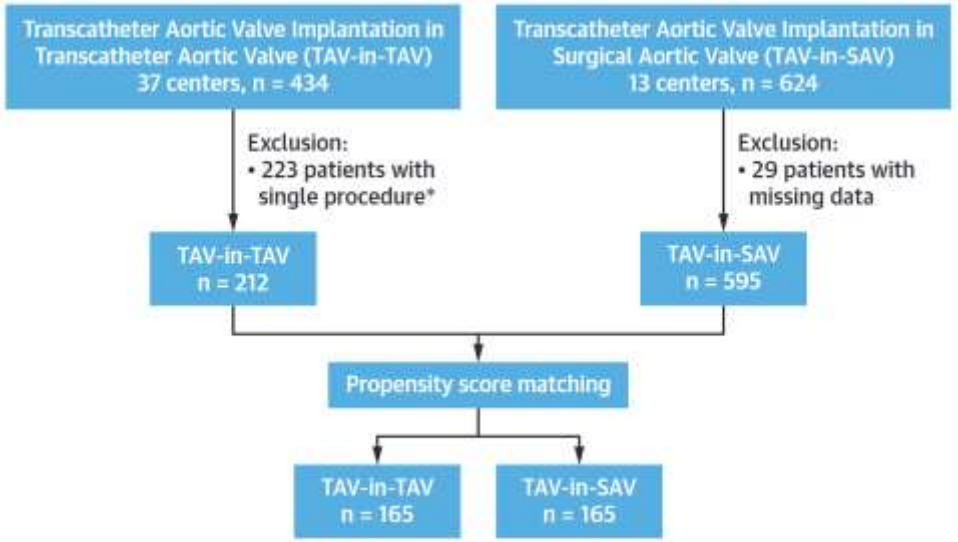
Follow-up (mo) post explantation	14.6 ± 20.7
30 d	
Mortality	34 (13.1)
Stroke	18 (8.6)
Readmission	28 (13.7)
Follow-up complete	259 (97.7)
1 y	
Mortality	53 (28.5)
Stroke	23 (18.7)
Follow-up complete	186 (86.1)

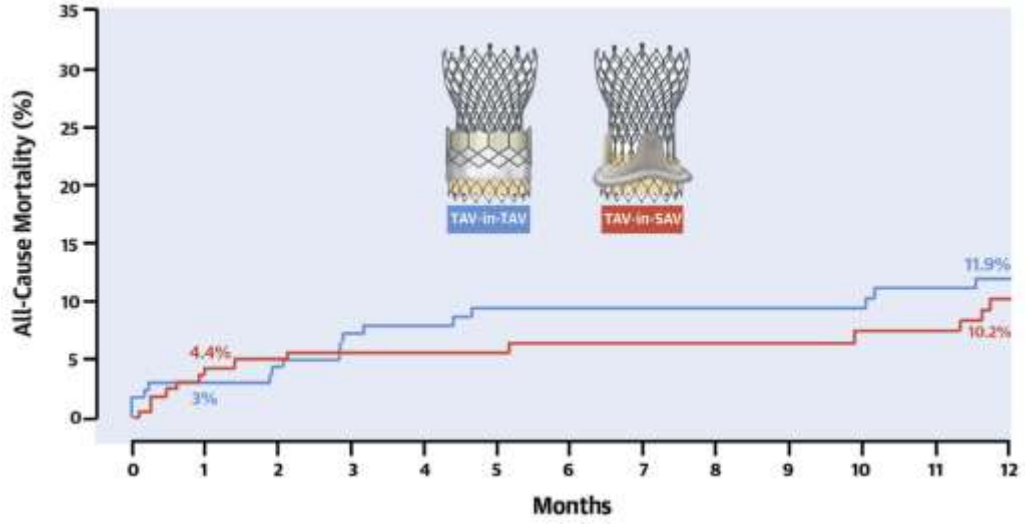
Bapat VN, et al. *JACC Int* 2021;14:1978-1991.

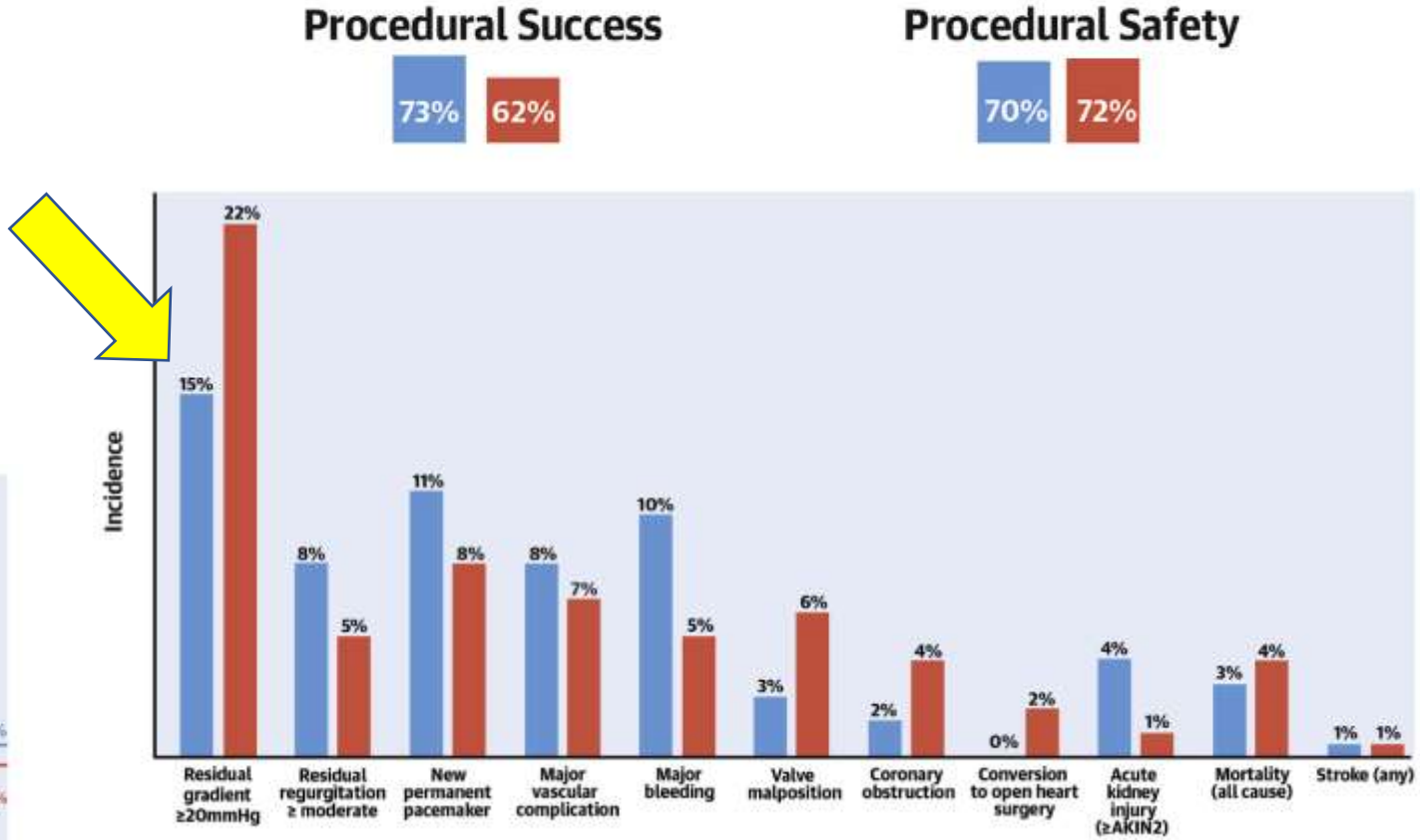
Brescia BA, et al. *Cirv CV Invt* 2021;14:e009927.

