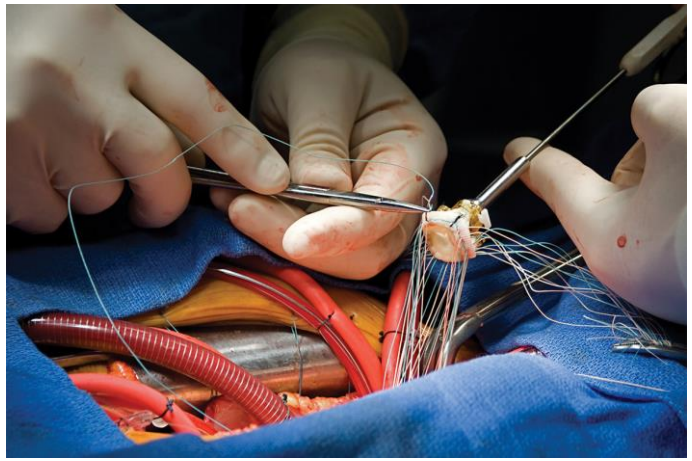
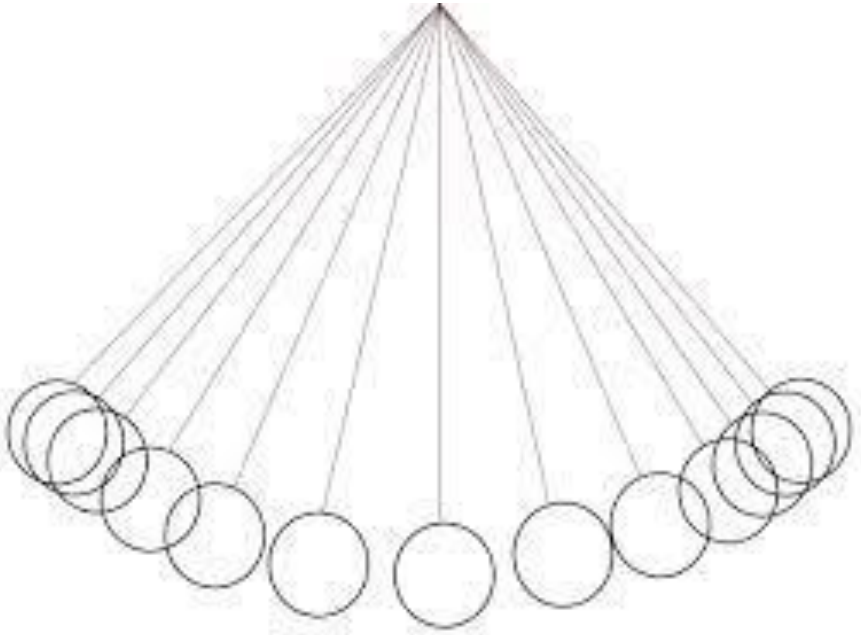
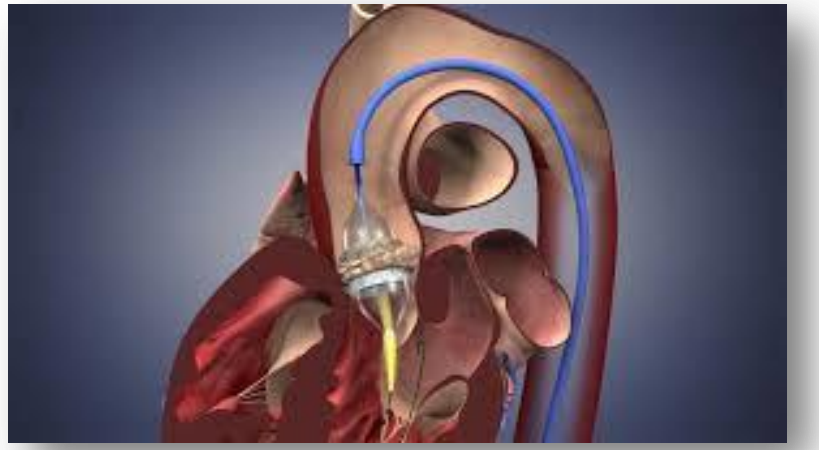
TAVI – kam gremo? Kdo bo še kandidat za SAVR v letu 2023?







Michael Mack, MD
Baylor Scott & White Health
Dallas, TX

Conflict of Interest Disclosure

Abbott- Co- PI of COAPT Trial of Abbott Vascular

Medtronic-Study Chair Apollo Trial

Edwards Lifesciences- Co-PI of PARTNER 3

The Most Famous Citizen of Slovenia

(and Dallas)

Luka Doncic

You’re Famous When Are Known By One Name!

Outline

Current Management of AS

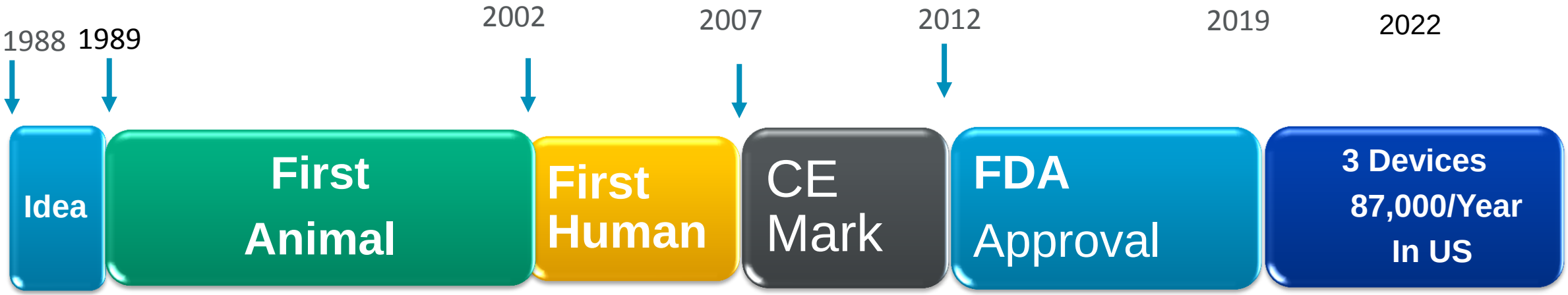
- Who Should Still Get SAVR

Where Are We Going?

- TAVR
- SAVR
- Management of AS

TAVR
How Did We Get Here?
SAVR

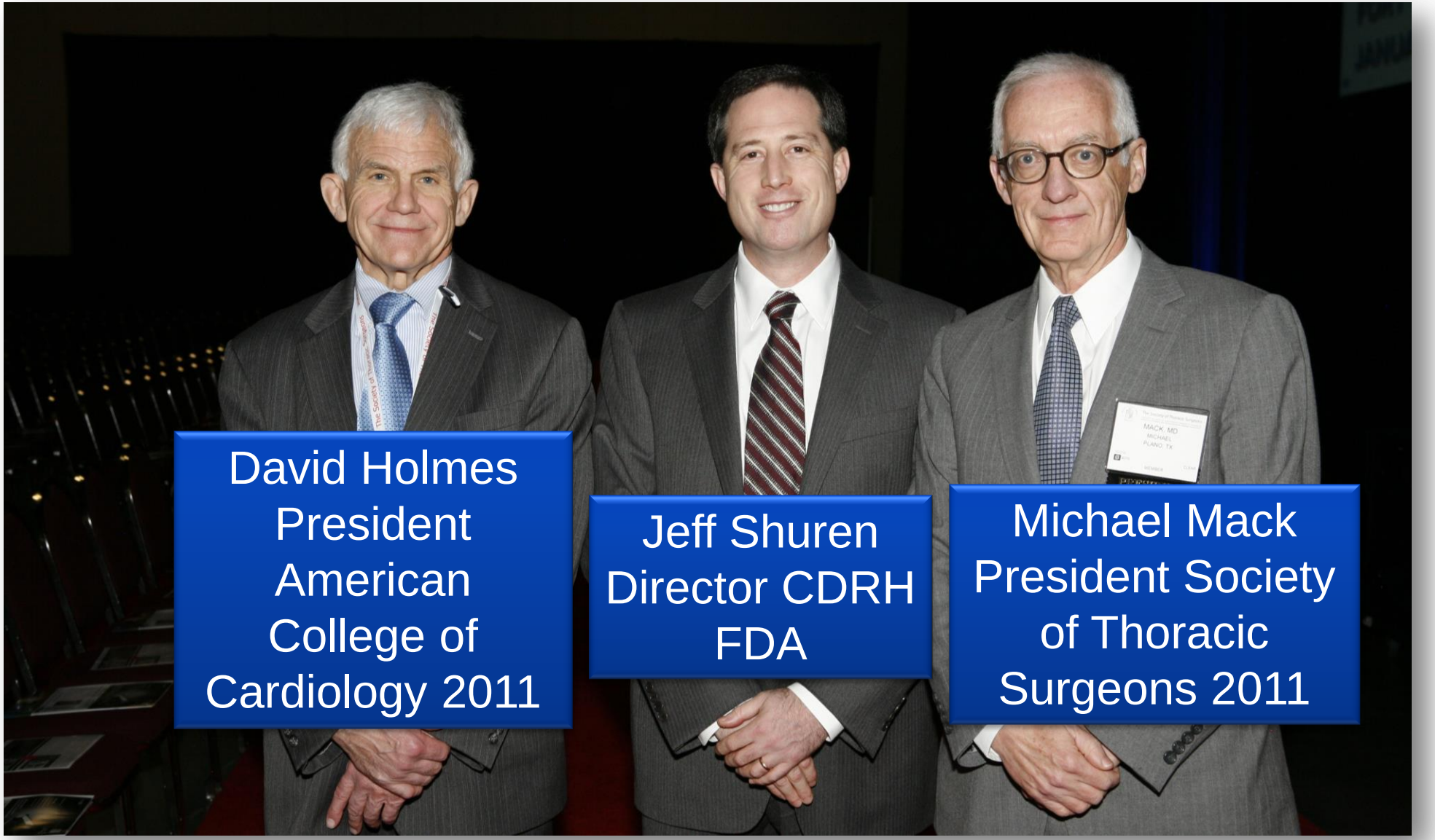
Timeline in the Evolution of TAVR



34 Years Since the Original Idea !

2004-Deal With The Devil?

History of STS/ACC TVT Registry- circa 2011



The STS-ACC Transcatheter Valve Therapy National Registry

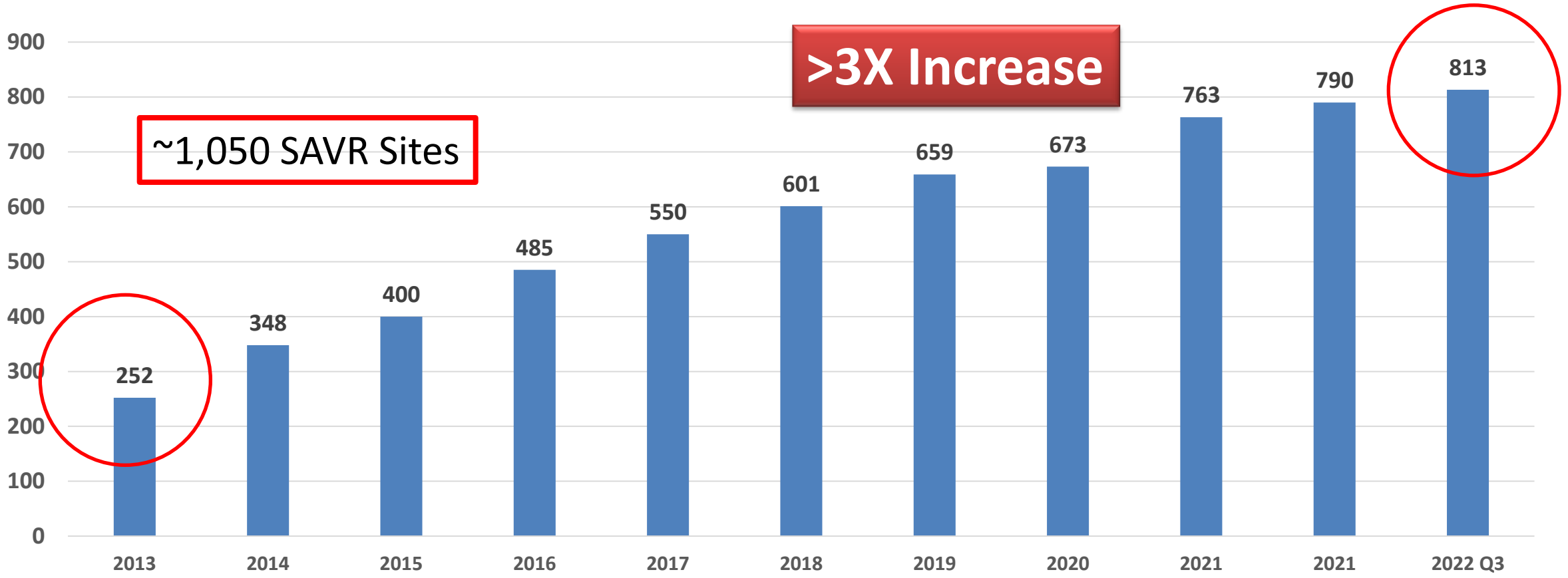
A New Partnership and Infrastructure for the Introduction and

- 400,000 TAVR Procedures
- Virtually Every Case in the US

John I
Ralph
E. Mu
Cynthia M. Shewan, PHD,†† Kathleen Hewitt, MSN, RN,‡‡ David R. Holmes, JR, MD,§§
Michael J. Mack, MD‖‖

Aurora and Denver, Colorado; Jacksonville, Florida; Washington, DC; San Francisco, California; Durham, North Carolina; Cleveland, Ohio; Boston, Massachusetts; Chicago, Illinois; Rochester, Minnesota; and Dallas, Texas

Centers Performing TAVR in US

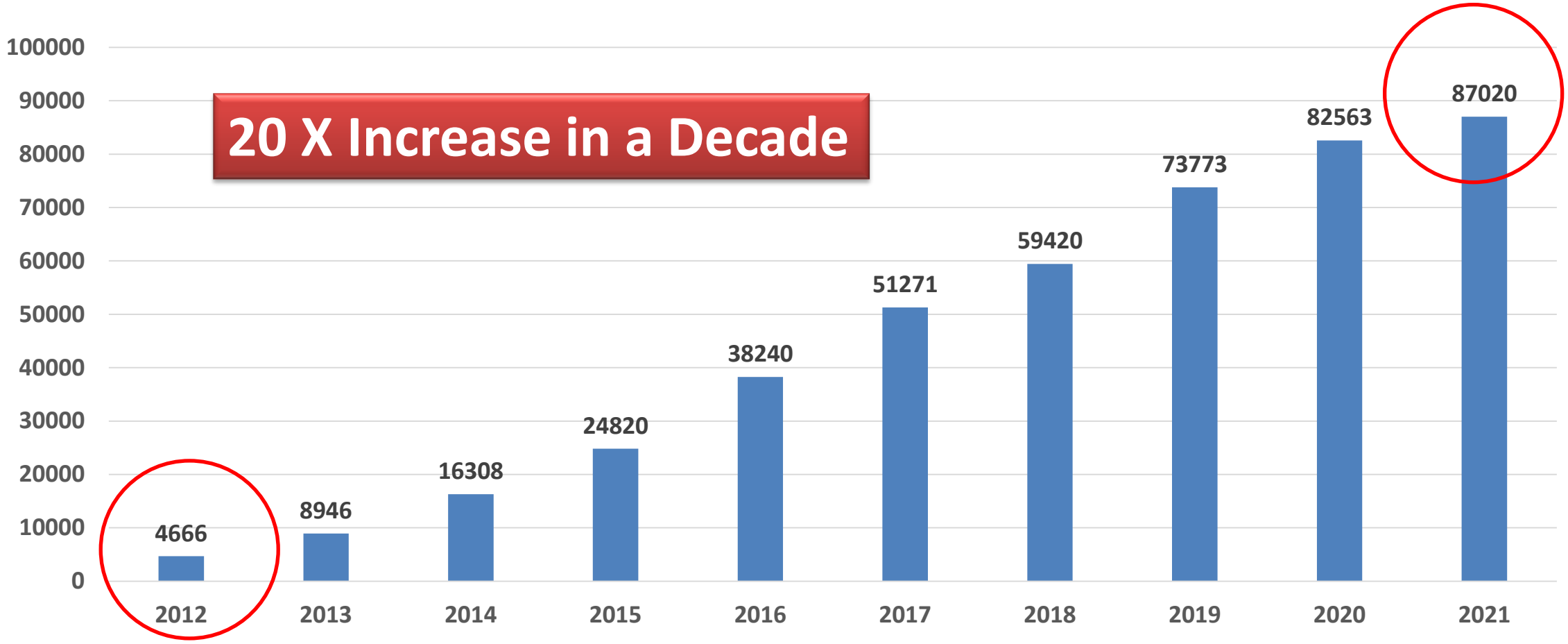


STS National Database™
Trusted. Transformed. Real-Time.

NCDR®
NATIONAL CARDIOVASCULAR DATA REGISTRY

Source: STS/ACC TVT Registry Database.