Transcatheter Replacement of Transcatheter Versus Surgically Implanted Aortic Valve Bioprostheses

Redo-TAVR international registry

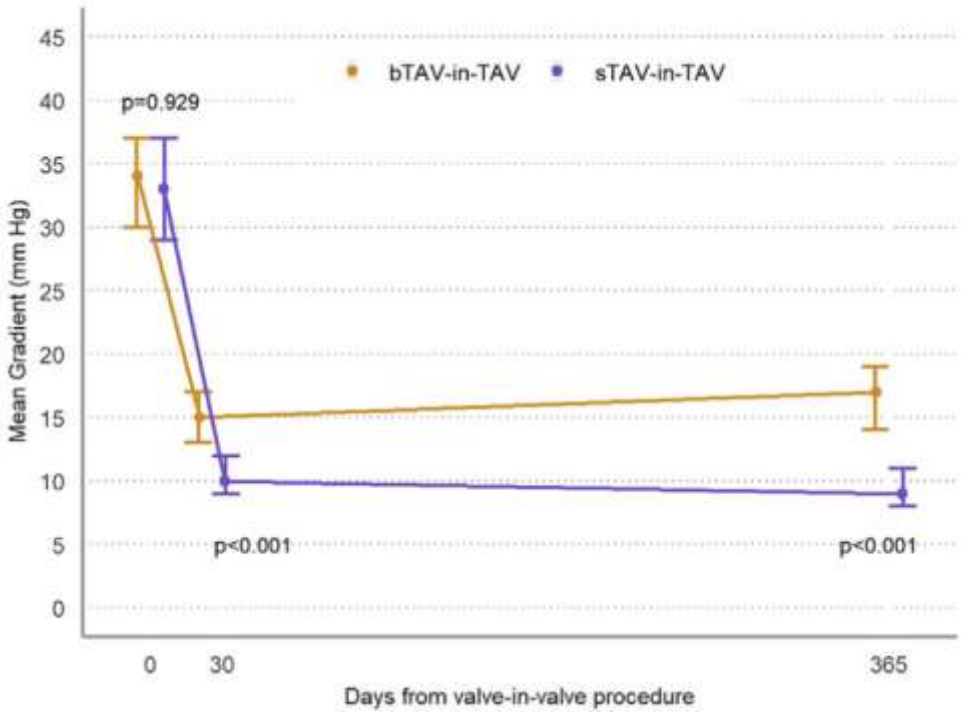


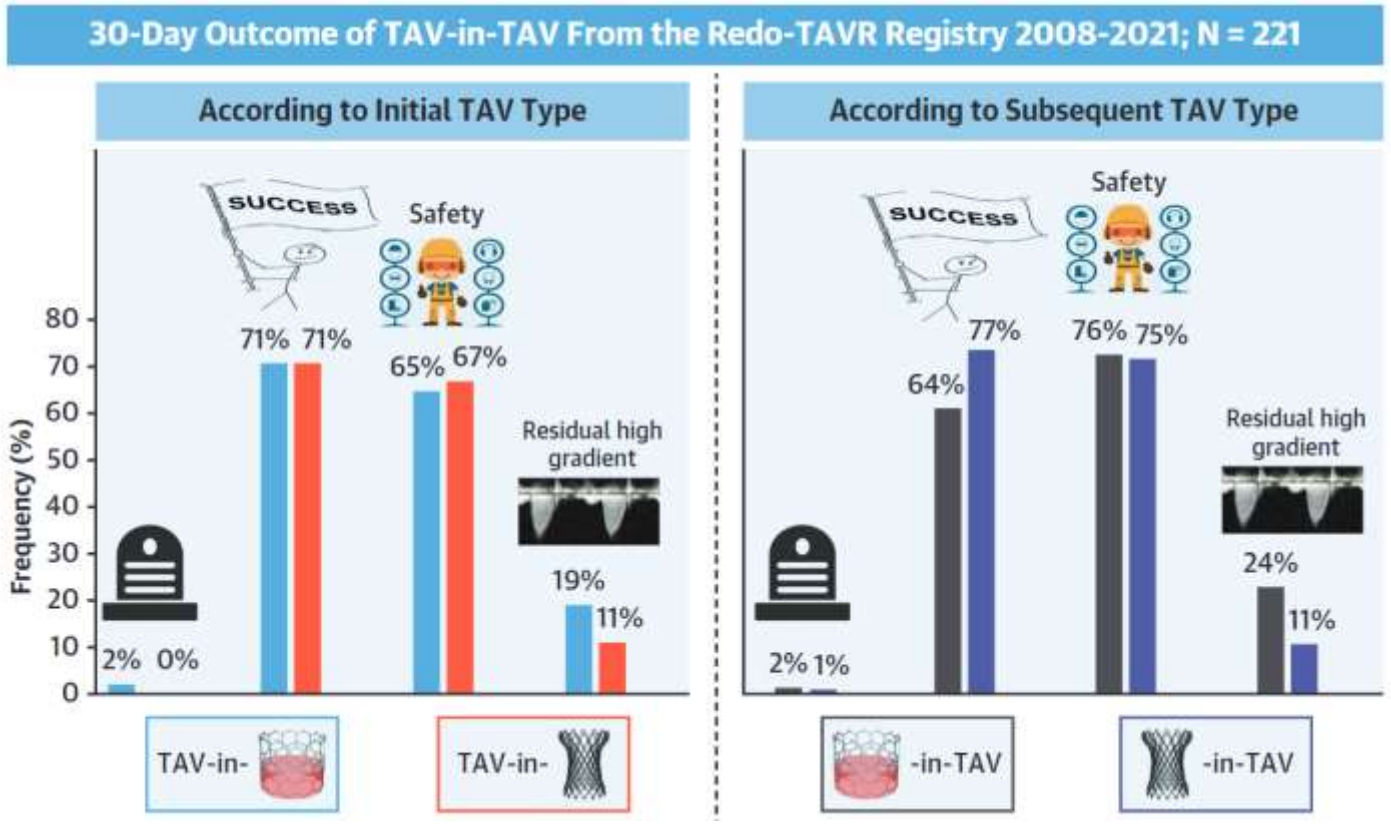




Landes U, et al. *J Am Coll Cardiol* 2021;77:1-14.

Outcomes of Redo Transcatheter Aortic Valve Replacement According to the Initial and Subsequent Valve Type



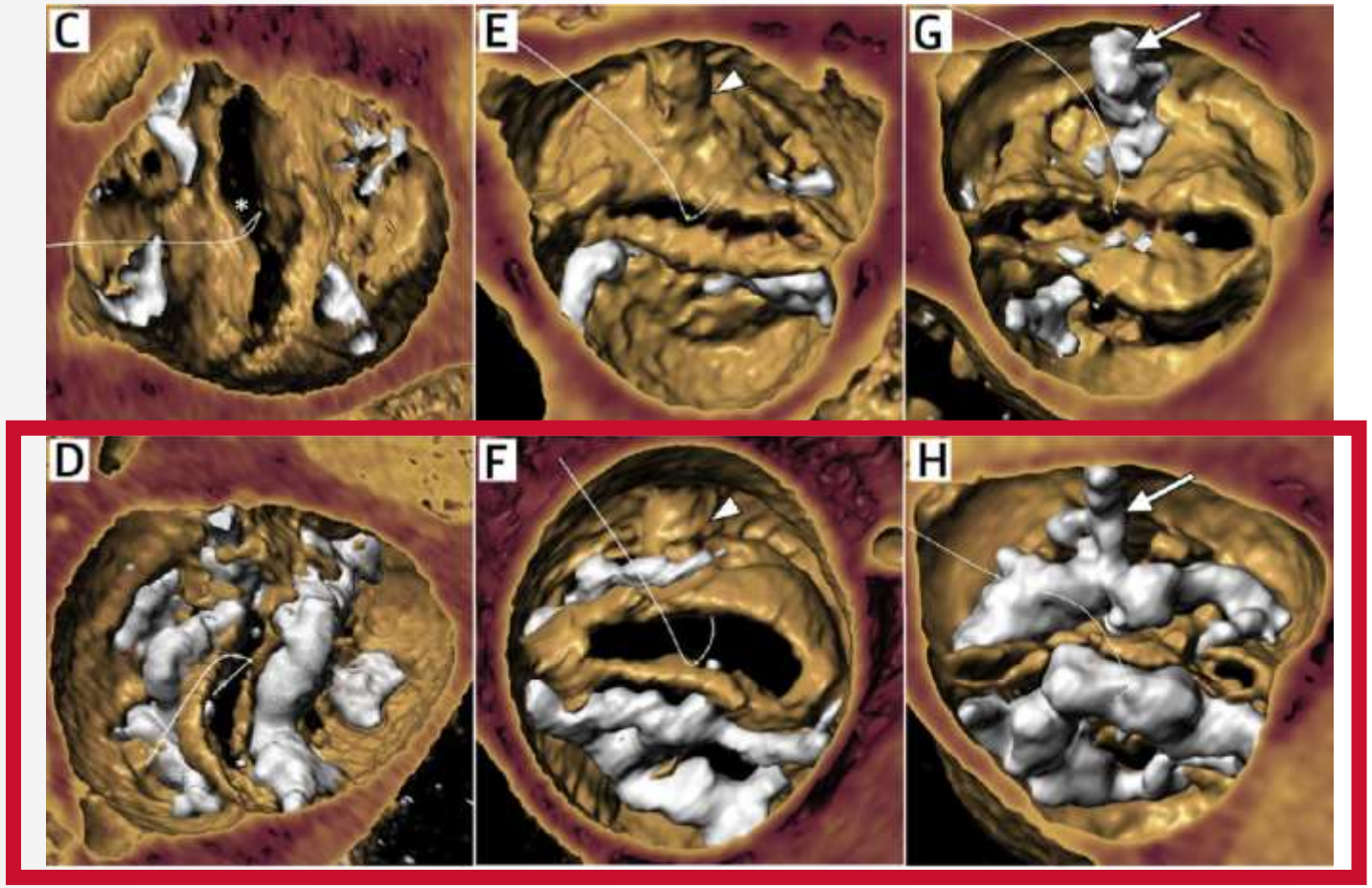


Landes U, et al. *JACC Invt* 2022;15:1543-1554.

Bicuspid Considerations

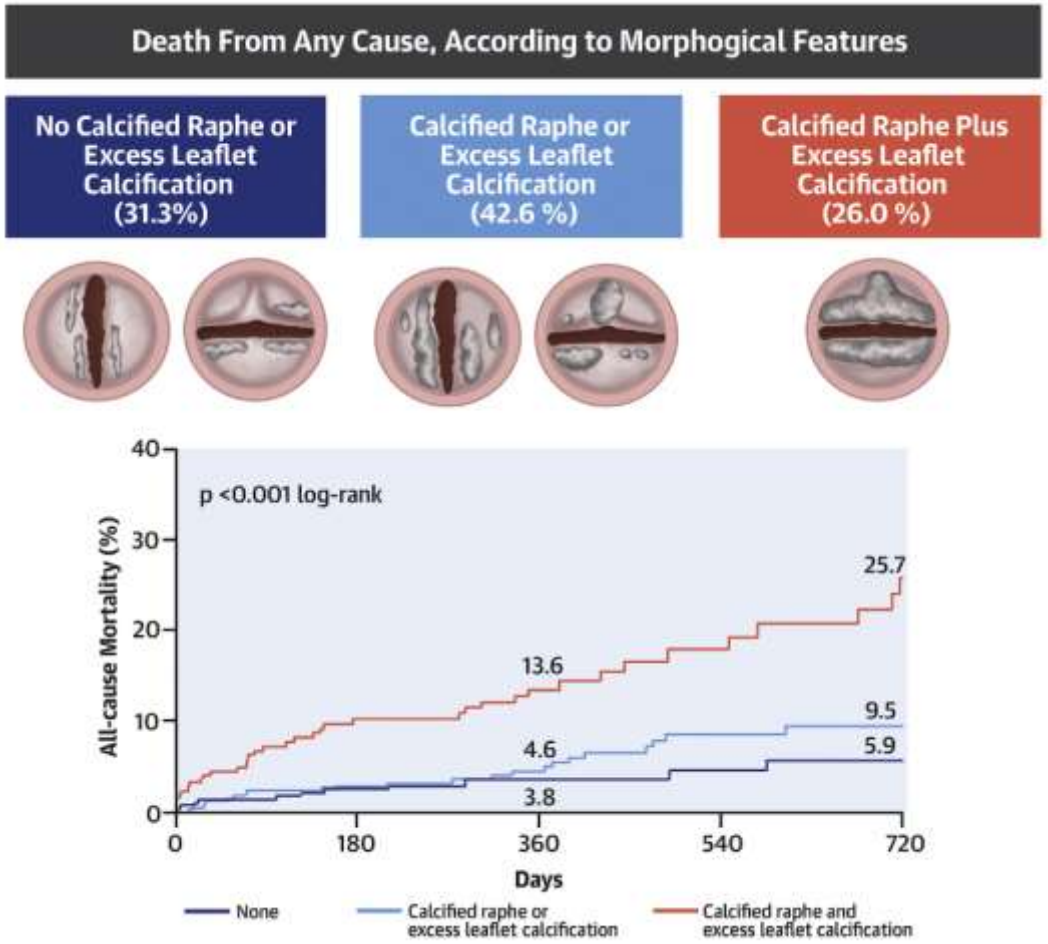
Bicuspid anatomies can show an increased calcification burden and root calcification asymmetries