Annual TAVR Procedure Volume in US



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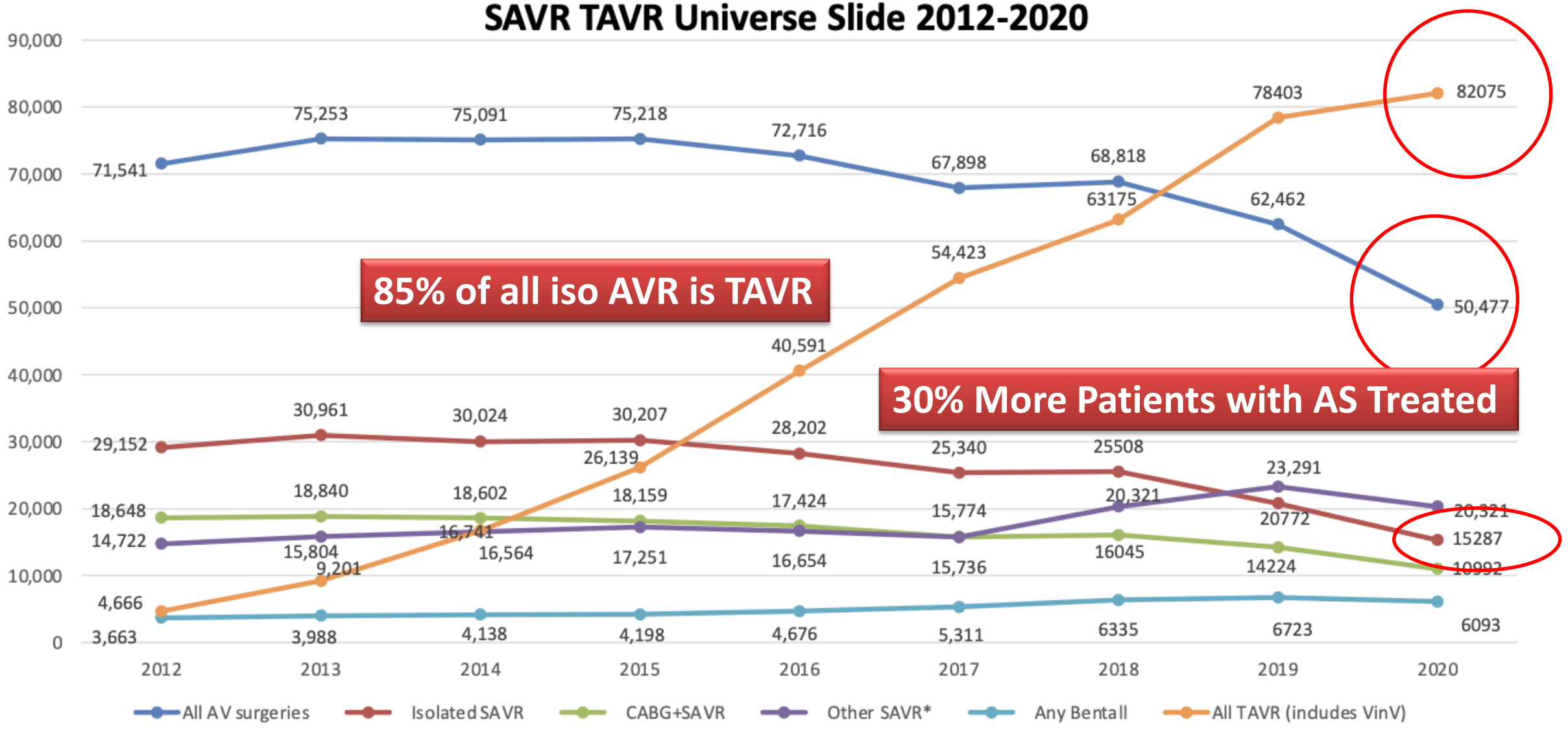
SAVR TAVR Universe Slide 2012-2020



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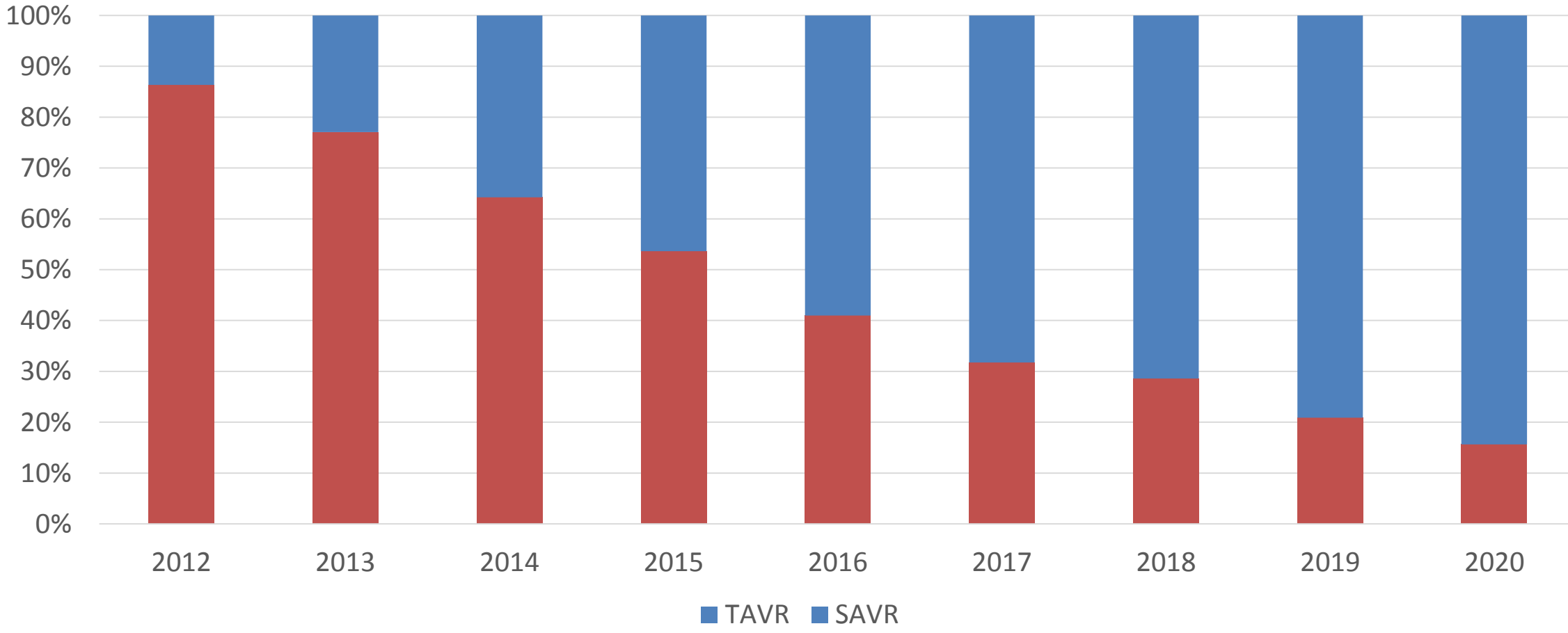
TAVR vs. SAVR in US



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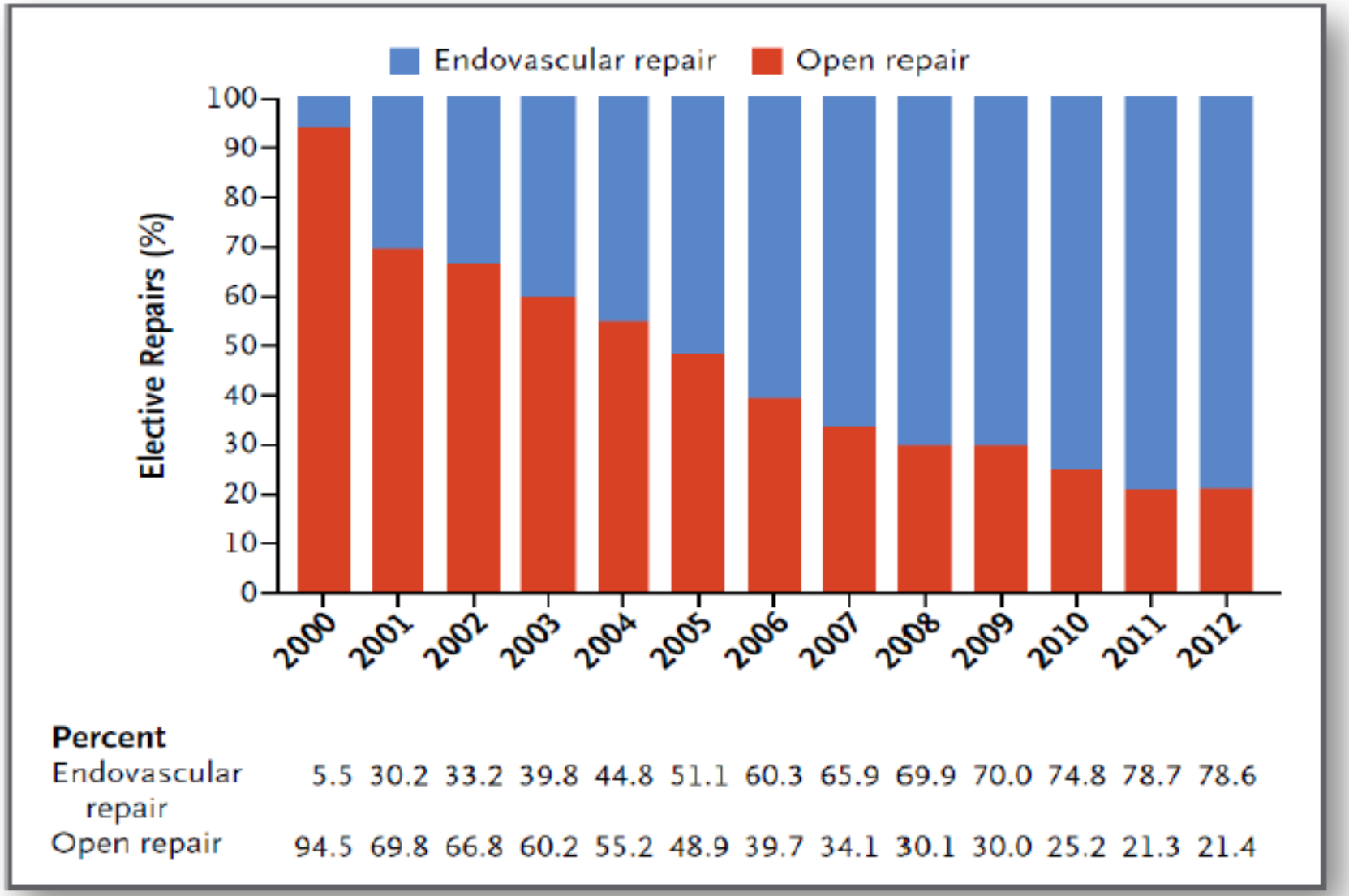
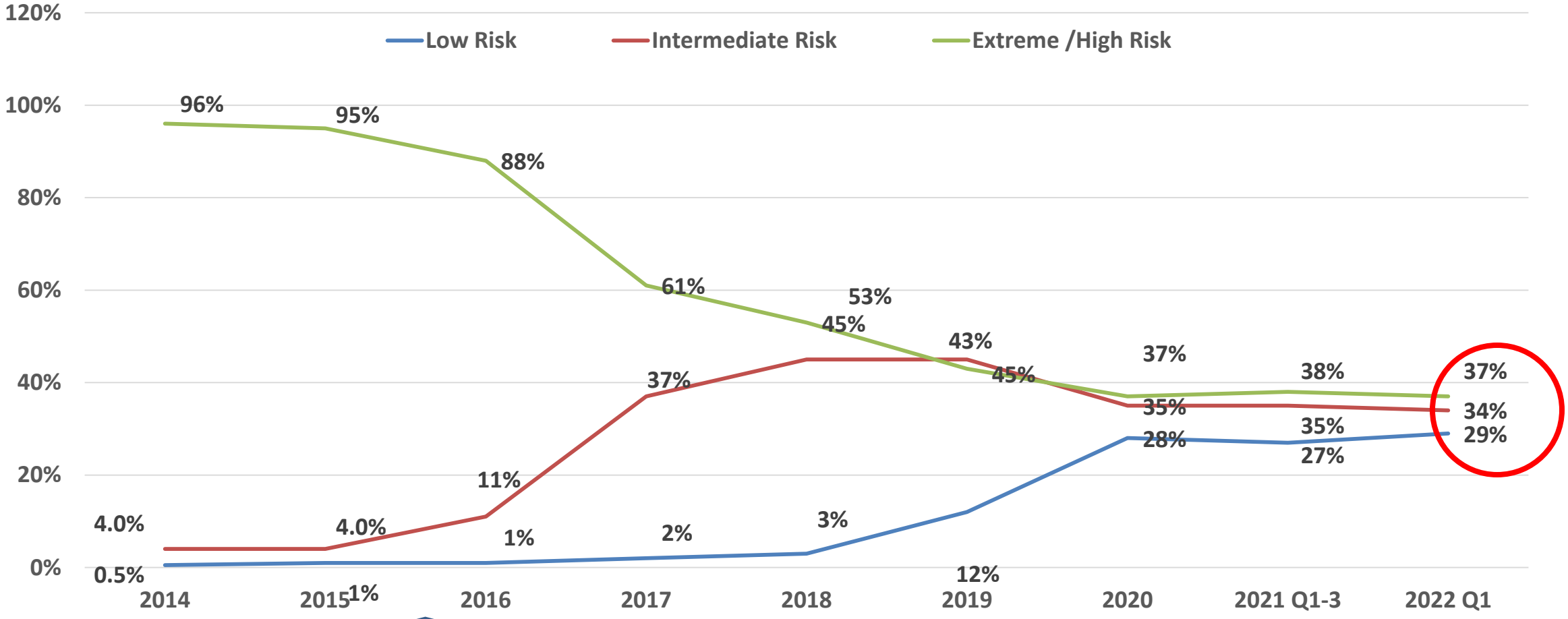
EVAR vs. Open Surgery



Percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Endovascular repair	5.5	30.2	33.2	39.8	44.8	51.1	60.3	65.9	69.9	70.0	74.8	78.7	78.6
Open repair	94.5	69.8	66.8	60.2	55.2	48.9	39.7	34.1	30.1	30.0	25.2	21.3	21.4

Kent KC. NEJM 2014; 371:2101-8

TAVR
Procedure Risk

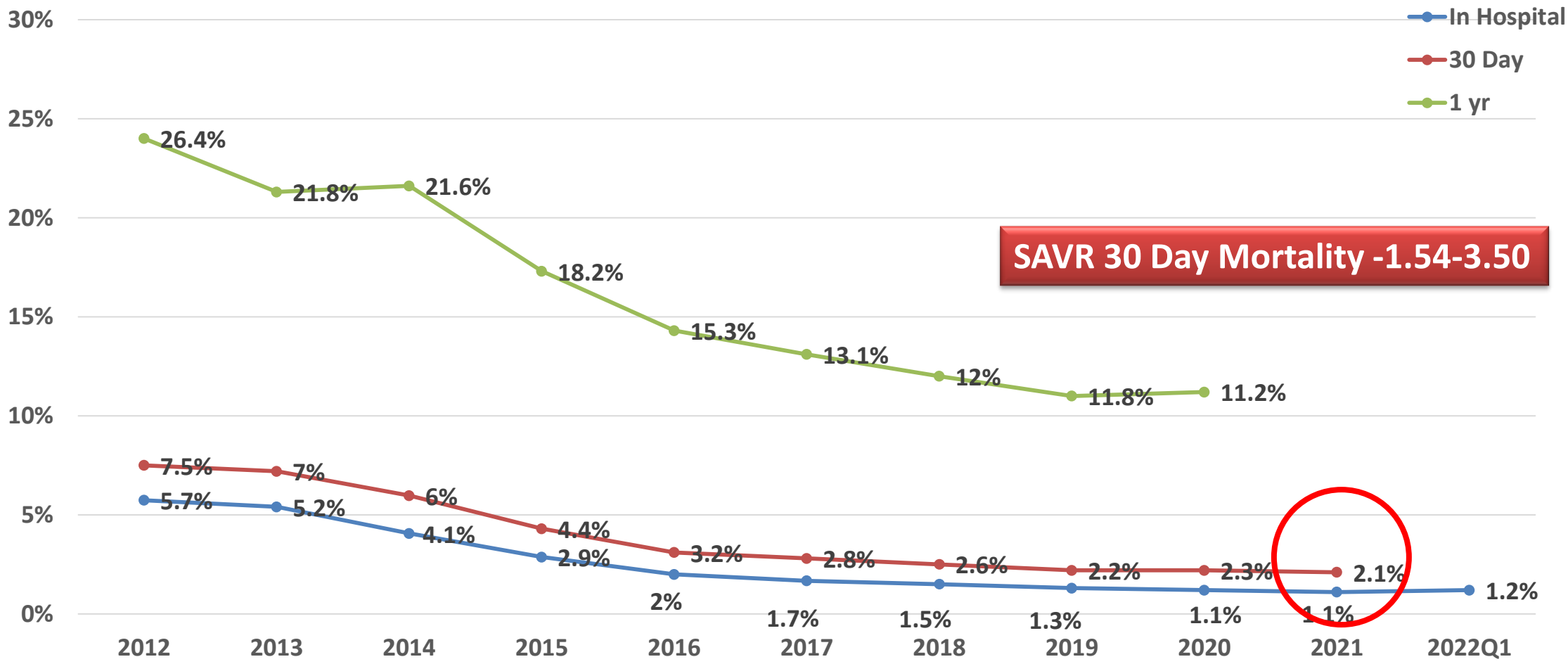


Source: STS/ACC TVT Registry Database

STS National Database™
Using data to drive quality

NCDR®
NATIONAL CARDIOVASCULAR DATA REGISTRY

TAVR Mortality



Source: STS/ACC TVT Registry Database

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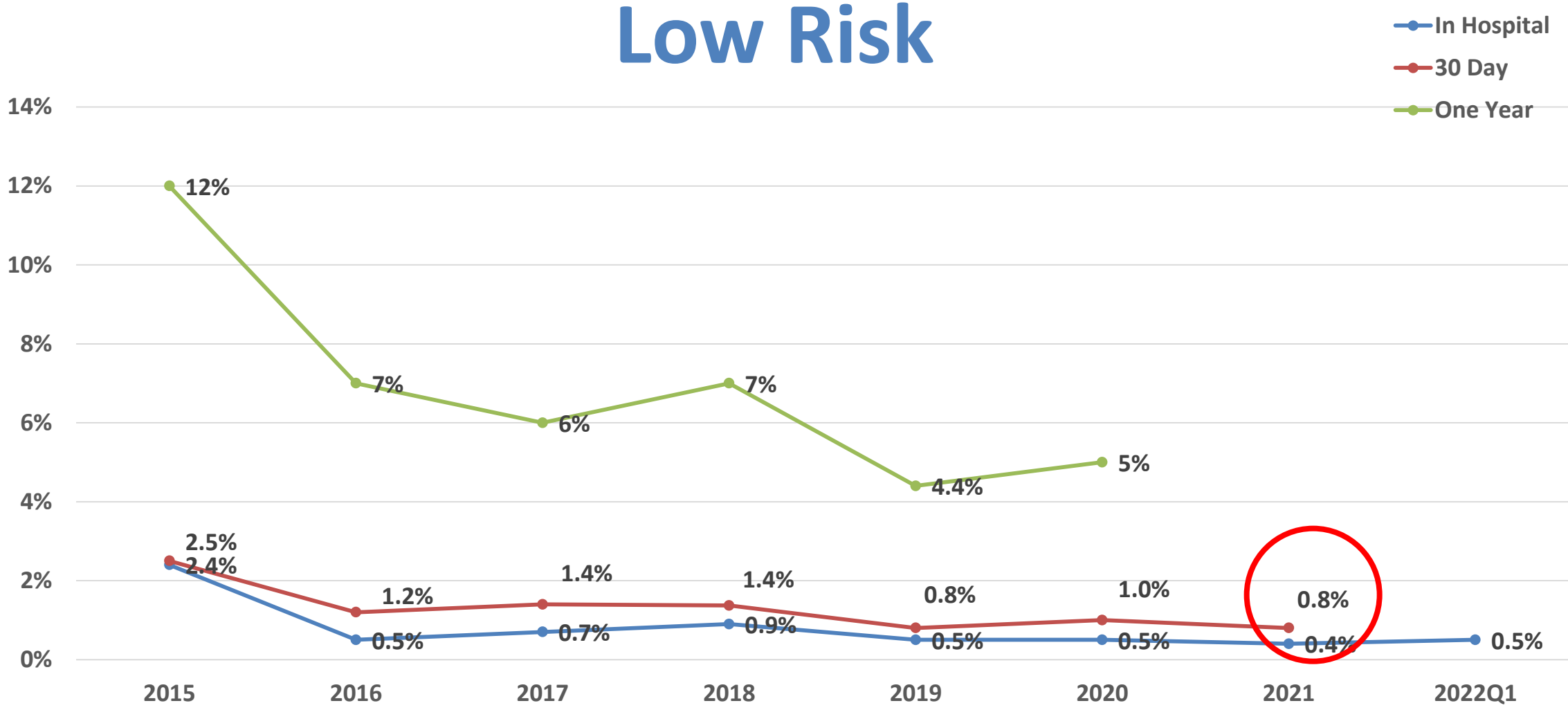
TAVR Mortality
Low Risk



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Source: STS/ACC TVT Registry Database