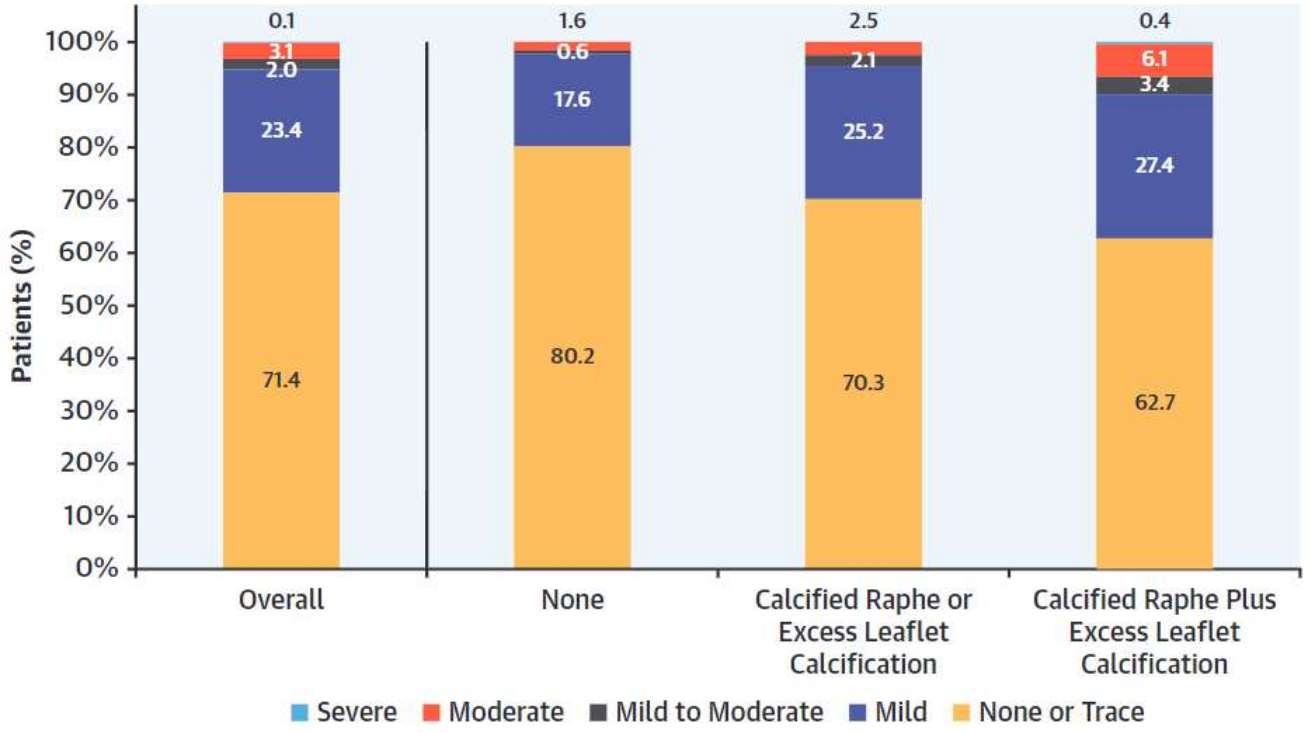
- Increased calcification burden[1]
- Asymmetric calcification[2]



1. Tchetche, D., de Biase C., et al. (2019). Bicuspid Aortic Valve Anatomy and Relationship With Devices: The BAVARD Multicenter Registry. *Circulation: Cardiovascular Interventions*, 12:e007107. doi: 10.1161/CIRCINTERVENTIONS.118.007107
2. Das R., Puri R. (2018). Transcatheter Treatment of Bicuspid Aortic Valve Disease: Imaging and Interventional Considerations. *Front. Cardiovasc. Med.* 5:91. doi: 10.3389/fcvm.2018.00091

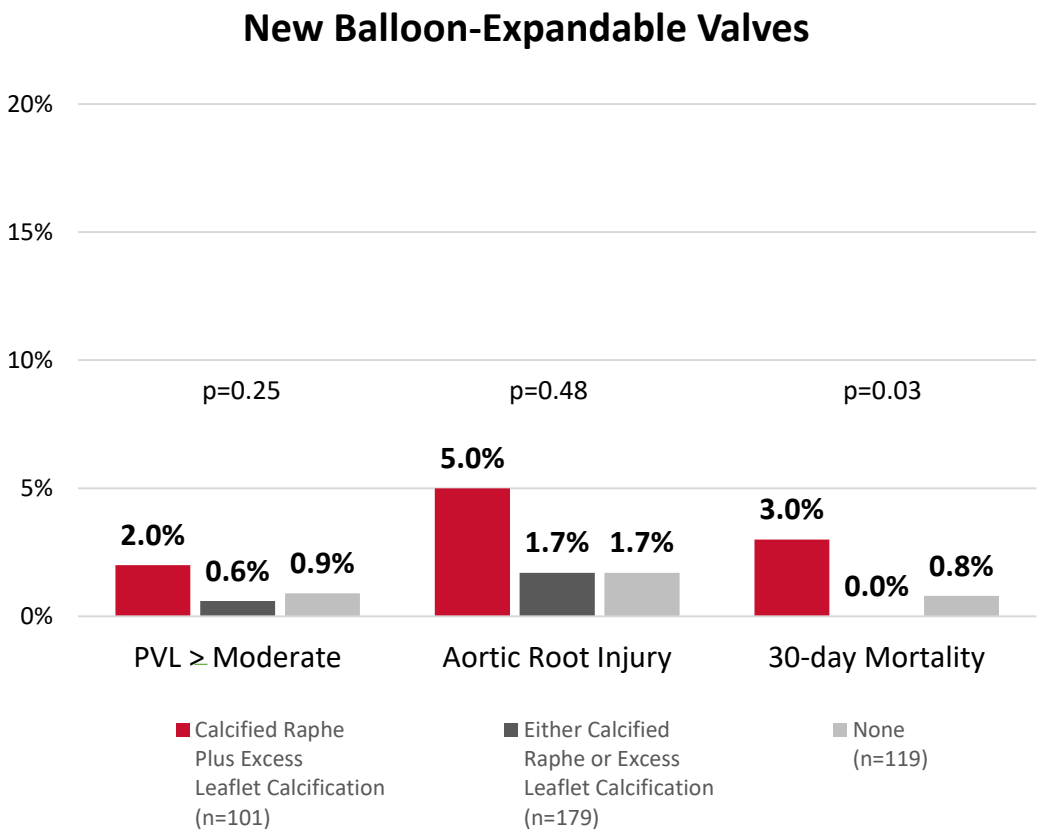
Bicuspid Aortic Valve Morphology and Outcomes After Transcatheter Aortic Valve Replacement

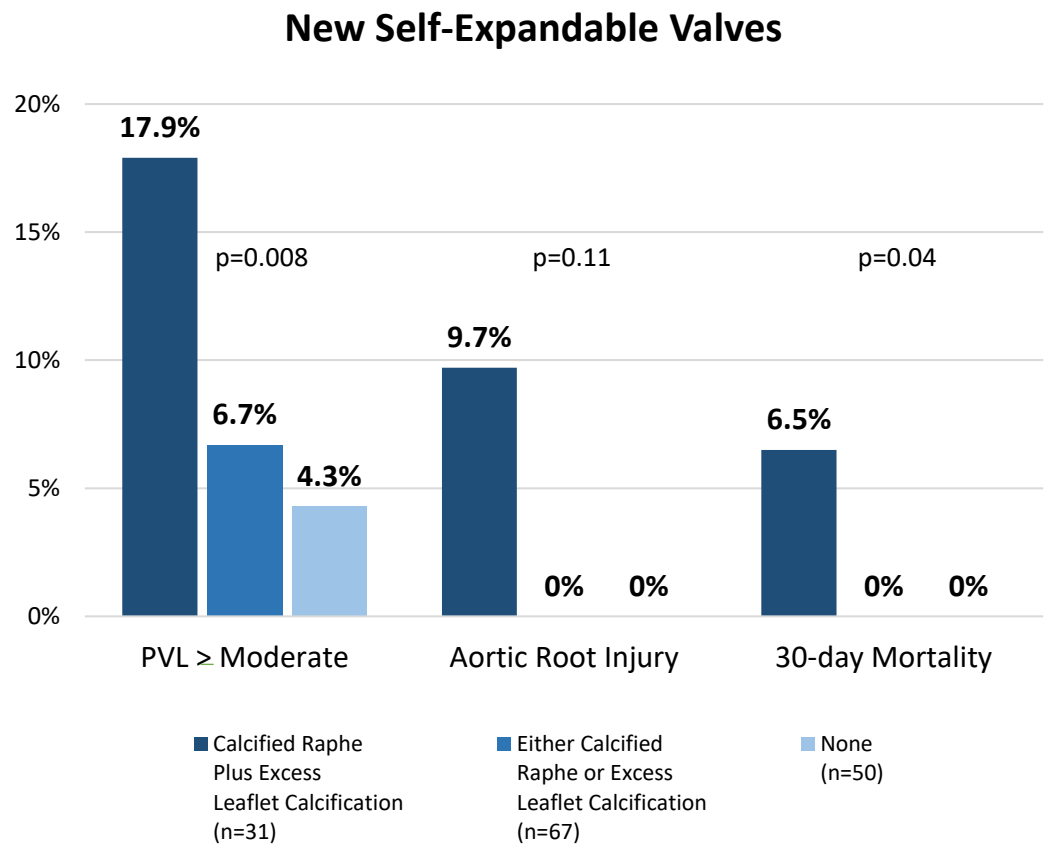




Yoon S-H, et al. *J Am Coll Cardiol*. 2020;76(9):1018-1030.

Outcomes according to phenotype in low-risk patients by valve type

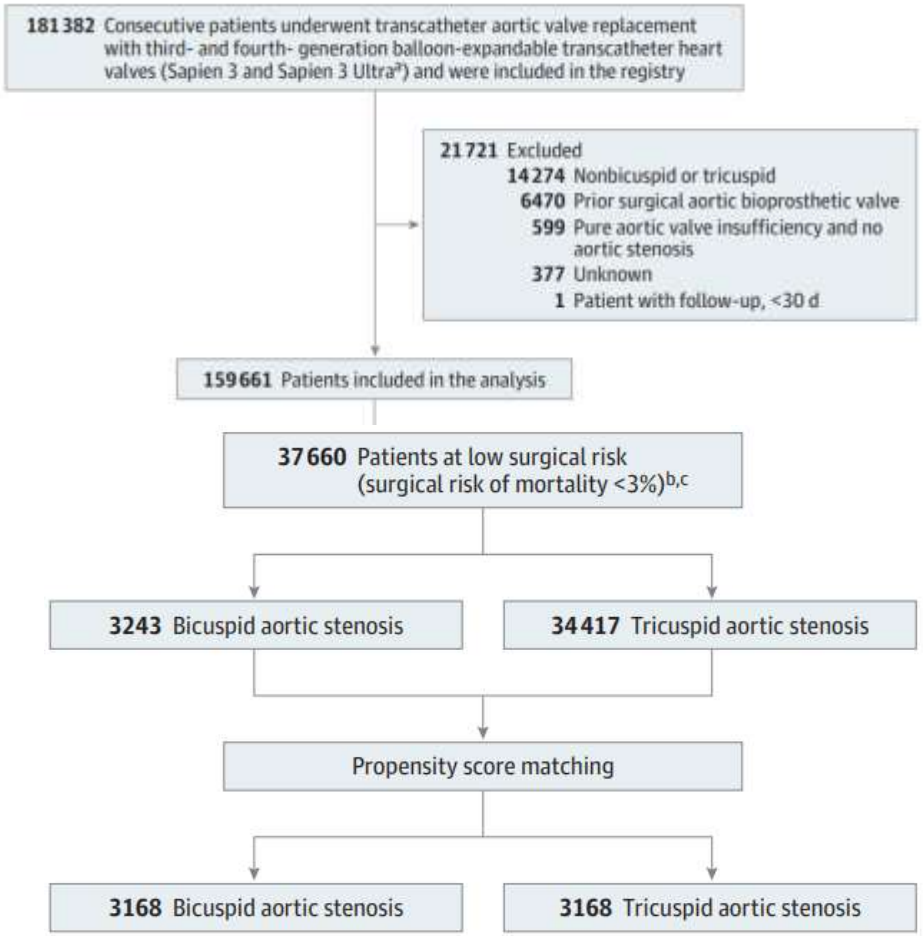




Makkar R, Yoon S. Bicuspid Aortic Valve Morphology and Outcomes after TAVR; Presented at EuroPCR 2019, Paris, France.

JAMA | Original Investigation

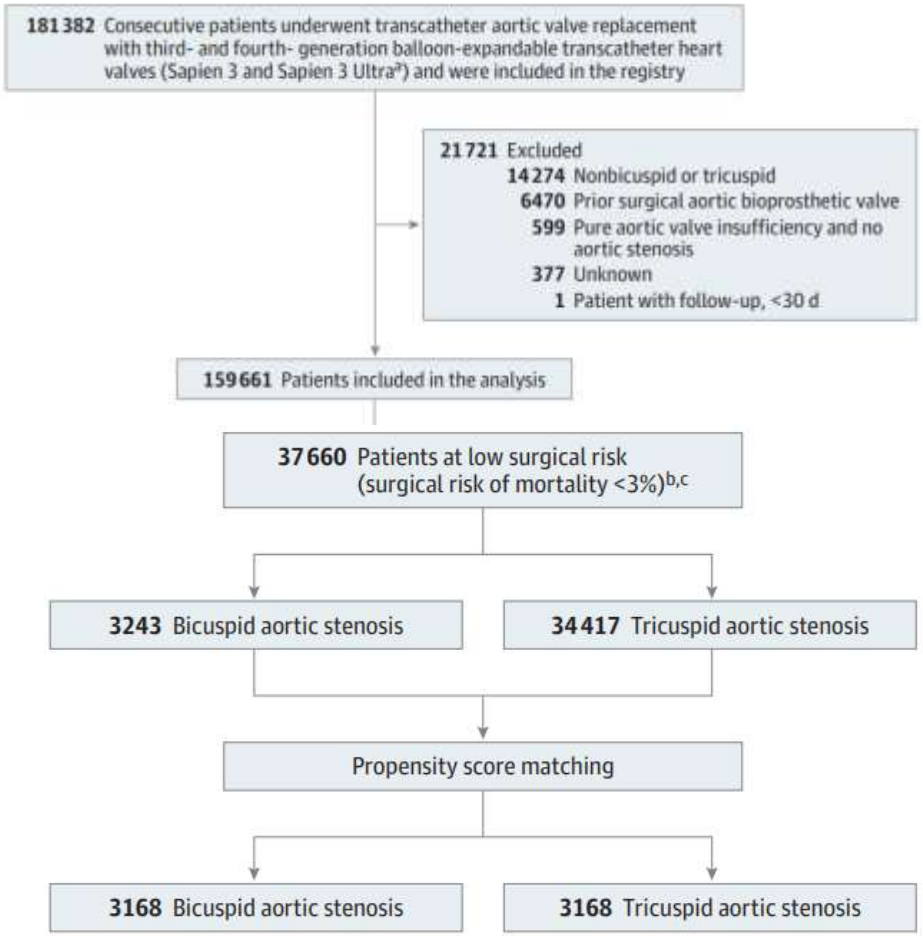
Association Between Transcatheter Aortic Valve Replacement for Bicuspid vs Tricuspid Aortic Stenosis and Mortality or Stroke Among Patients at Low Surgical Risk