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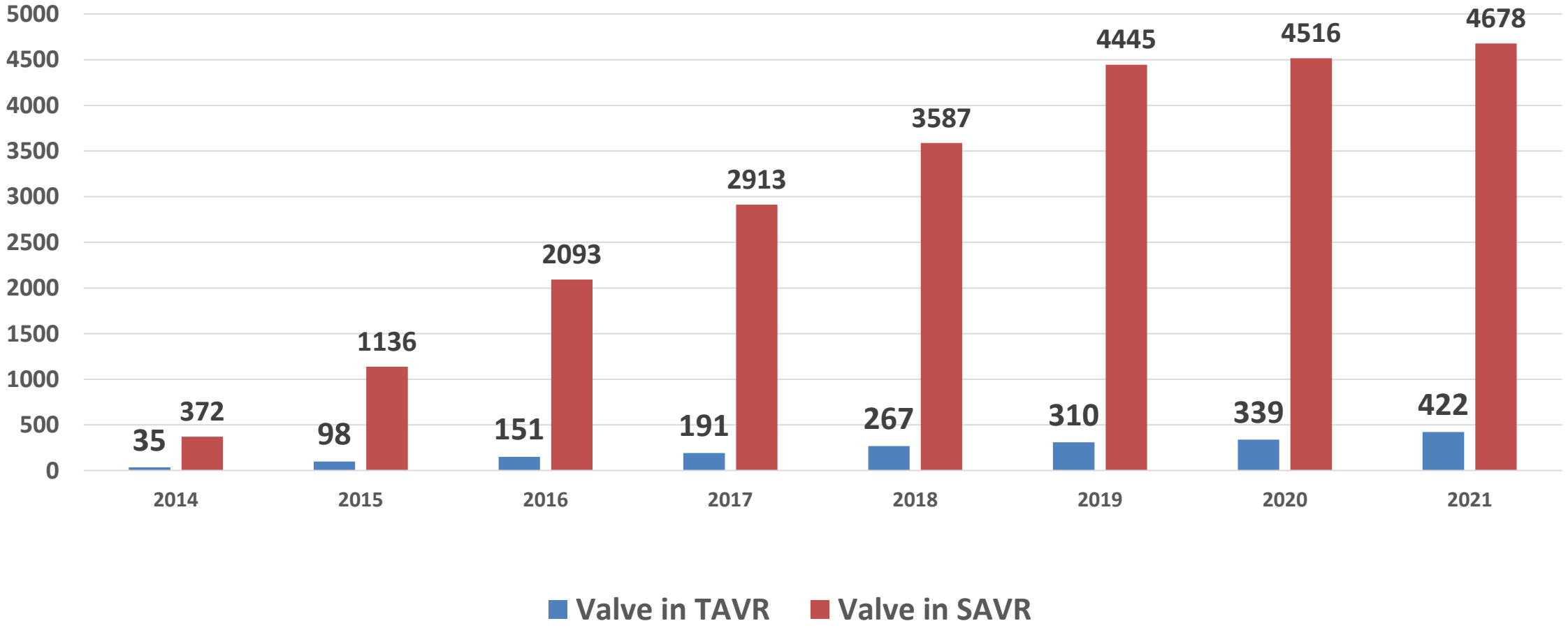
NATIONAL CARDIOVASCULAR DATA REGISTRY

TAVR Valve in Valve

Valve in SAVR/ Valve in TAVR



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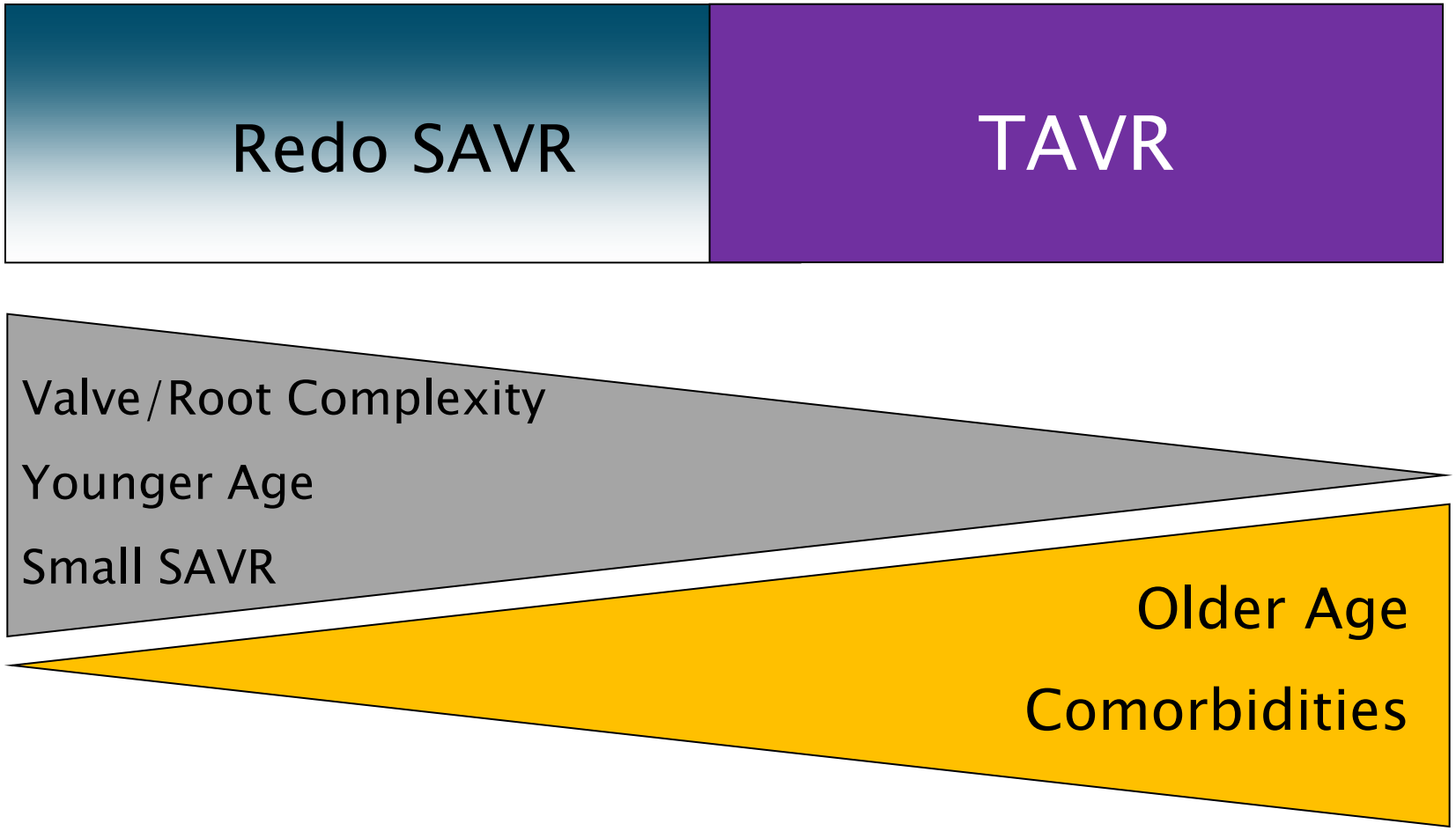
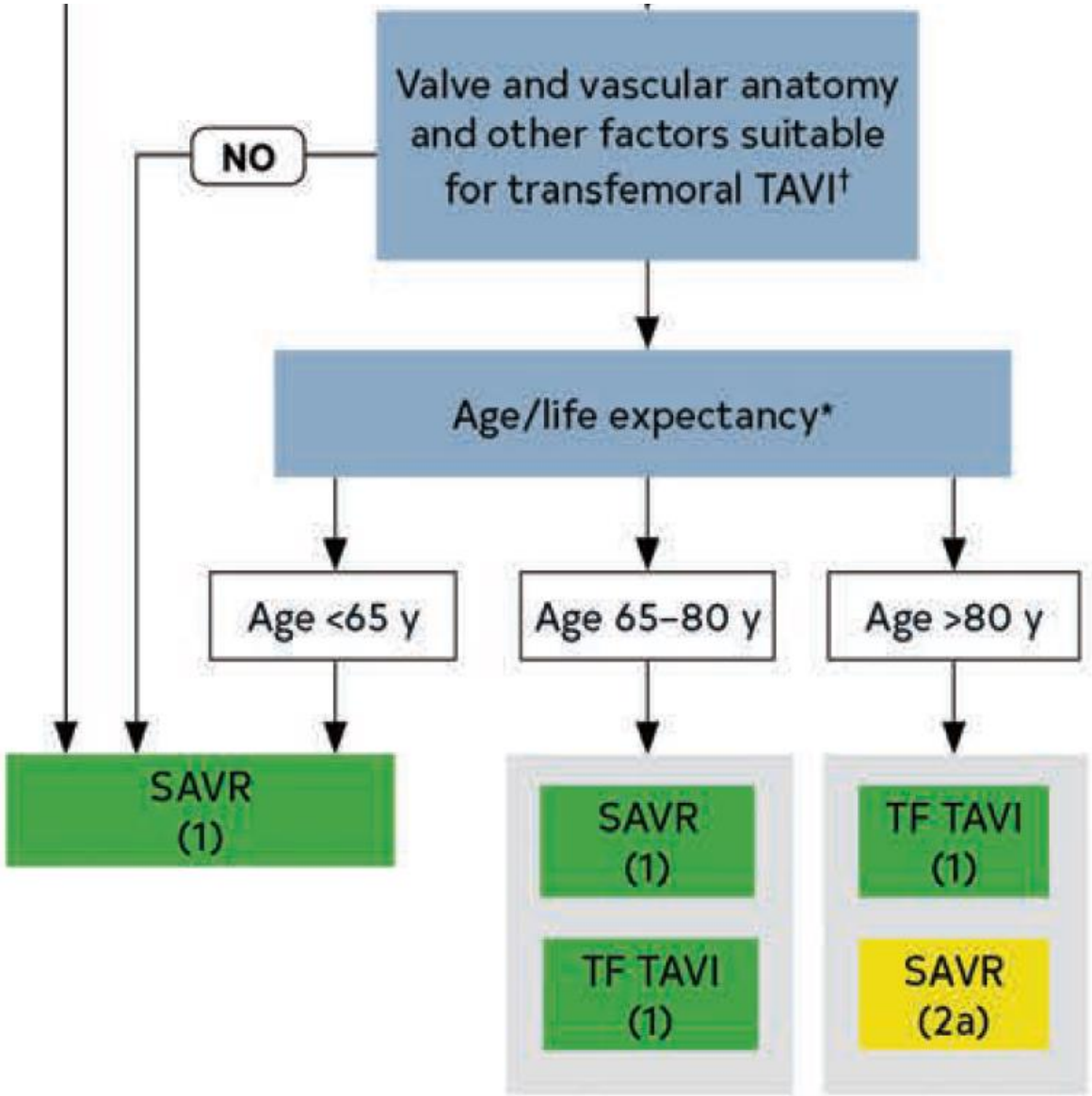
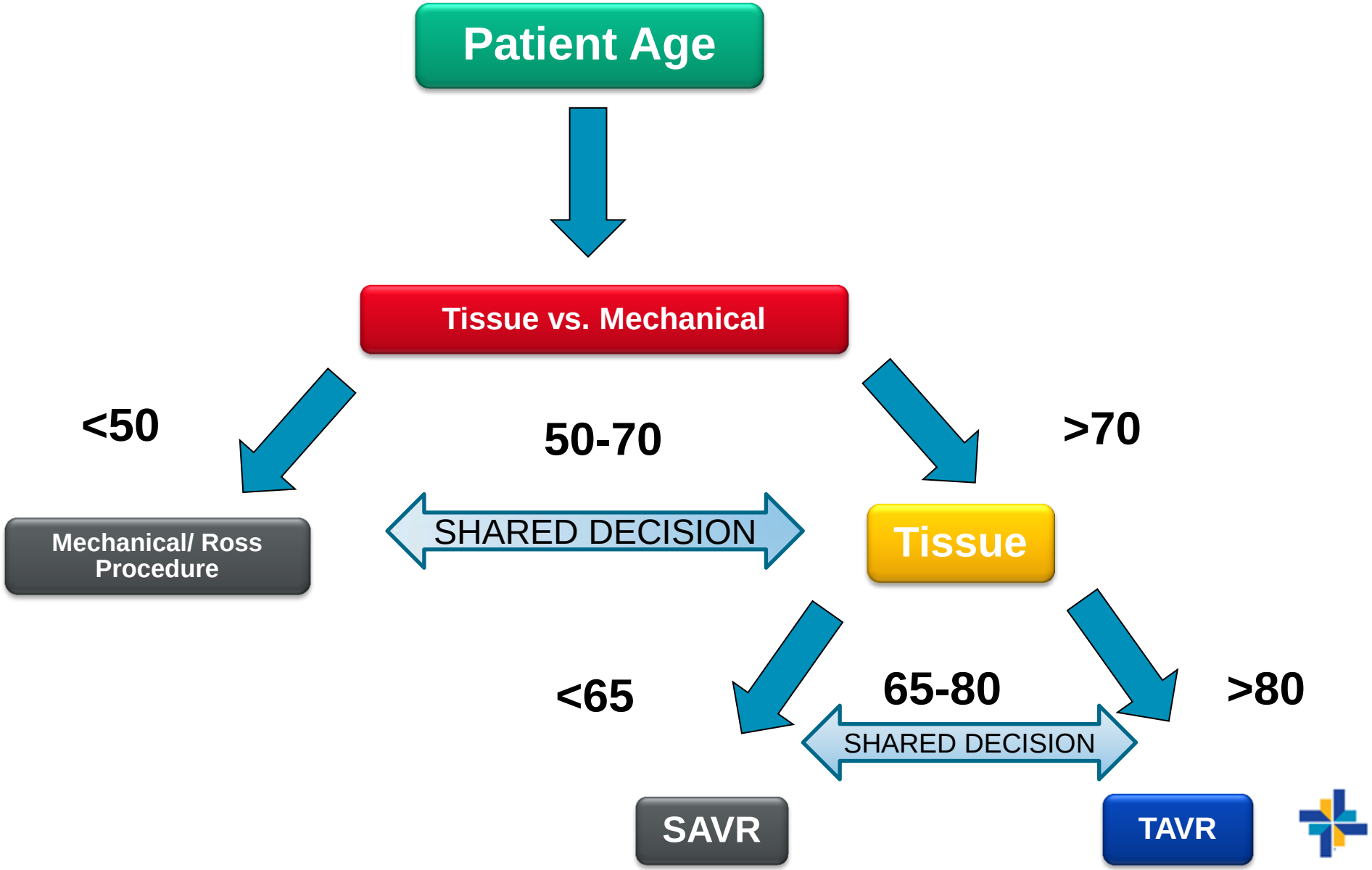
Patient Treatment Decision-making



ACC/AHA Guidelines for Treatment of AS



Clinical Decision Making in Aortic Stenosis



Patients With AS to Consider SAVR vs. TAVR

- Patient preference
- Younger
- Not frail with co-morbidities- long life expectancy
- High Risk for TAVR- valve/aortic root anatomy/pathology
- Bicuspid AS
- Aortopathy
- Previous TAVR/SAVR with Structural Valve Deterioration- especially with small valve
- Concomitant Diseases

Concomitant Conditions With AS That Mitigate Toward SAVR in Patients 65-80 Years

Coronary Artery Disease- especially SYNTAX≥ 33

Mitral Regurgitation- especially primary MR

Tricuspid Regurgitation

Ascending Aortic Aneurysm

Atrial Fibrillation – if candidate for Maze Procedure

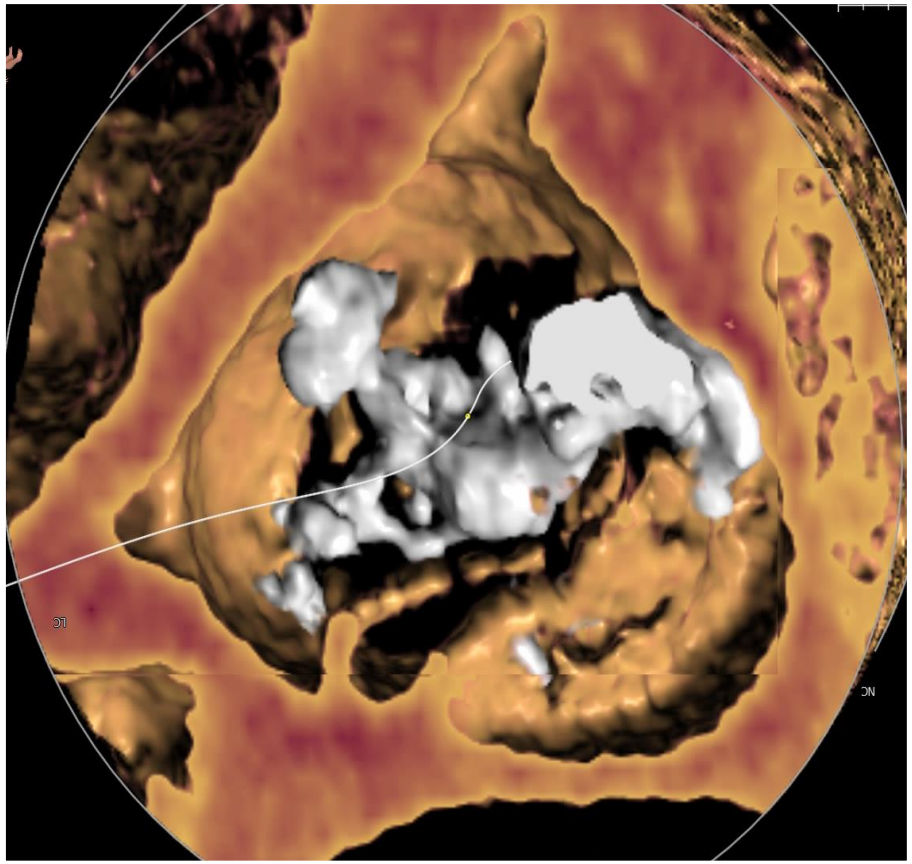
Current Questions/Issues

Bicuspid Aortic Valve

Lifetime Management

- Durability
- Procedure Sequence

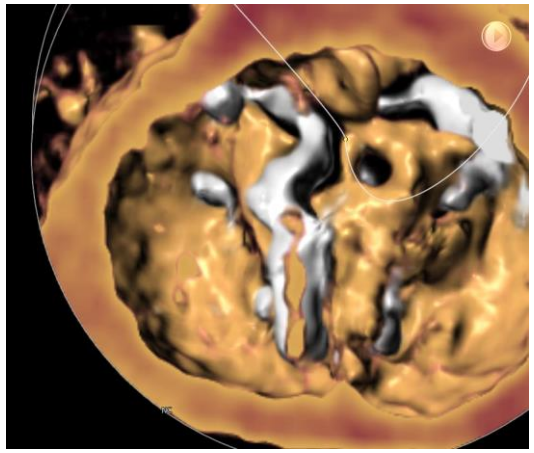
TAVI in Bicuspid AS

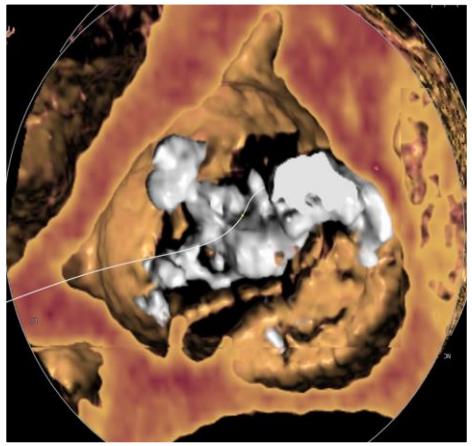


Bicuspid Valve With Bulky Eccentric Calcification

Bicuspid Aortic Valve

Unfavorable Features of BAV Anatomy for TAVR

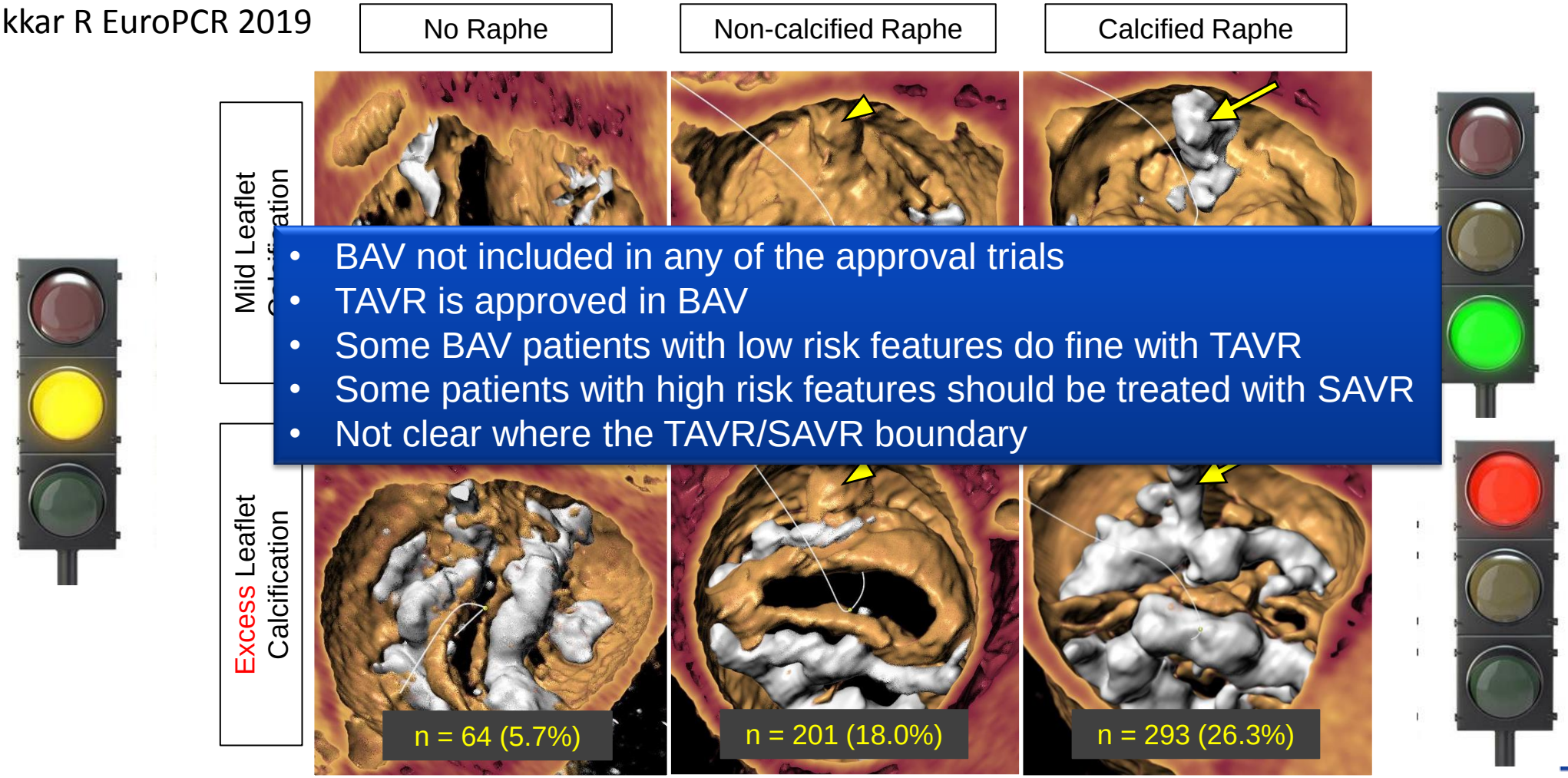




- Anulus more elliptical
- Asymmetric calcium distribution
- Bulky calcification extending into LVOT
- Lower coronary heights
- Ascending aortic dilation