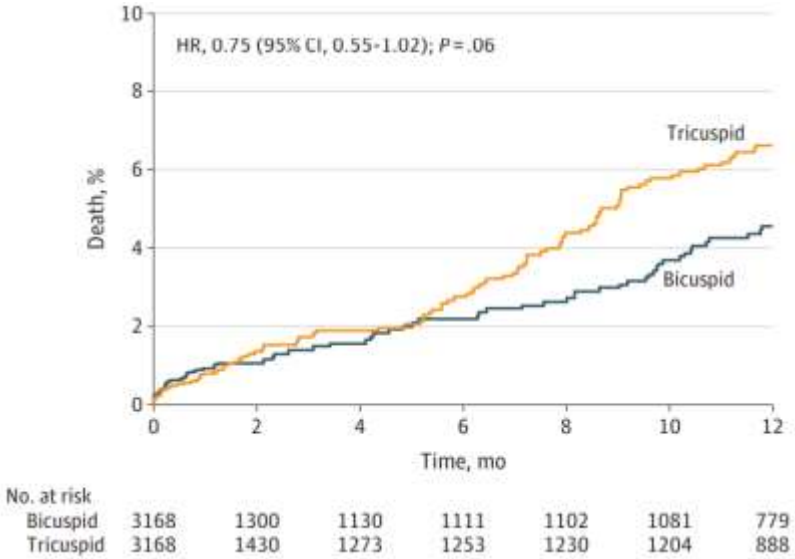
Makkar RR, et al. *JAMA* 2021; 326: 1034-1044.

JAMA | Original Investigation

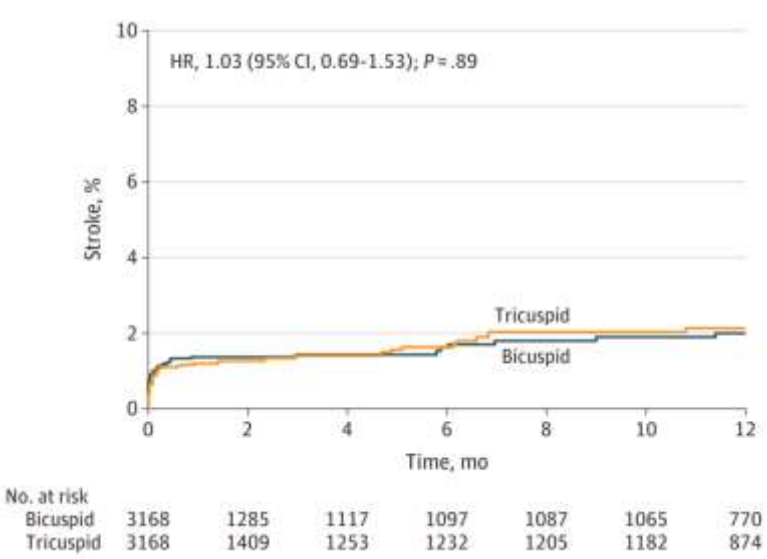
Association Between Transcatheter Aortic Valve Replacement for Bicuspid vs Tricuspid Aortic Stenosis and Mortality or Stroke Among Patients at Low Surgical Risk



All-cause mortality



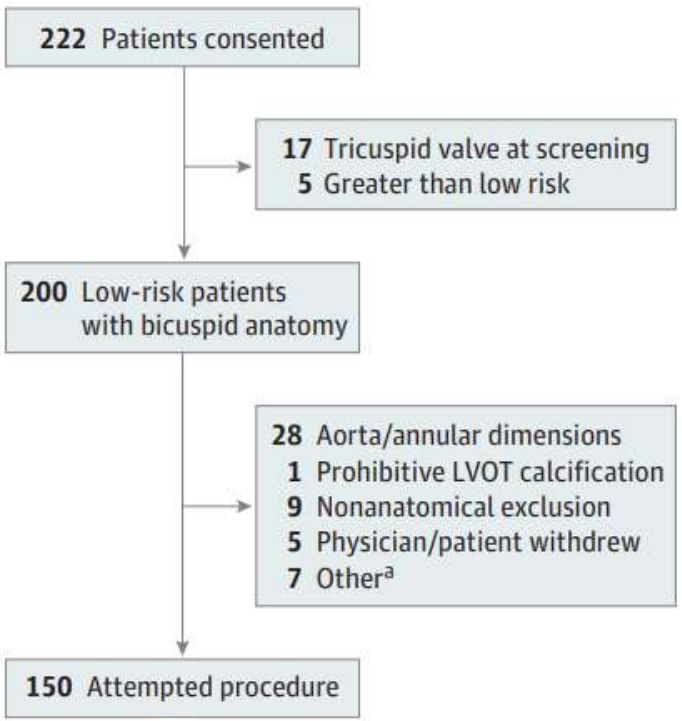
Stroke



Makkar RR, et al. *JAMA* 2021; 326: 1034-1044.

JACC: Cardiovascular Interventions

The PARTNER 3 Bicuspid Registry for Transcatheter Aortic Valve Replacement in Low-Surgical-Risk Patients



169 patients enrolled (out of 320)

Mean age 71.0 years

45% Female

85.8% Sievers type I

STS score 1.4%

Williams MR, et al. *JACC Intv*. 2022;15:523-532.

JACC: Cardiovascular Interventions

The PARTNER 3 Bicuspid Registry for Transcatheter Aortic Valve Replacement in Low-Surgical-Risk Patients

30 Day Outcomes

Death		0.0%
Stroke		1.2%
Pacemaker		6.5%
Conversion		0.0%
AI	None/Trace	71.8%
	Mild	26.3%
	>Mild	1.9%

Williams MR, et al. *JACC Intv*. 2022;15:523-532.