Bicuspid Aortic Stenosis

Yoon S, Makkar R EuroPCR 2019



- BAV not included in any of the approval trials
- TAVR is approved in BAV
- Some BAV patients with low risk features do fine with TAVR
- Some patients with high risk features should be treated with SAVR
- Not clear where the TAVR/SAVR boundary

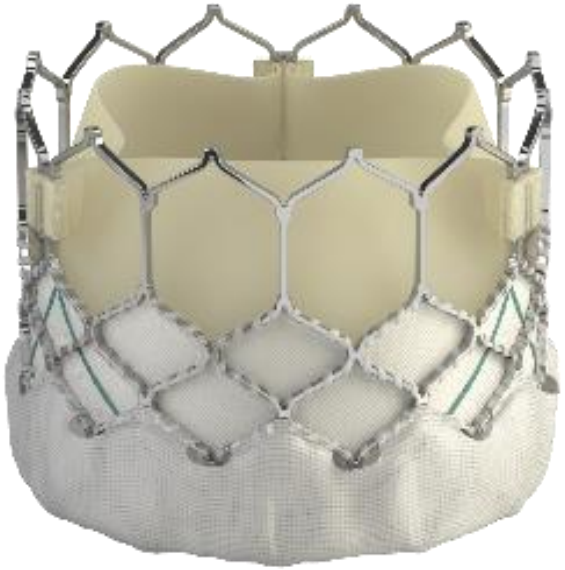
Options For Decision-making Evidence in Bicuspid Aortic Stenosis

Continue Current Practice

RCT of TAVR vs. SAVR

Pragmatic Trial with CT Phenotyping of the AS with Long--term Follow-up

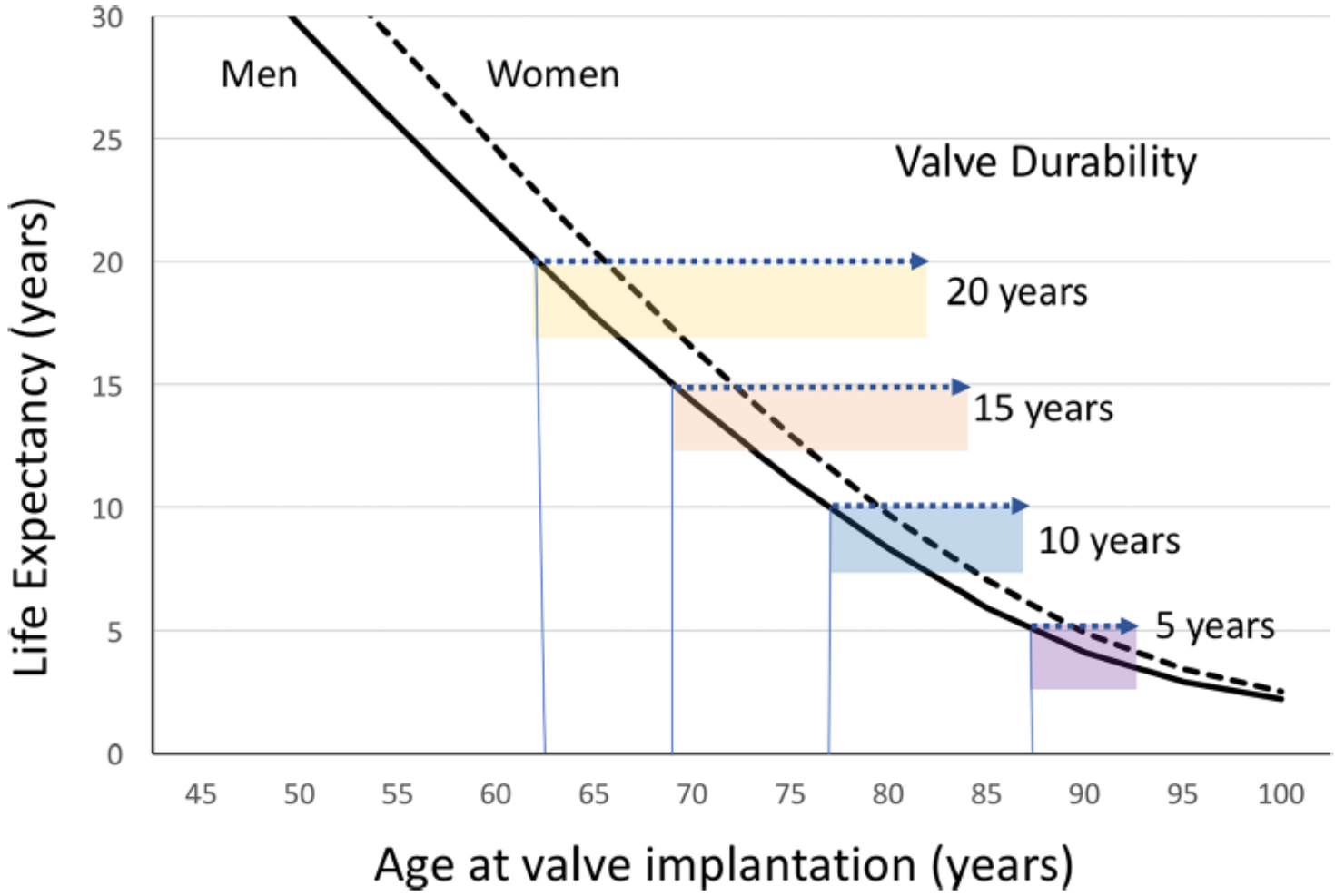
What is the Durability of TAVI Valves Compared to SAVR?



Better ?
Same ?
Worse ?

Durability of ViV (TAV in SAV or TAV in TAV) is not likely to be the same as the index procedure

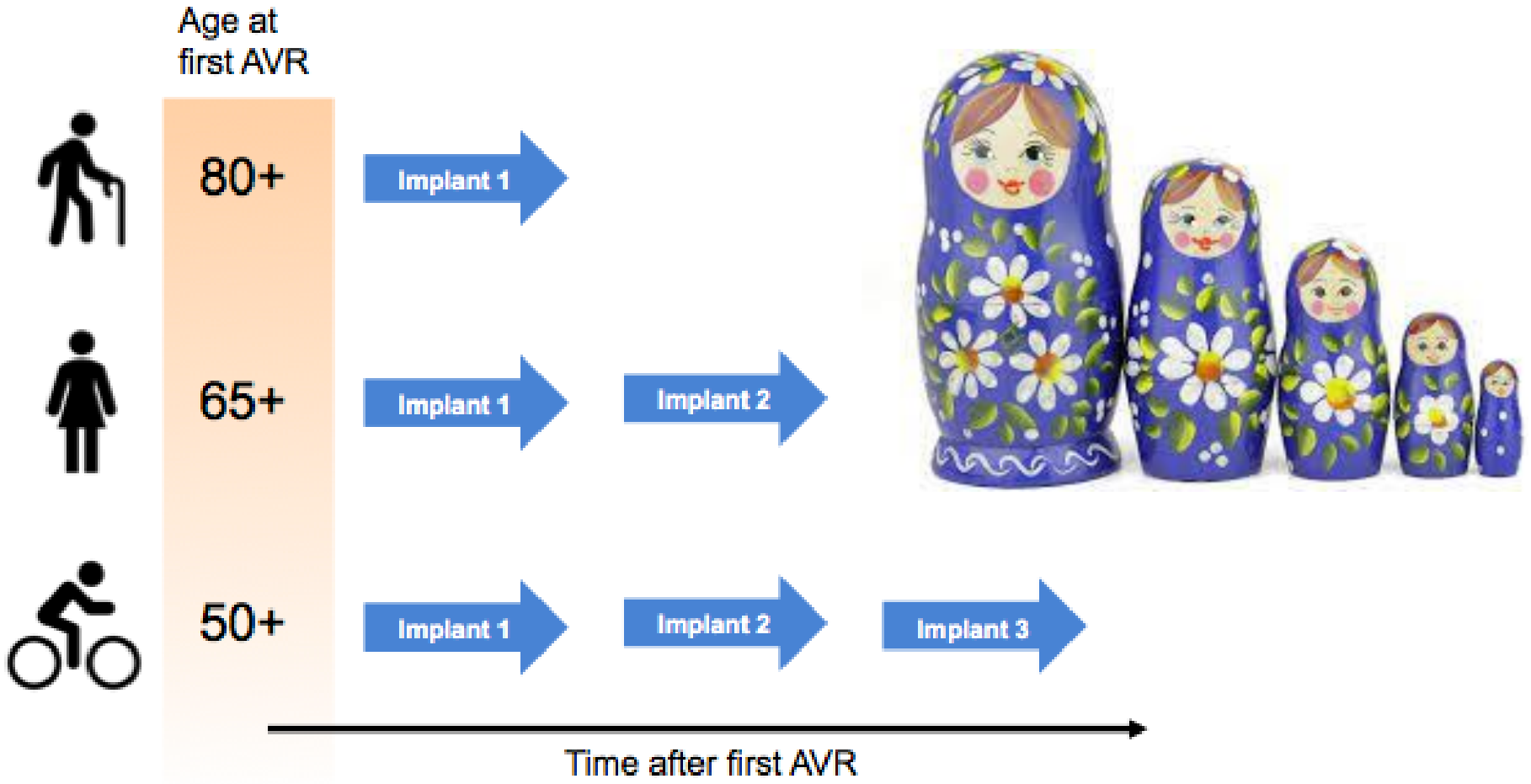
Life Expectancy Versus Durability in Low Risk Patients



Bagur et al. Heart 2017

Choose your Sequence…

Key Factors: Anatomy and Patient Preference

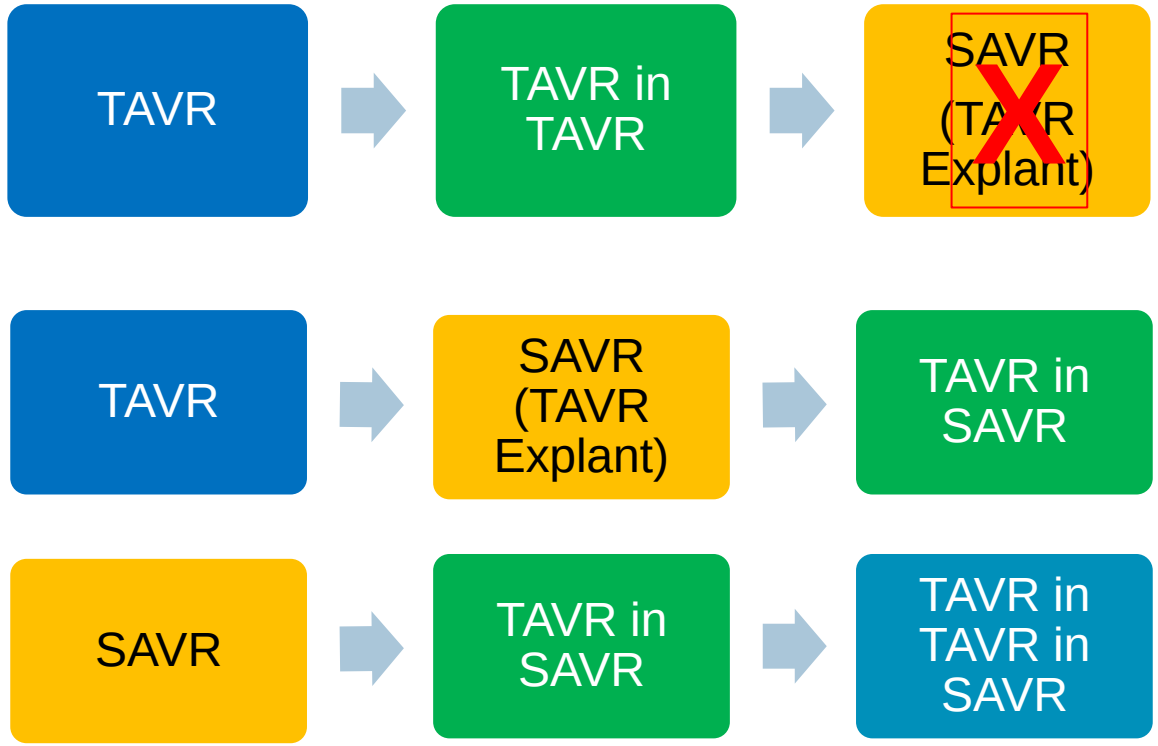


If 3 Interventions- Which First (and Second) ?

The younger the patient, the higher chance of 3 interventions

Each intervention adding additional unknown issues

Higher cumulative risk of stroke, mortality, need for anticoagulation



Future Directions TAVR

Next Generation

SAPIEN X4

Evolut Fx

Other New Valves

Abbott Navitor

Acurate neo2

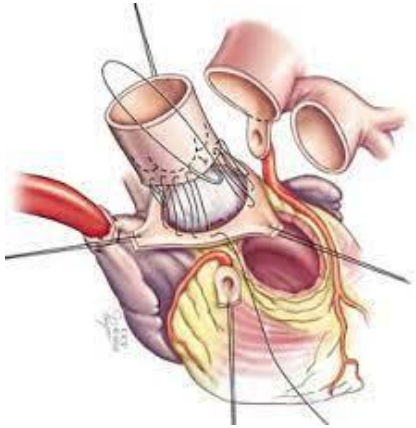
JenaValve

What Populations Next?

- Younger Patients/Durability/ Lifelong Management
- Bicuspid Valves
- Aortic Regurgitation
- Rheumatic Heart Disease
- Concomitant Coronary Disease
- Concomitant Valve Disease
- Earlier Diagnosis/Disease Prevelance
- Asymptomatic AS
- Moderate AS
- Medical Therapy to Slow Progression of AS

Future Directions SAVR

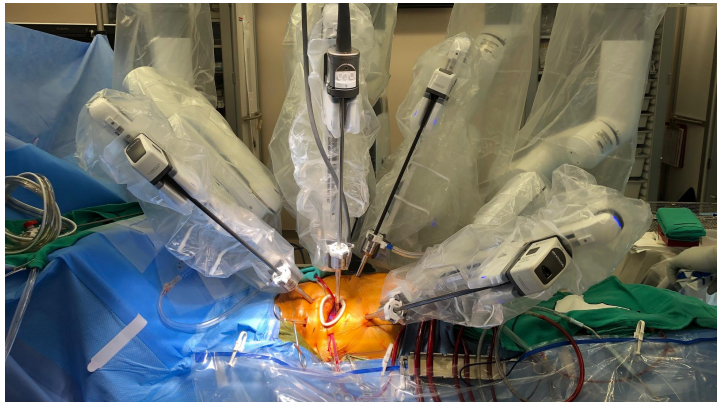
Future Aortic Valve Surgery



Ross
Procedure

Bio Bentall

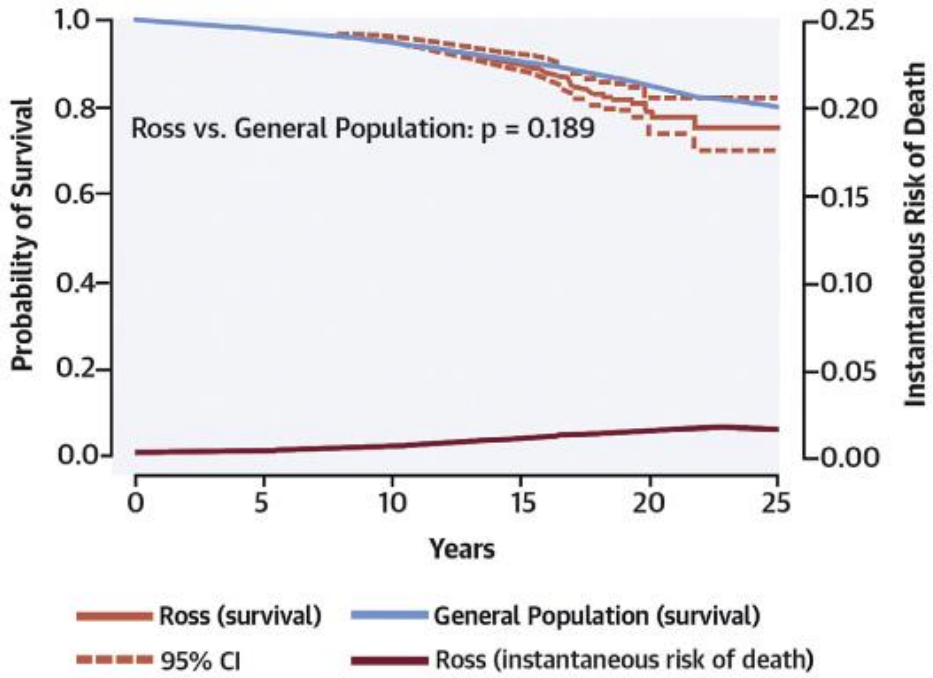
TAVR Explant
SAVR



Robotic AVR

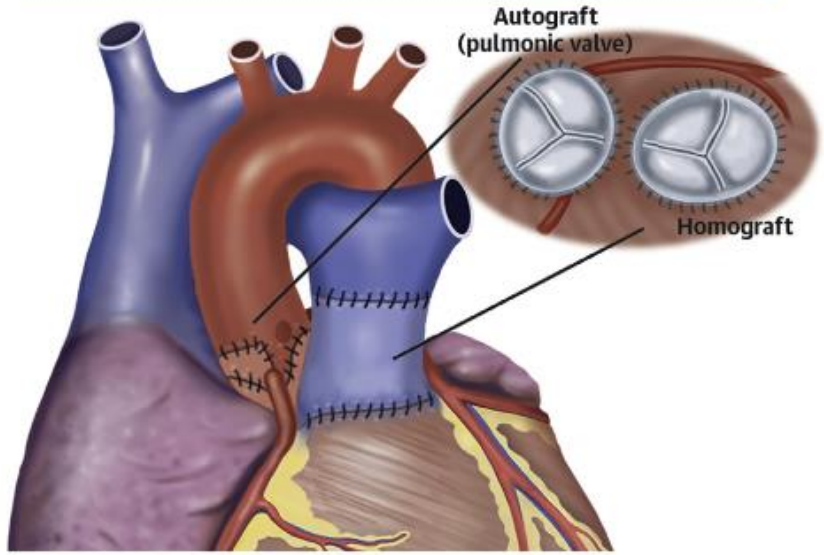
CENTRAL ILLUSTRATION Overall Survival of Patients After Ross Procedures

Adult Population



Patients at Risk					
2,271	1,694	1,104	568	116	30

Ross Procedure



Autograft Reintervention	0.69%/Patient Year
RVOT Reintervention	0.62%/Patient Year
Major Bleeding	0.15%/Patient Year
Permanent stroke	0.13%/Patient Year
Valve Thrombosis	0.07%/Patient Year
Endocarditis	0.36%/Patient Year

Aboud, A. et al. J Am Coll Cardiol. 2021;77(11):1412-22.