JACC: Cardiovascular Interventions

The PARTNER 3 Bicuspid Registry for Transcatheter Aortic Valve Replacement in Low-Surgical-Risk Patients

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Conversion		0.0%
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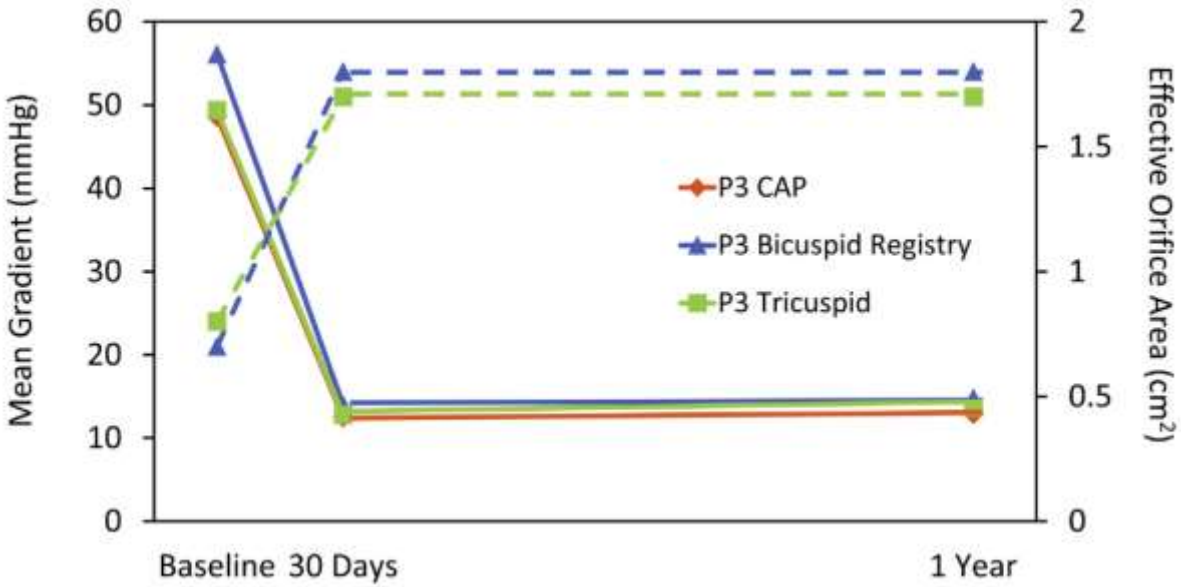
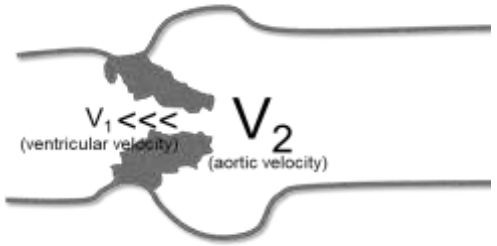
	Mild	26.3%
	>Mild	1.9%

Through 1 year

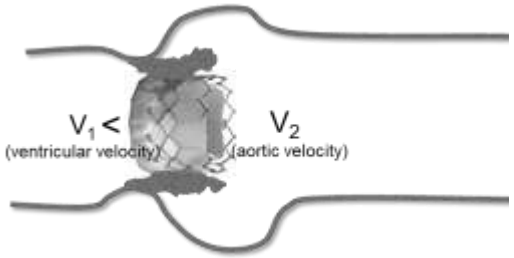


Williams MR, et al. *JACC Intv*. 2022;15:523-532.

Diagnosis of Aortic Stenosis

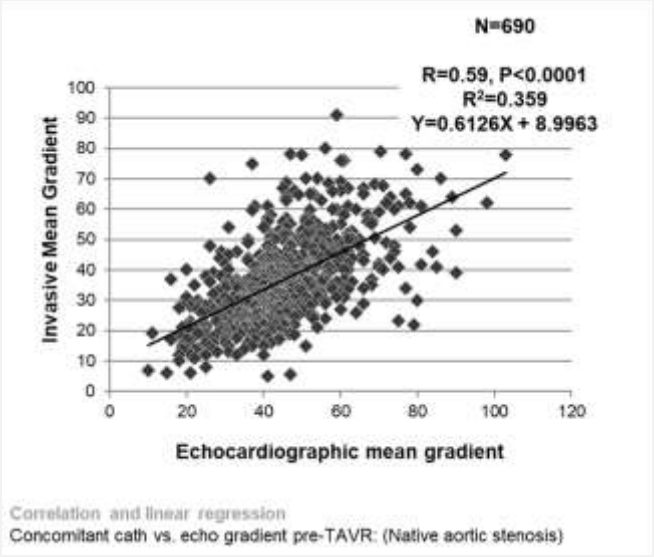


Monitoring Post-AVR

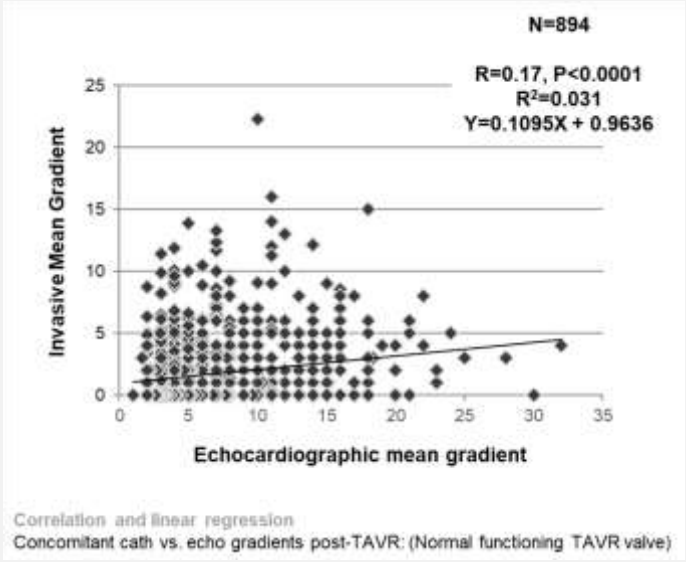


AVR

CONCORDANCE



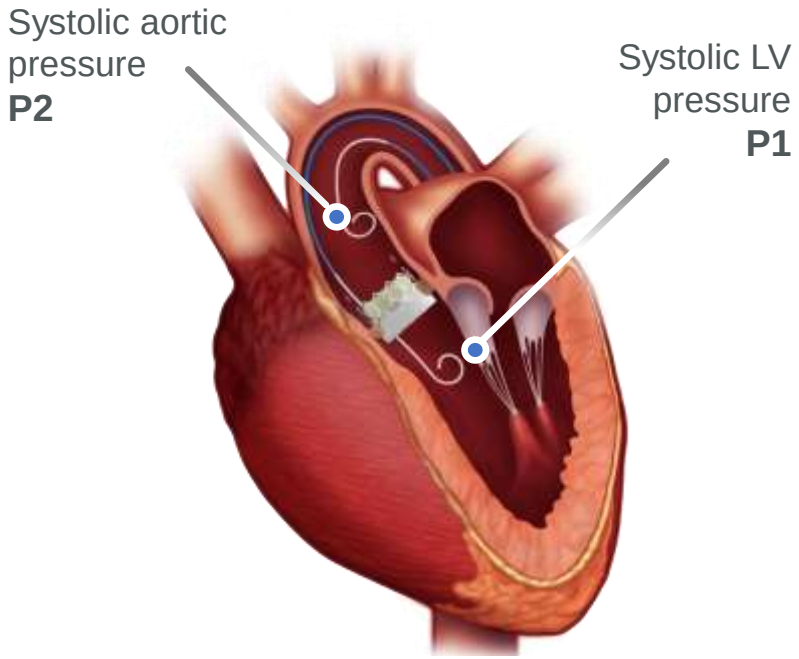
DISCORDANCE



Abbas et al. TCT 2020

Simple CATH

Gold standard cath measures directly the difference in **pressure** across the valve

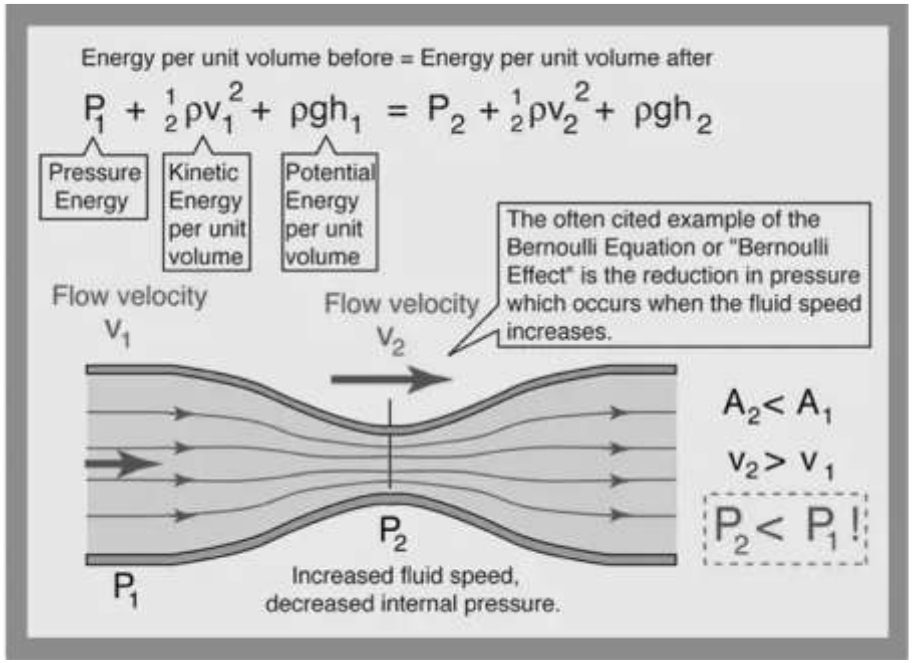


Peak pressure gradient = **P1- P2 mmHg**

vs

Complex ECHO

Highly complex and measures **velocity**, not pressure

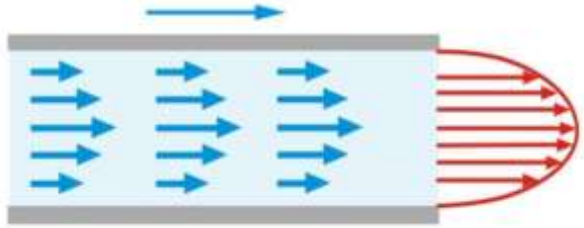


Peak pressure gradient = $4V^2$

Velocity – flow patterns matter

Laminar flow

An **efficient** design results in laminar flow and maintained velocity between the LV and the aorta.

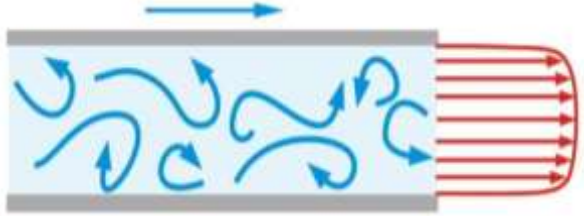


Laminar flow = higher velocity

Higher echo derived gradient ↑

Turbulent flow

An **inefficient** design results in turbulent flow and inconsistent velocity between LV and the aorta.

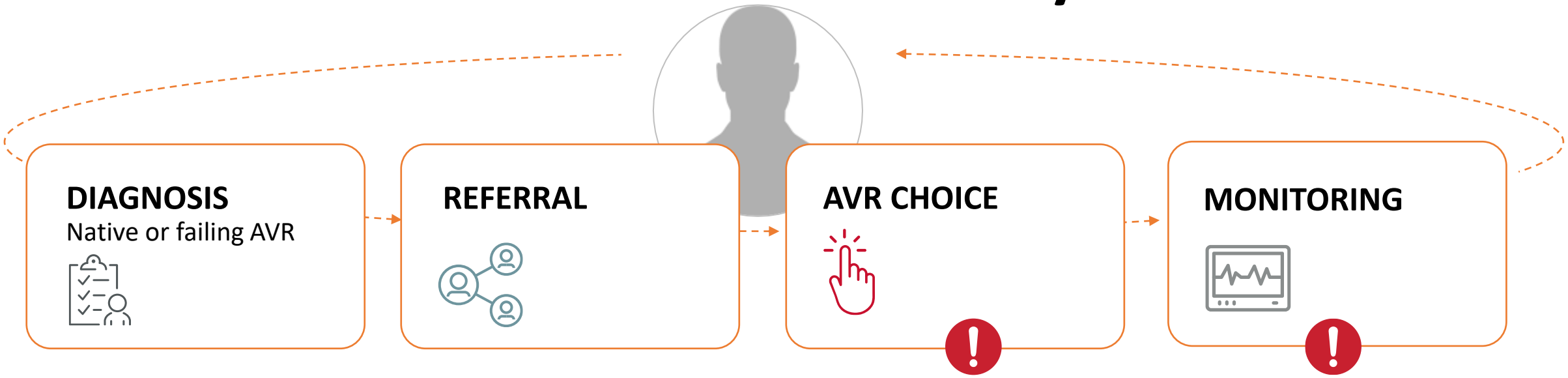


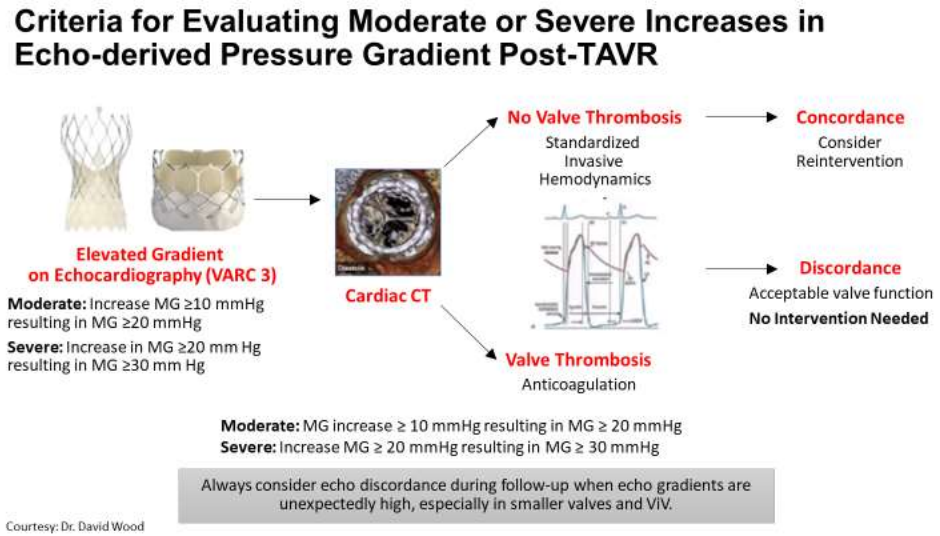
Turbulent flow = lower velocity

Lower echo derived gradient ↓

Because laminar flow maintains velocity, **echo overestimates the pressure gradient in a valve with laminar flow** compared to a valve with turbulent flow perversely rewarding valve design with turbulent flow.

Important to Understand Limitations of Echo-Derived AV Gradients to Avoid Unnecessary Interventions





If echo-derived gradients do not correlate to outcomes then **choice of AVR should not be solely made on this information**

If modality for monitoring patients has limitations, **a caution needs to be applied in interpretation**