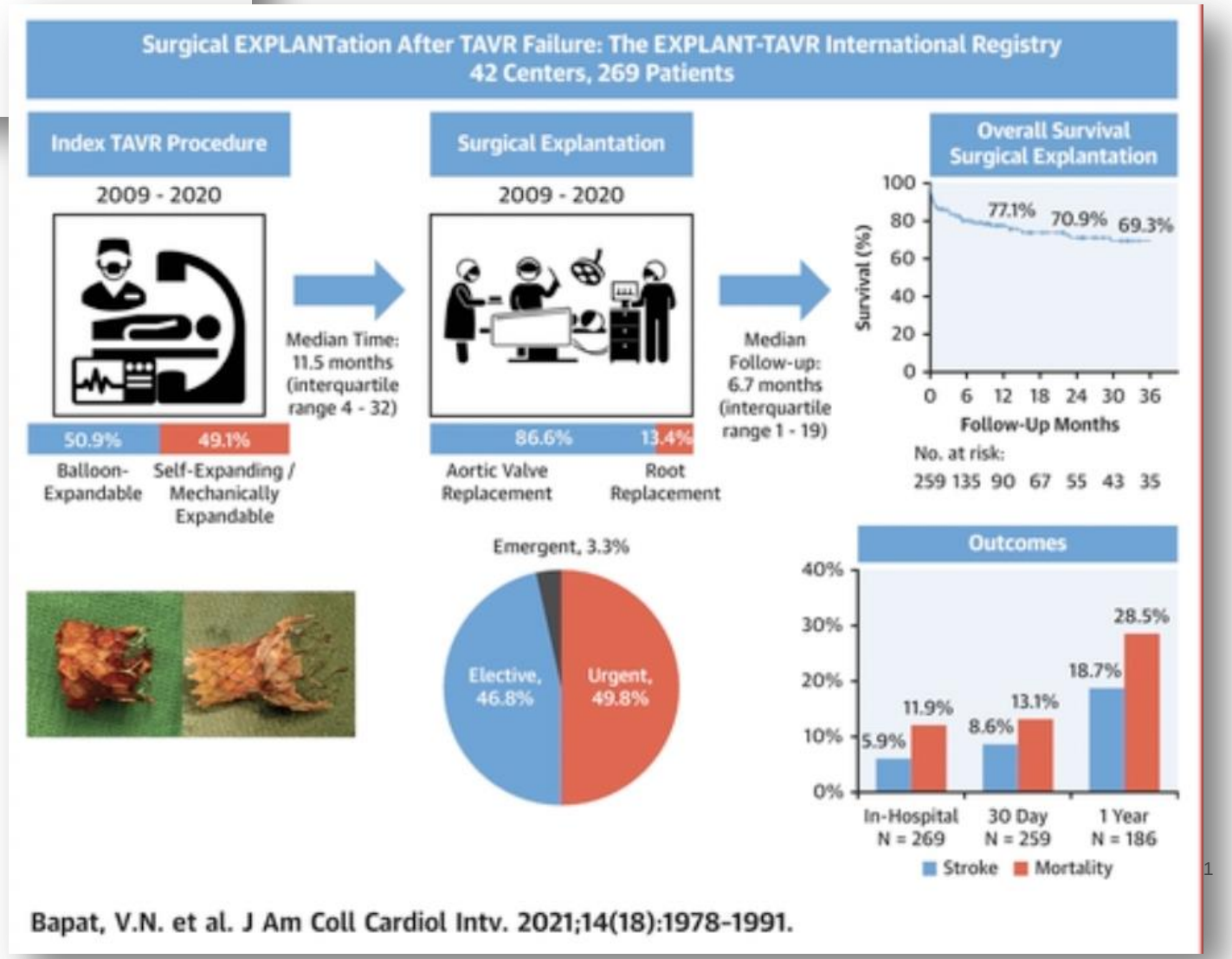
Surgical Explantation After TAVR Failure: Mid-Term Outcomes From the EXPLANT-TAVR International Registry

Structural

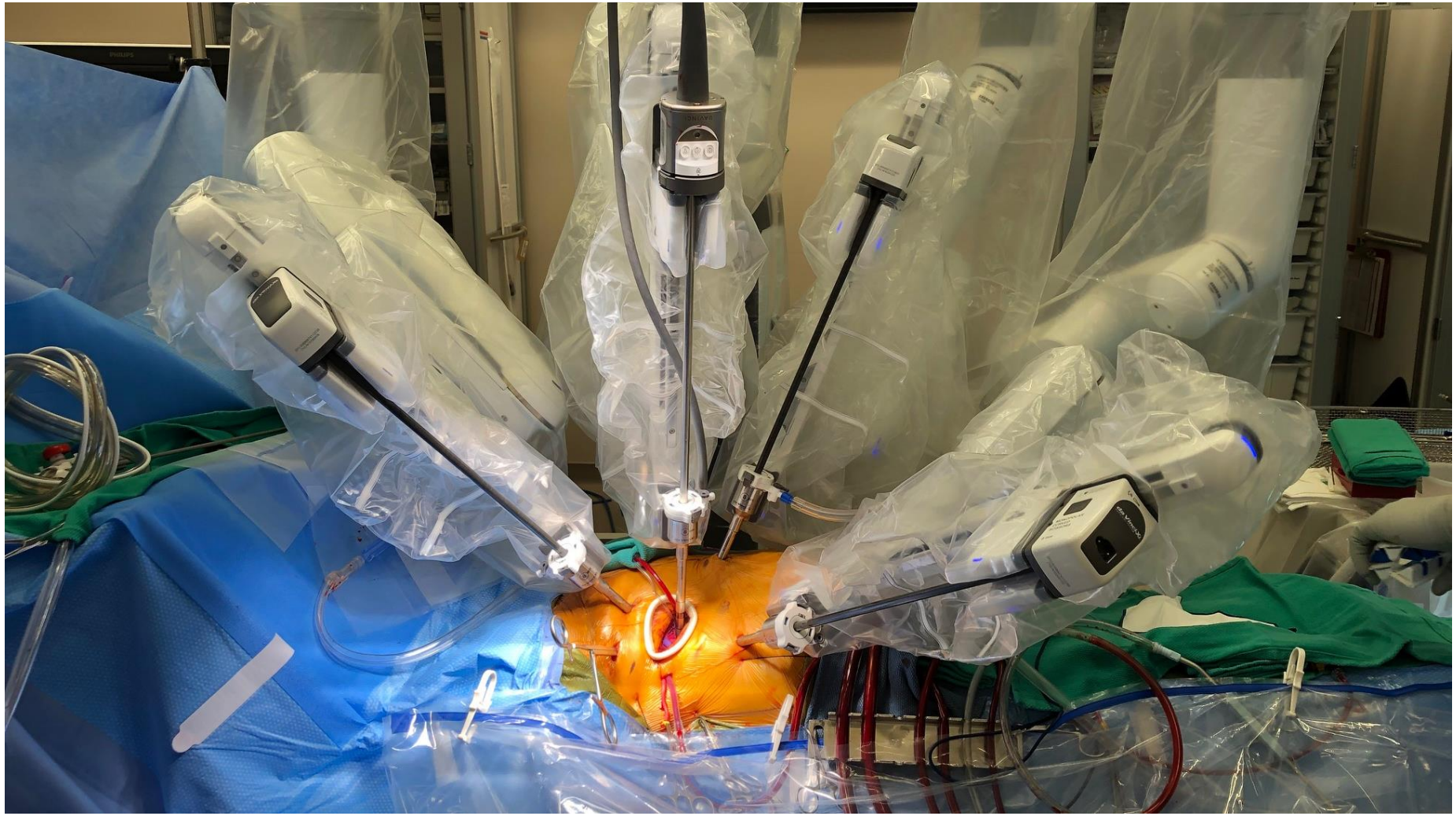
Vinayak N. Bapat, Syed Zaid, Shinichi Fukuhara, Shekhar Saha, Keti Vitanova, Philipp Kiefer, John J. Squiers, Pierre Voisine, Luigi Pirelli, Moritz Wyler von Ballmoos, Michael W.A. Chu, Josep Rodés-Cabau, J. Michael DiMaio, Michael A. Borger, Rudiger Lange, Christian Hagl, Paolo Denti, Thomas Modine, Tsuyoshi Kaneko, Gilbert H.L. Tang, and on behalf of EXPLANT-TAVR Investigators SEE FEWER AUTHORS

J Am Coll Cardiol Intv. 2021 Sep, 14 (18) 1978–1991

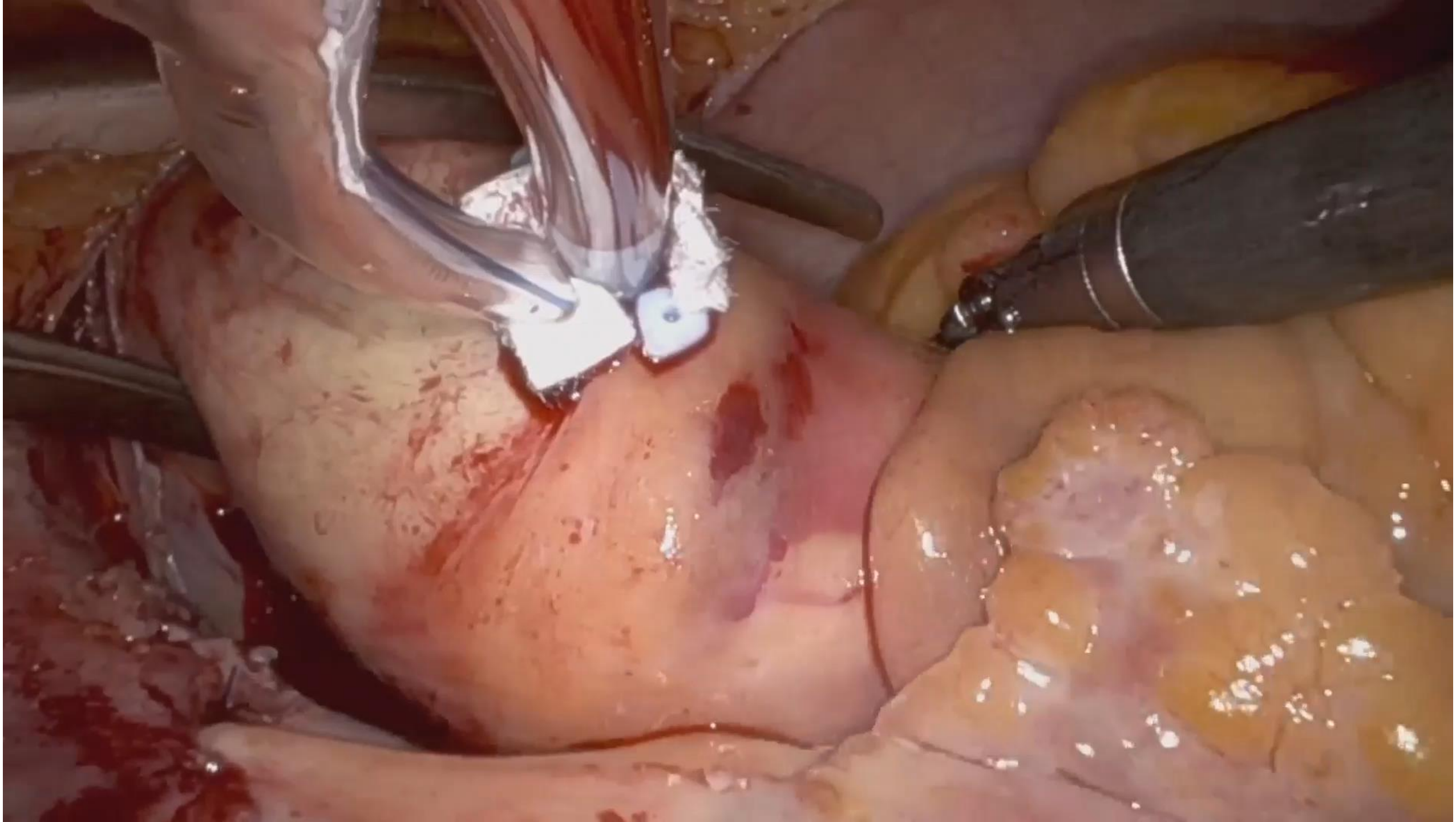
30-day Mortality-13.1%

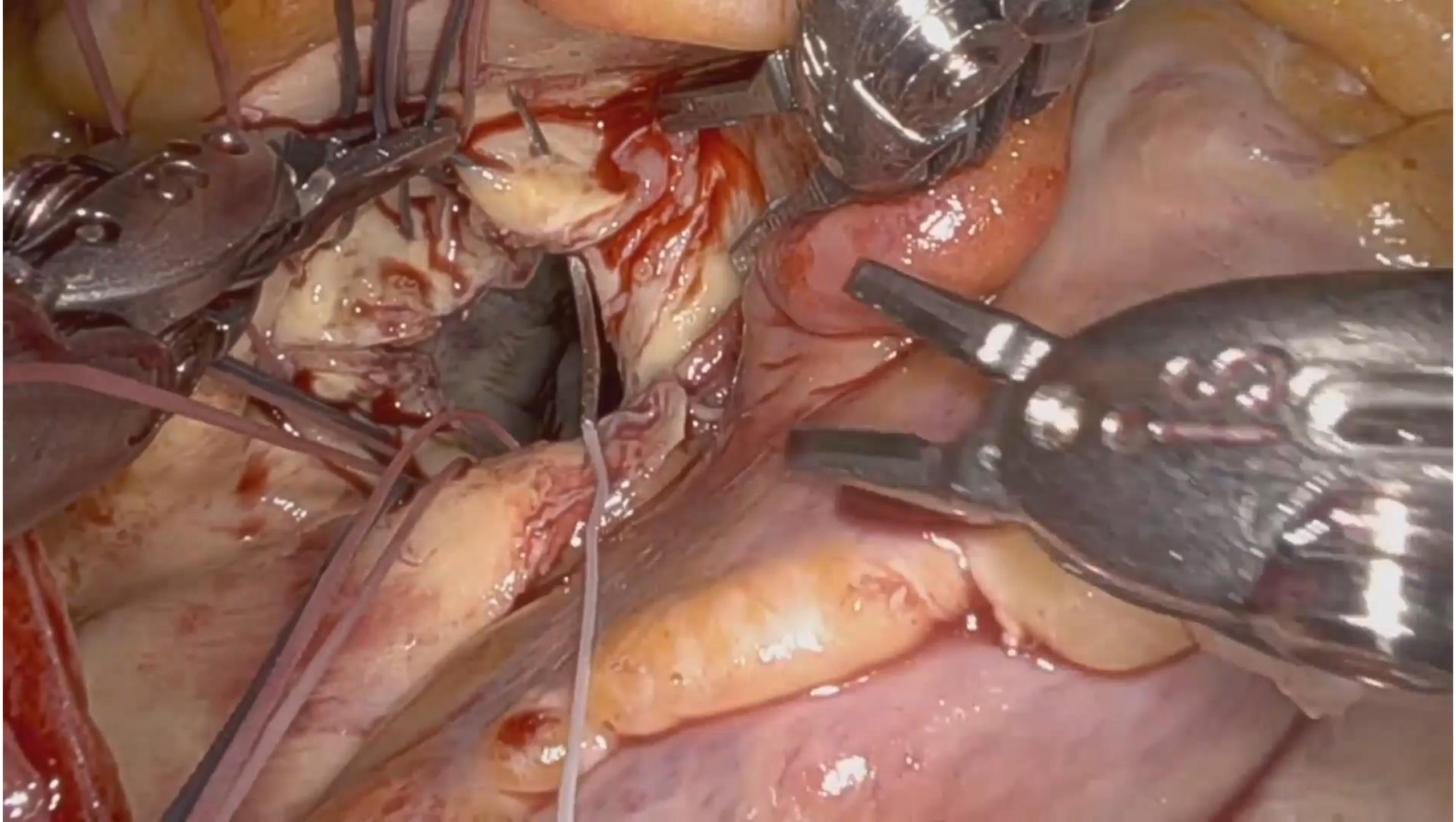


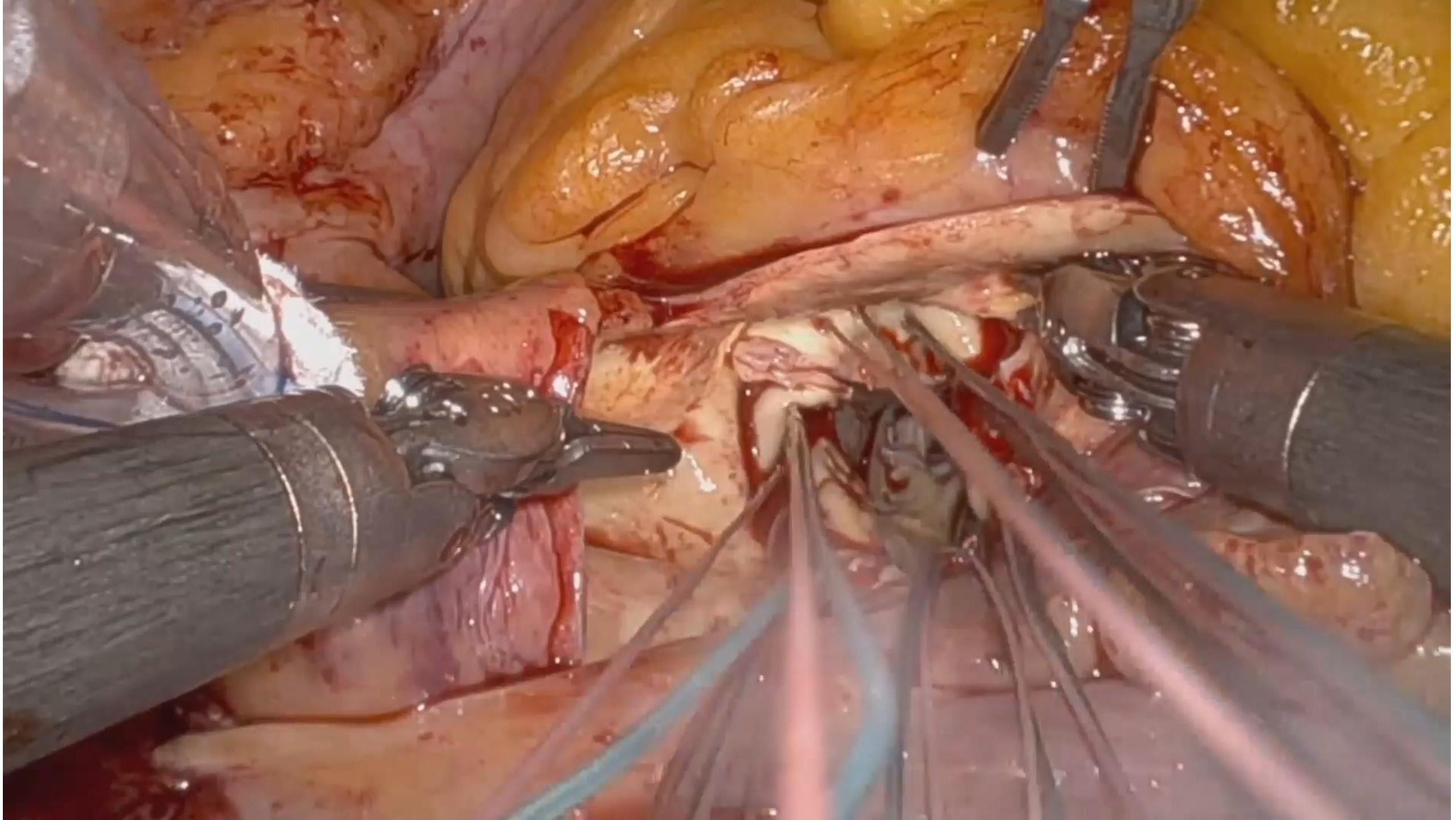
Robotic AVR

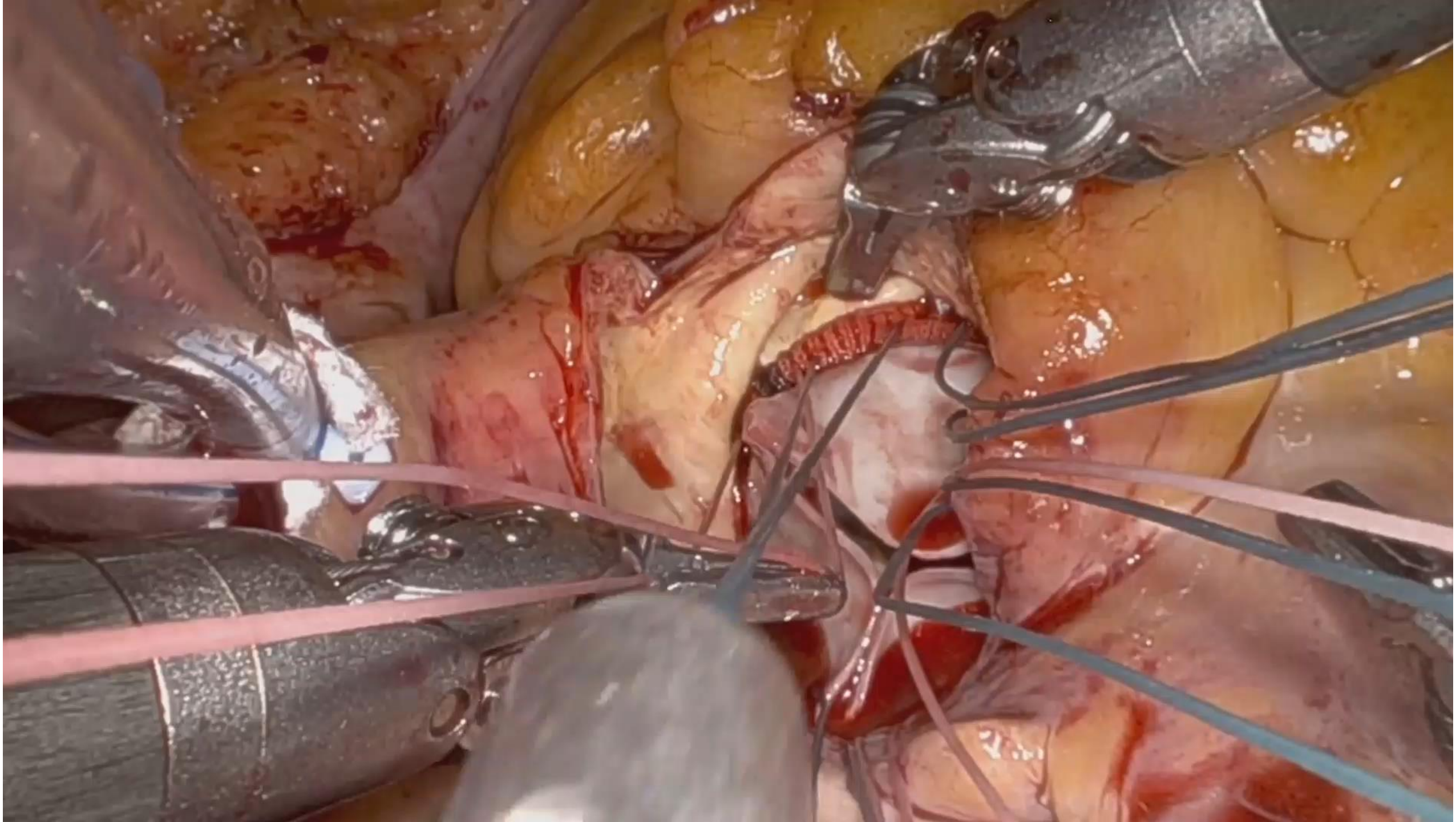


Courtesy
Vinay Badhwar









Aortic Regurgitation

Jena Valve- Aortic Regurgitation

1. Setting

2. Seating

3. Sealing

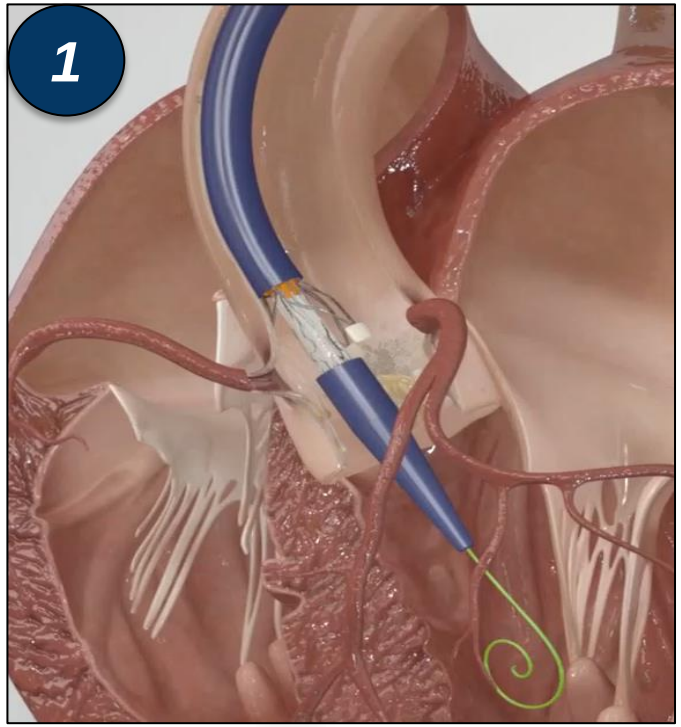
Locator Technology = Designed for Secure Fixation and Sealing

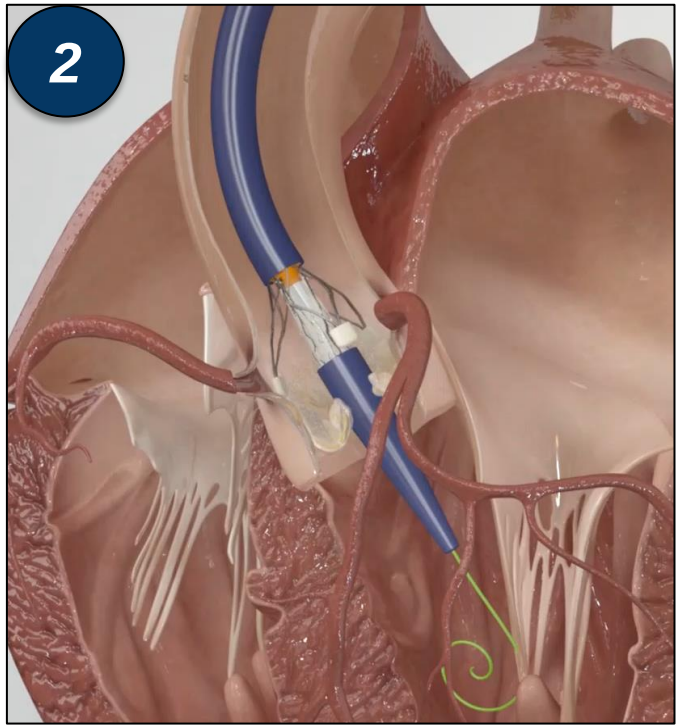
Commissure to Commissure Alignment

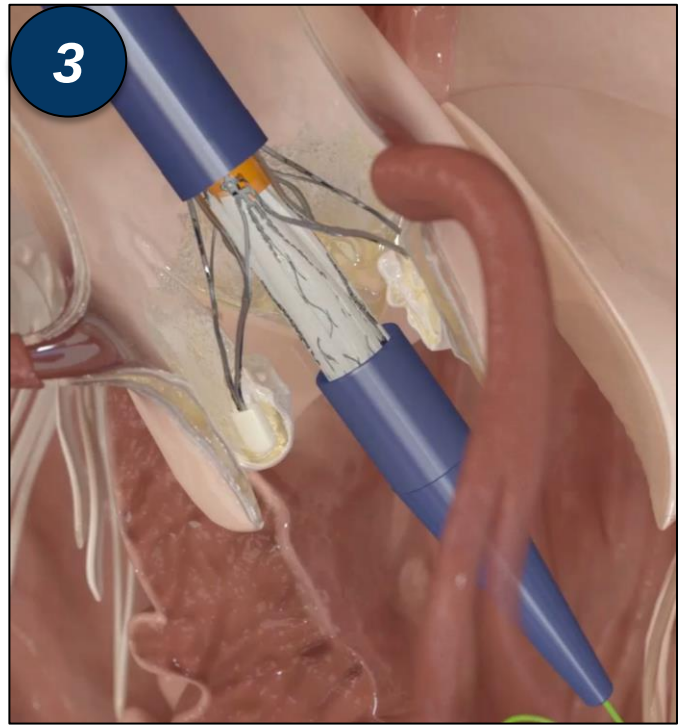
Sets Depth Avoiding “Low” Placement

Clips Onto Native Leaflets

JenaValve Positioning & Deployment







Deployment

- Rotate Deployer to Deploy and Release Valve

TAVR in Rheumatic AS

ORIGINAL INVESTIGATIONS

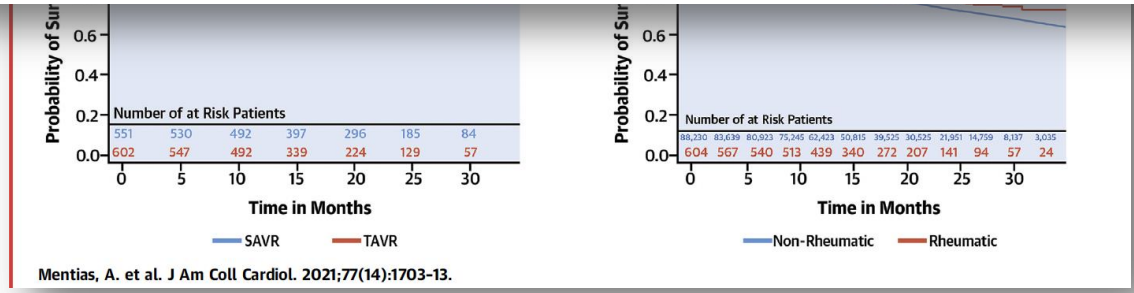
Transcatheter Versus Surgical Aortic

EDITORIAL COMMENT

TAVR for Patients With Rheumatic Heart Disease

Opening the Door for the Many?*

Peter Zilla, MD, PhD,[a,b,c] David F. Williams, PhD,[d] Deon Bezuidenhout, PhD[a]



Mentias, A. et al. J Am Coll Cardiol. 2021;77(14):1703-13.

JACC April 2021

Concomittant Coronary and Valve Disease

AS with CAD or MR/TR

AS+CAD

- Make treatment decision based on CAD
  - If CABG, then SAVR+CABG
  - If PCI, then Staged PCI+TAVR

AS+MR/TR

- If Primary MR
  - SAVR+MV Repair or staged TAVR+ TEER
- If secondary MR
  - TAVR or SAVR
- If moderate or severe TR
  - Planned simultaneous or staged TV procedure

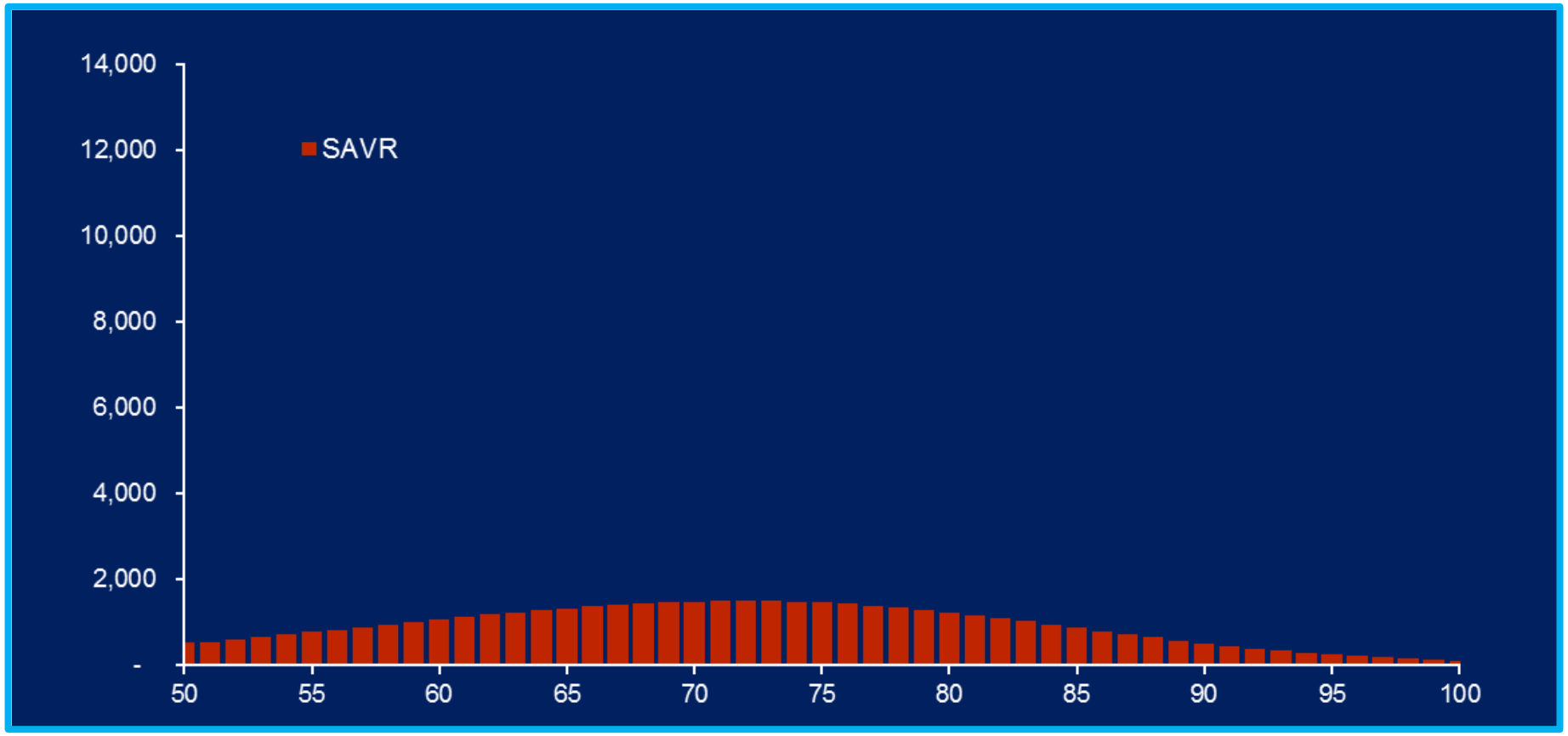
Management of AS- New Directions and Questions

- **Should Asymptomatic Aortic Stenosis be Treated ?**
  - Early TAVR Trial
- **Management of Moderate AS**
  - Progress AS Trial
- **Prevalence of Valvular Heart Disease**
  - PREVUE Trial
- **Can We Diagnose AS Earlier?**
  - AS Screening with AI EKG Interpretation
- **Can Medical Therapy Slow AS Progression?**

- **Earlier Diagnosis/Disease Prevalence**

Underdiagnosis and Undertreatment Issues

2015 Severe Symptomatic AS Patients in the U.S.



Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, Freed 2010, Iung 2007, Pellikka 2005, Brown 2008, Thourani 2015

Underdiagnosis and Undertreatment Issues

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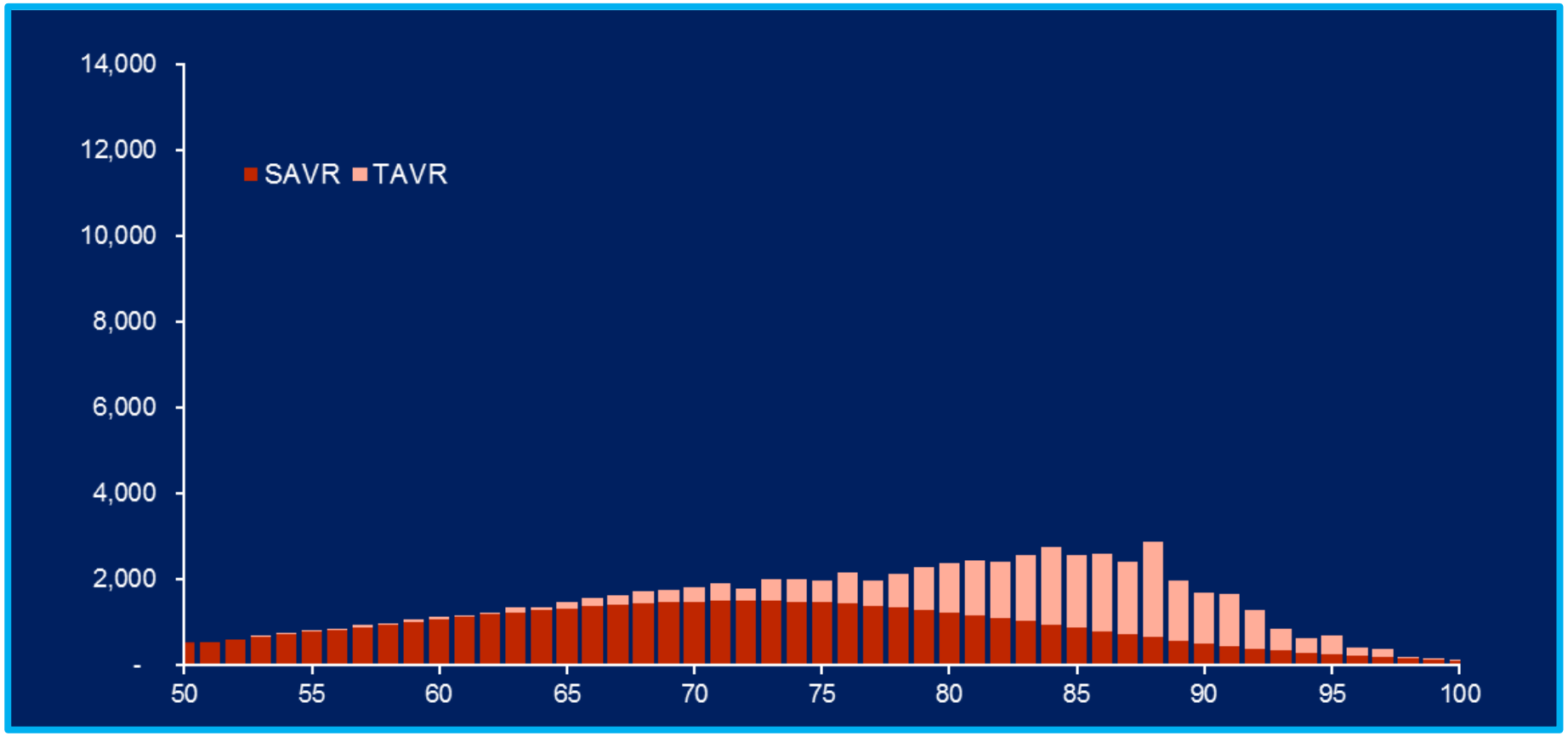
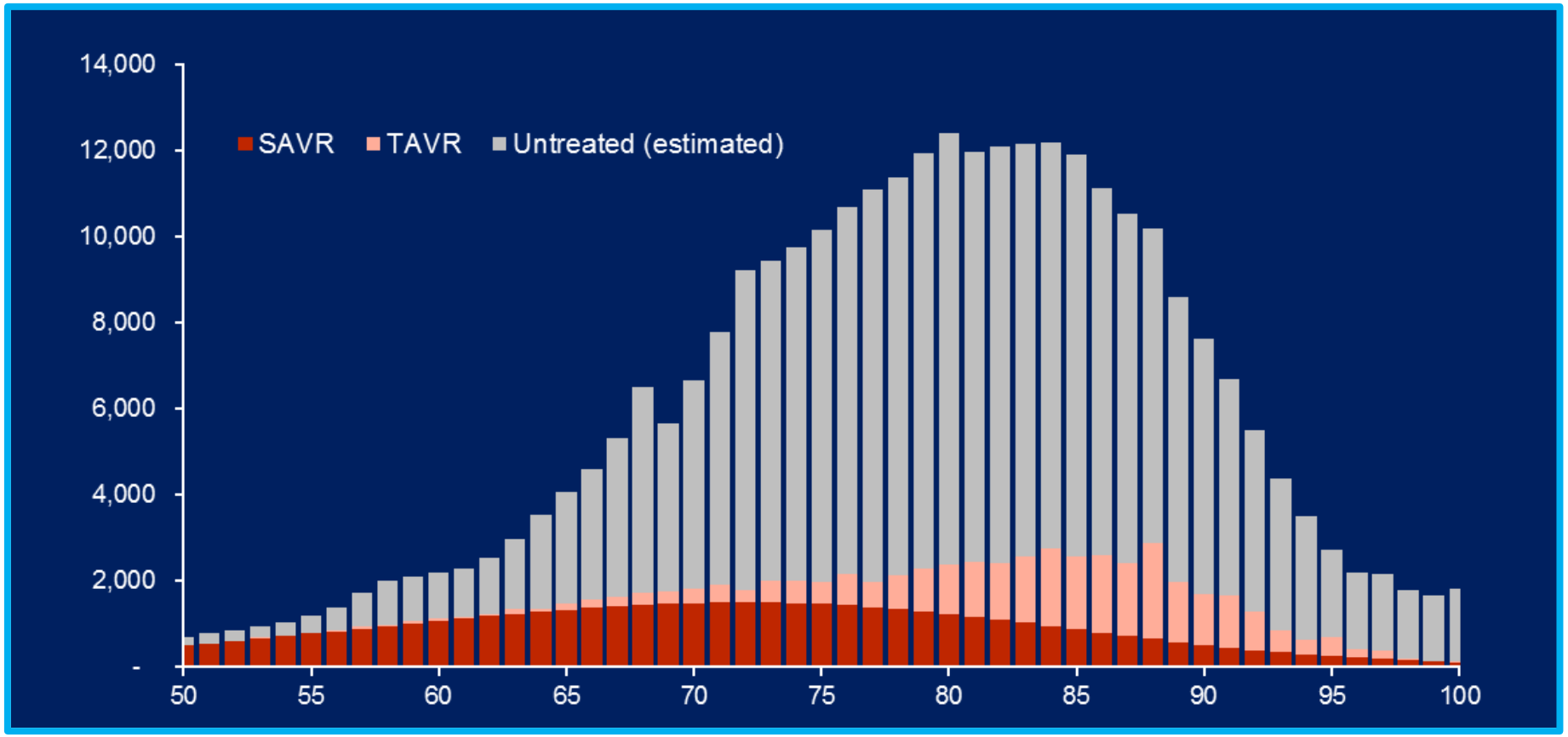


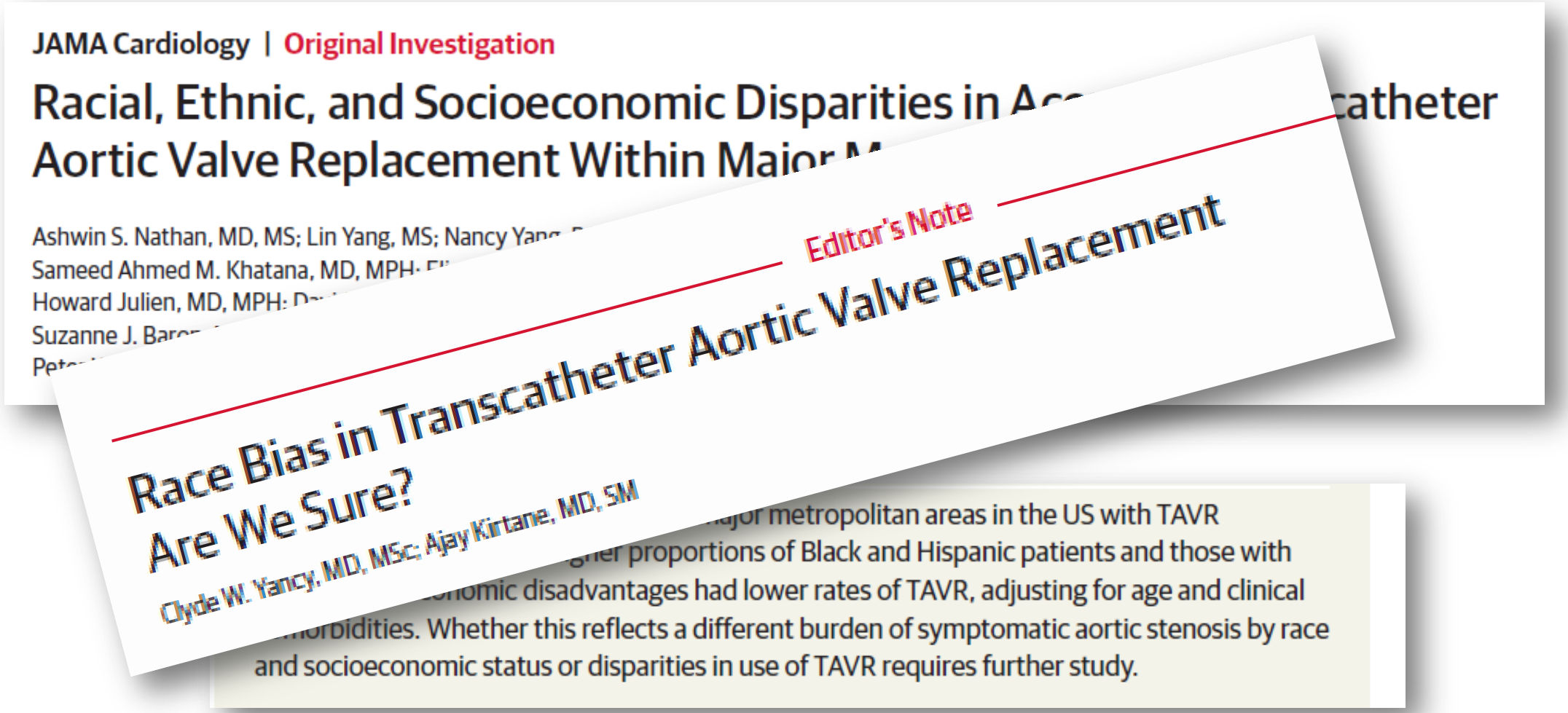
Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, Freed 2010, Iung 2007, Pellikka 2005, Brown 2008, Thourani 2015

Underdiagnosis and Undertreatment Issues

2015 Severe Symptomatic AS Patients in the U.S.



Underdiagnosis and Undertreatment Issues



Nathan AS et al. JAMA Cardiol 2021

ECG Diagnosis of AS

Future Screening Tools for Valvular Heart Disease

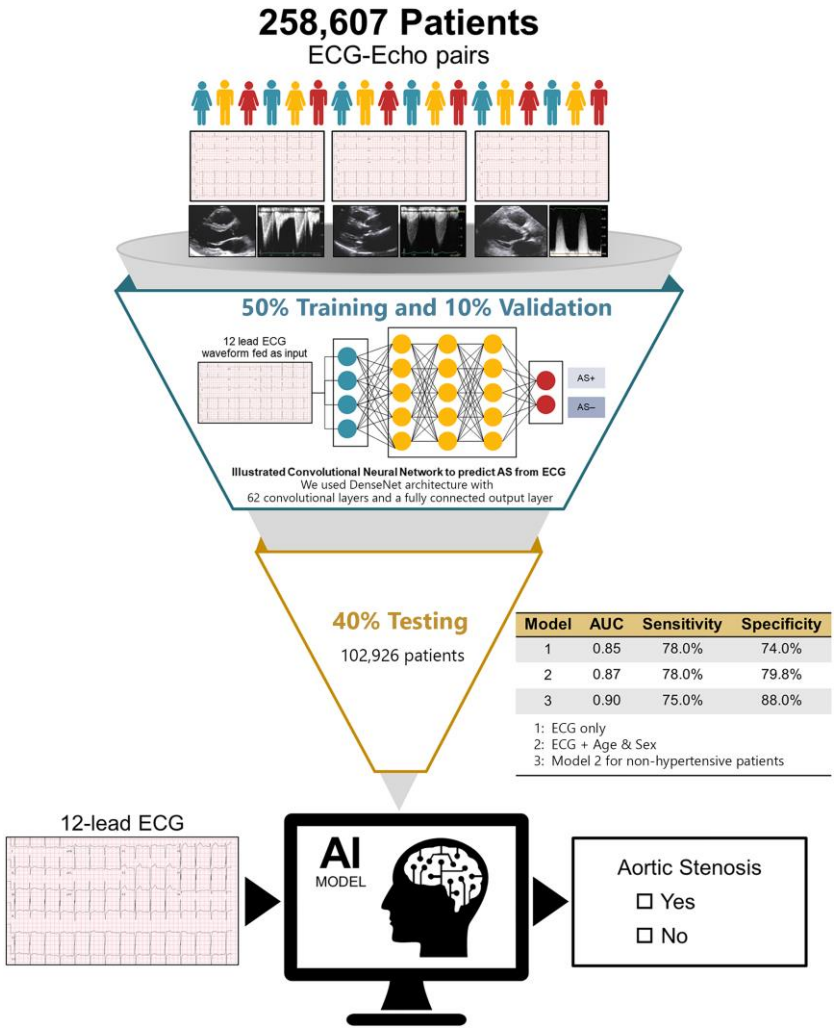
Artificial Intelligence/Machine Learning

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–12
doi:10.1093/eurheartj/ehab153

CLINICAL RESEARCH
Valvular heart disease

Electrocardiogram screening for aortic valve stenosis using artificial intelligence

Michal Cohen-Shelly [1], Zachi I. Attia [1], Paul A. Friedman[1], Saki Ito[1], Benjamin A. Essayagh [1], Wei-Yin Ko[1],Dennis H. Murphree [1], Hector I. Michelena [1], Maurice Enriquez-Sarano[1], Rickey E. Carter [2], Patrick W. Johnson [2], Peter A. Noseworthy[1], Francisco Lopez-Jimenez [1], and Jae K. Oh[1]*



In the test group, the AI-ECG labelled 3833 (3.7%) patients as positive with the area under the curve (AUC) of 0.85. The sensitivity, specificity, and accuracy were 78%, 74%, and 74%, respectively.

Future Screening Tools for Valvular Heart Disease

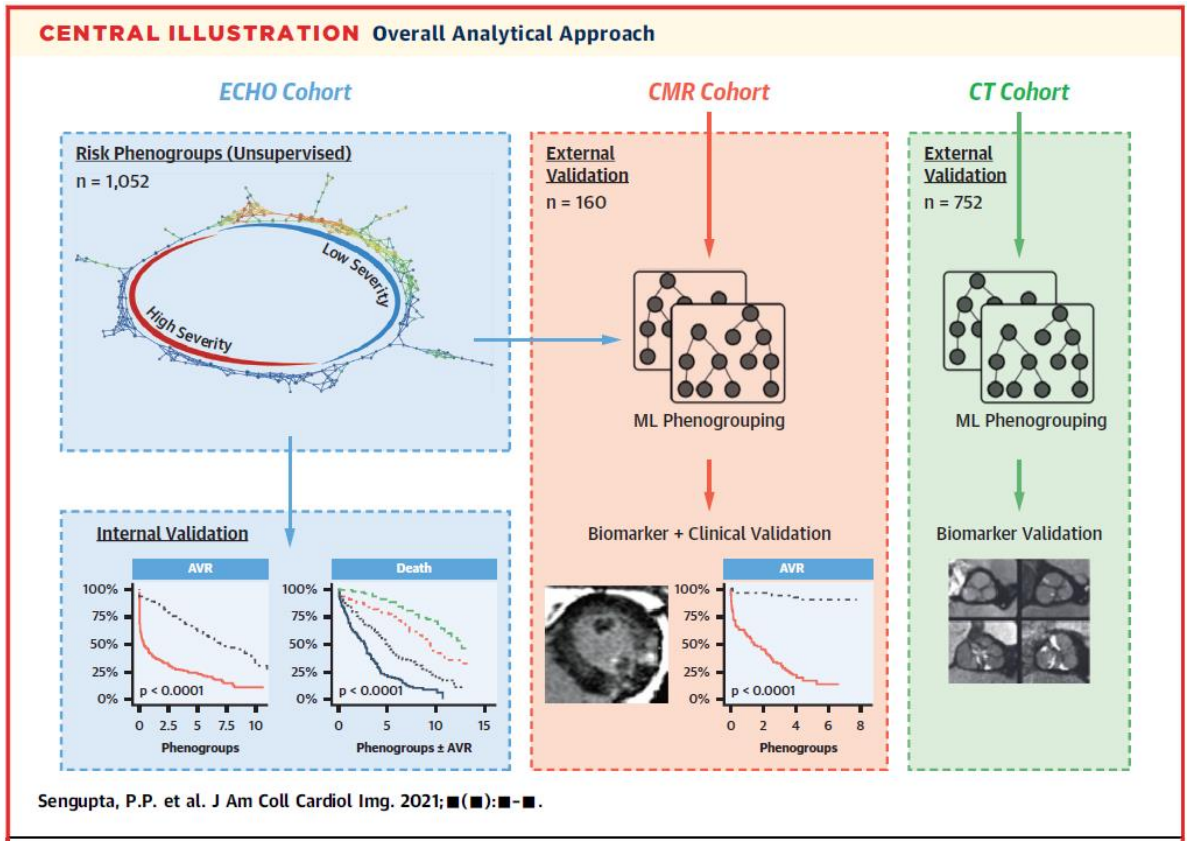
Artificial Intelligence/Machine Learning

A Machine-Learning Framework to Identify Distinct Phenotypes of Aortic Stenosis Severity

Partho P. Sengupta, MD, DM,[a] Sirish Shrestha, MS,[a] Nobuyuki Kagiyama, MD, PhD,[a] Yasmin Hamirani, MD,[a] Hemant Kulkarni, MD,[a,b] Naveena Yanamala, PhD,[a] Rong Bing, MBBS,[c] Calvin W.L. Chin, MD, PhD,[d] Tania A. Pawade, MD, PhD,[c] David Messika-Zeitoun, MD,[e] Lionel Tastet, MSc,[f] Mylène Shen, PhD,[f] David E. Newby, MD, PhD,[c] Marie-Annick Clavel, DVM, PhD,[f] Phillippe Pibarot, DVM, PhD,[f] Marc R. Dweck, MD, PhD,[c] for the Artificial Intelligence for Aortic Stenosis at Risk International Consortium

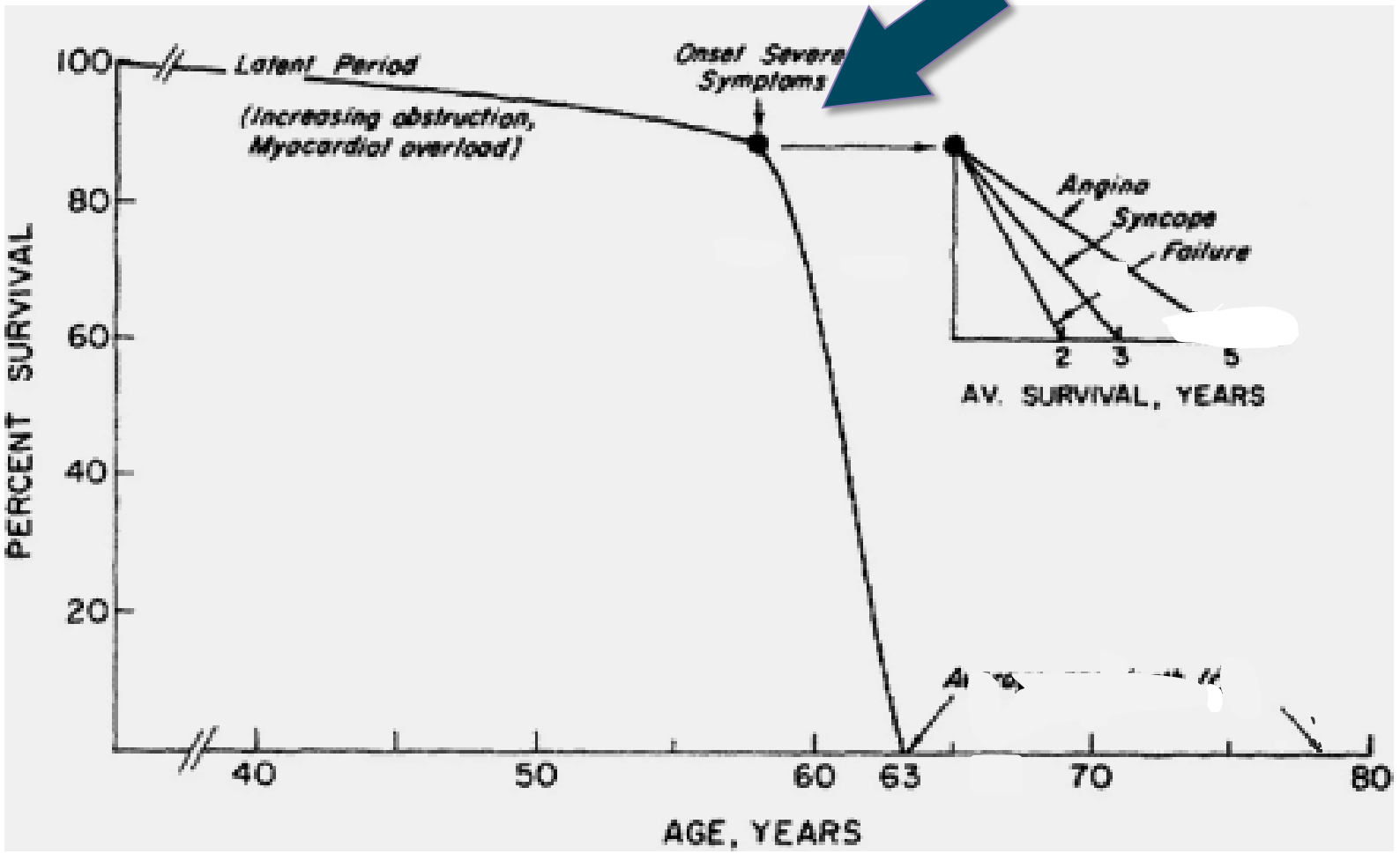
Conclusions:

Machine learning can integrate ECHO measurements to augment the classification of disease severity in most patients with AS, with major potential to optimize the timing of AVR. (JACC Imaging 2021)



Asymptomatic and Moderate AS

Should We Wait Until Symptoms? Is That Too Late ?



Ross and Braunwald, *Circulation* 1968;38:V-61

The RECOVERY Surgical AVR Trial

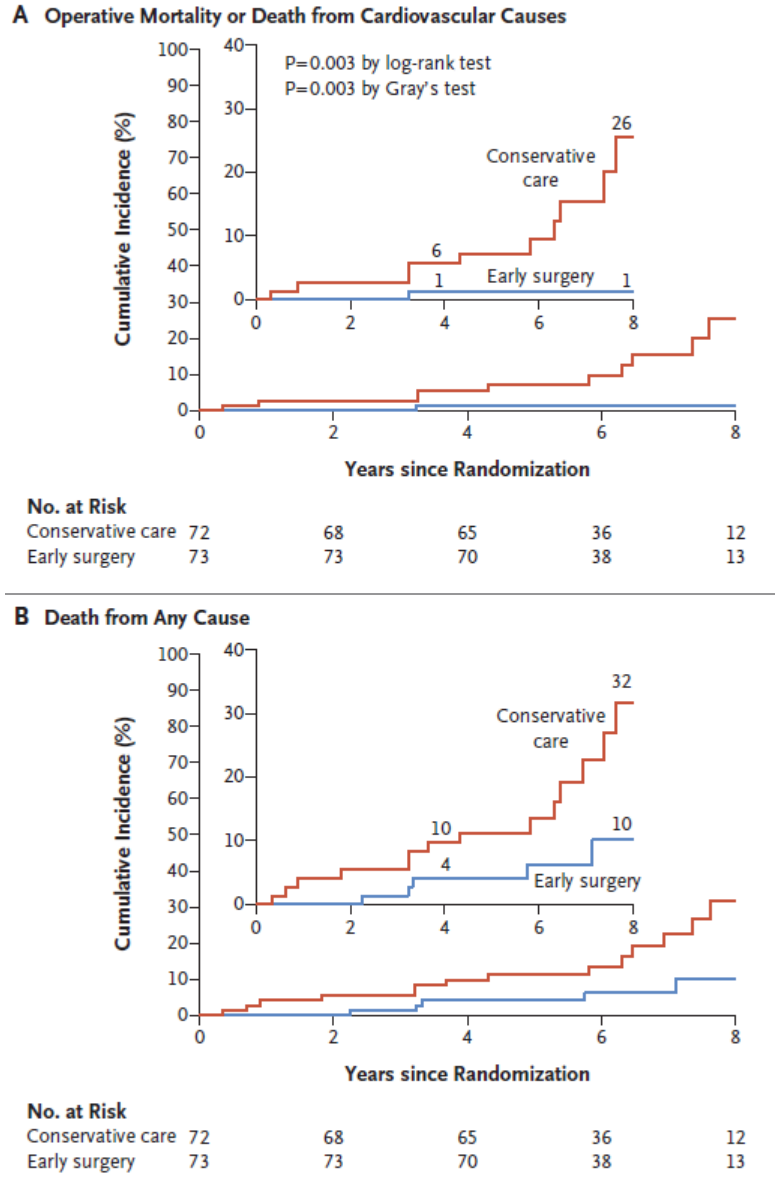
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 9, 2020 VOL. 382 NO. 2

Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis

Duk-Hyun Kang, M.D., Ph.D., Sung-Ji Park, M.D., Ph.D., Seung-Ah Lee, M.D., Sahmin Lee, M.D., Ph.D., Dae-Hee Kim, M.D., Ph.D., Hyung-Kwan Kim, M.D., Ph.D., Sung-Cheol Yun, Ph.D., Geu-Ru Hong, M.D., Ph.D., Jong-Min Song, M.D., Ph.D., Cheol-Hyun Chung, M.D., Ph.D., Jae-Kwan Song, M.D., Ph.D., Jae-Won Lee, M.D., Ph.D., and Seung-Woo Park, M.D., Ph.D.

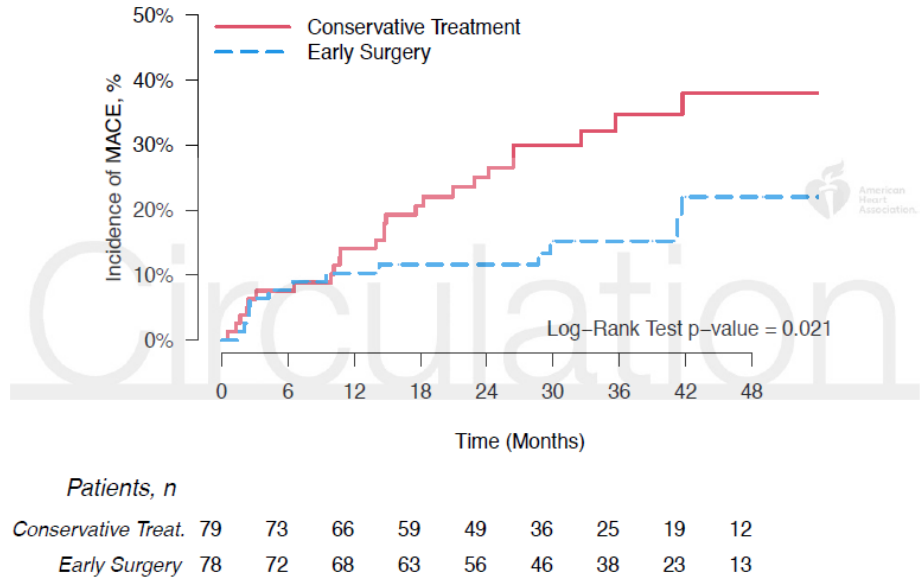
- 145 asymptomatic patients w **very severe AS** randomized to early surgery or conservative care
- 1^{ry} endpoint (operative and FU death) was 1% vs. 15% in early surgery vs. conservative care (P=0.003)



The AVATAR Surgical AVR Trial

Aortic Valve Replacement versus Conservative Treatment In Asymptomatic Severe Aortic Stenosis: The AVATAR Trial

- 157 asymptomatic patients (ETT confirmed) w severe AS, randomized to early surgery or conservative care at 9 centers from 7 EU countries; median FU 32 months
- Early surgery operative mortality 1.4%
- 1^{ry} endpoint (MACE = death, MI, stroke and HF rehosp) was lower with early surgery vs. conservative care (HR 0.46, 95% CI 0.23-0.90; p=0.02)



The EARLY TAVR Trial

Asymptomatic Severe AS and 2D-TTE (PV ≥4m/s or AVA ≤1 cm²)
Exclusion if patient is symptomatic, age <65 yo, EF<50%, concomitant surgical indications, or STS >8

Treadmill Stress-Test

Stress-Test Normal

CTA and Angiography
TF- TAVR eligibility

Early-TAVR Randomized Trial

Randomization 1:1
Stratified by STS (<3 vs ≥3)

TF-TAVR

Clinical Surveillance

Stress-Test Abnormal

Early TAVR Registry

1109 pts, 75 US sites

Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)

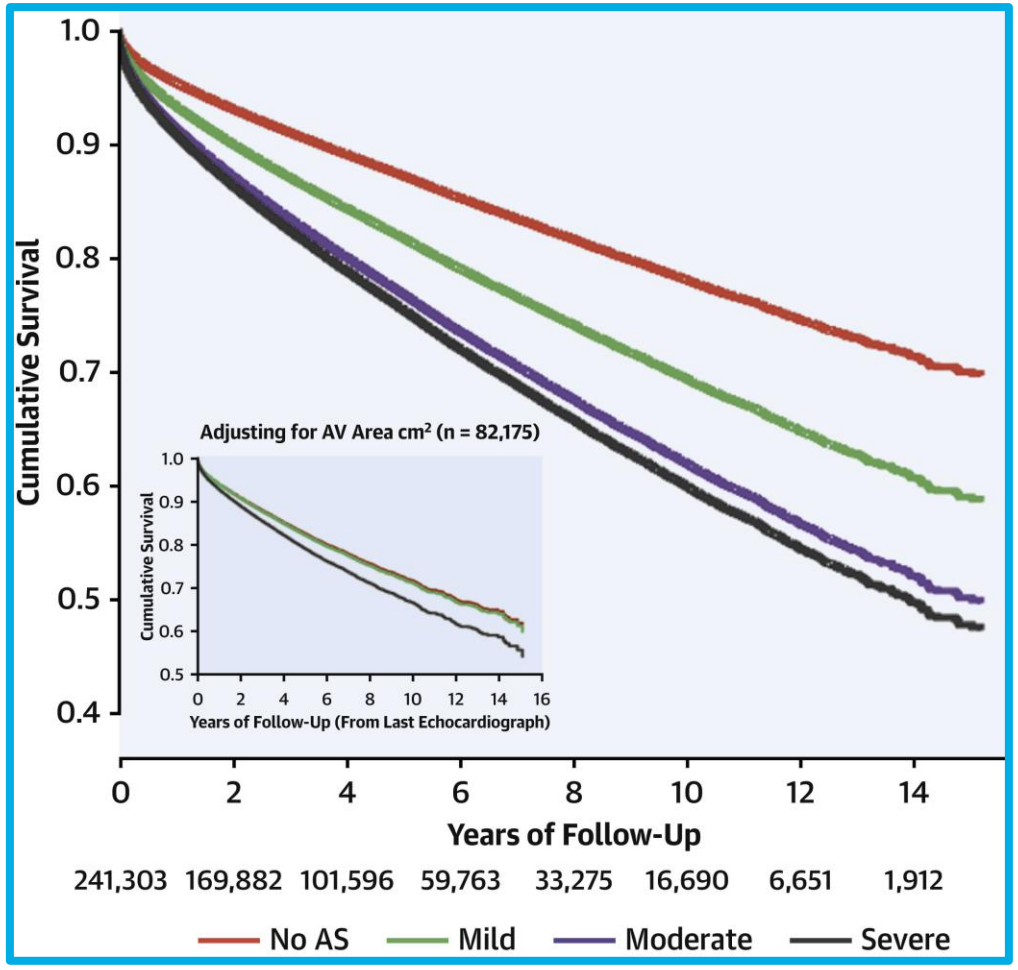
Principal Investigators:
Philippe Généreux, Allan Schwartz
Chair: Martin B. Leon

Cardiovascular Research Foundation

Columbia University Medical Center
NewYork-Presbyterian

Natural History of Untreated Mod AS

National Echo Database



Poor Long-Term Survival in Patients With Moderate Aortic Stenosis

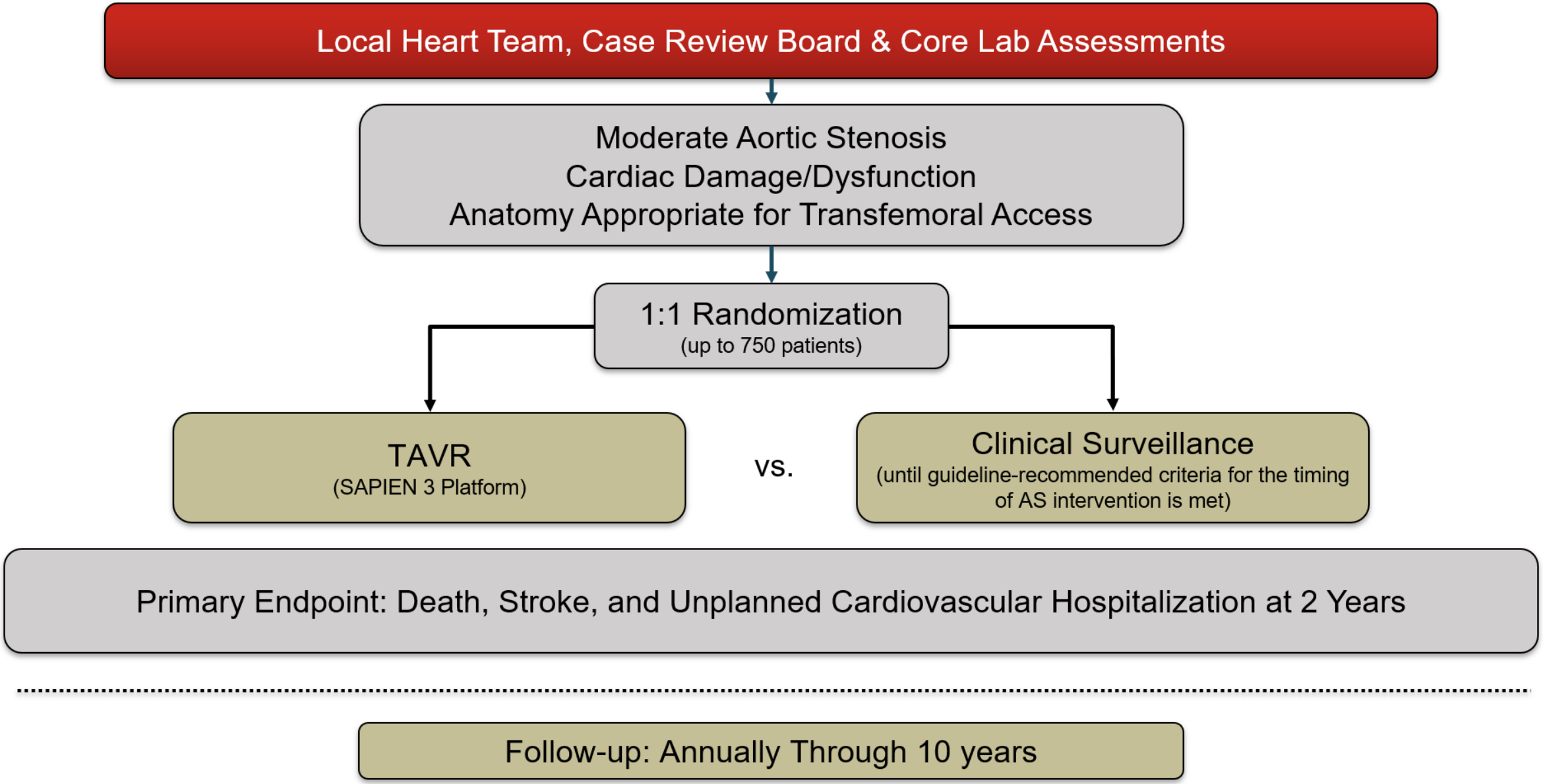
Geoff Strange, PhD,[a] Simon Stewart, PhD,[b] David Celermajer, MD, PhD,[c] David Prior, MBBS, PhD,[d] Gregory M. Scalia, MBBS (Hons), MMedSc,[e] Thomas Marwick, MBBS, PhD,[f] Marcus Ilton, MD,[g] Majo Joseph, MBBS,[h] Jim Codde, PhD,[i] David Playford, MBBS, PhD,[a] on behalf of the National Echocardiography Database of Australia contributing sites

Reasons…

- Misclassification issues?
- Echocardiography challenges
- Rapid progression to severe AS
- Already too much cardiac damage
- Intervention too late (missed opportunities) with limitations of active surveillance strategy

Study Design

THE PROGRESS TRIAL



CAUTION: Investigational device. Limited by Federal (USA) law to investigational use. Disclaimer: This is a high-level tool meant to facilitate pre-screening activities. Please refer to approved protocols for all details. Edwards Proprietary. Do not reproduce or redistribute.

Medical Therapy to Slow the Progression of AS

The "Statin Era" of Medical Rx for CAVD

AS is a degenerative process resulting from "wear and tear", predominantly of the valve leaflets.

AS shares many similarities with atherosclerosis (risk factors, mechanisms).

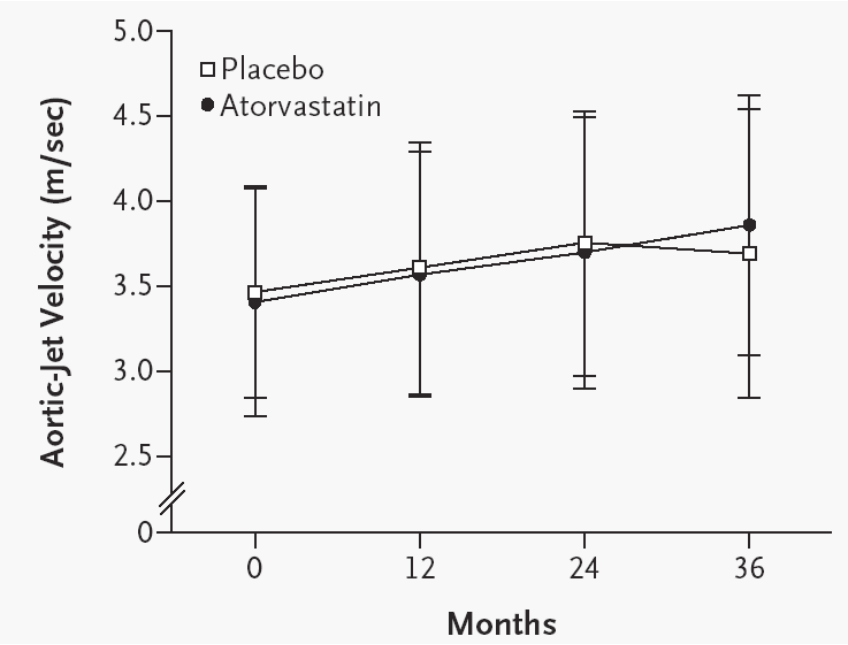
Thus, AS is a potentially modifiable atherosclerotic disease.

Hope for pharmacotherapy in AS: STATINS!

Failure of Statin Rx to Treat CAVD

SALTIRE (2005)

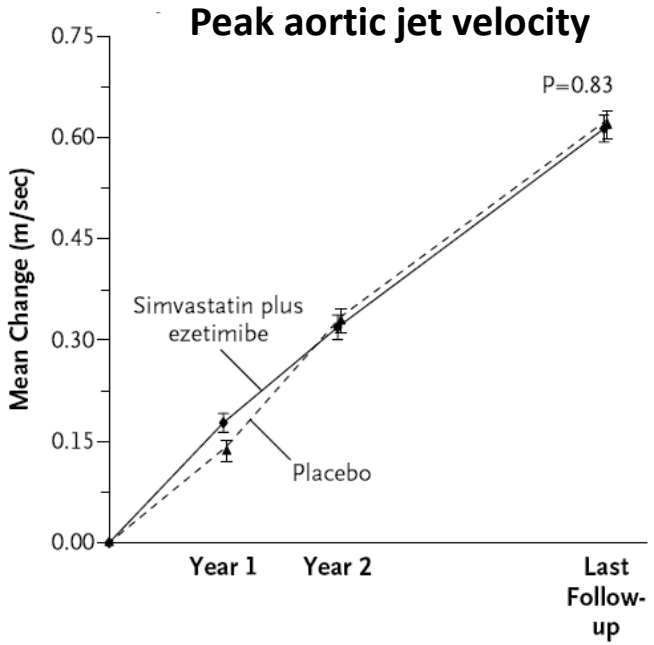
N = 155 pts



Cowell et al, NEJM, 352:2389-97,2005

SEAS (2008)

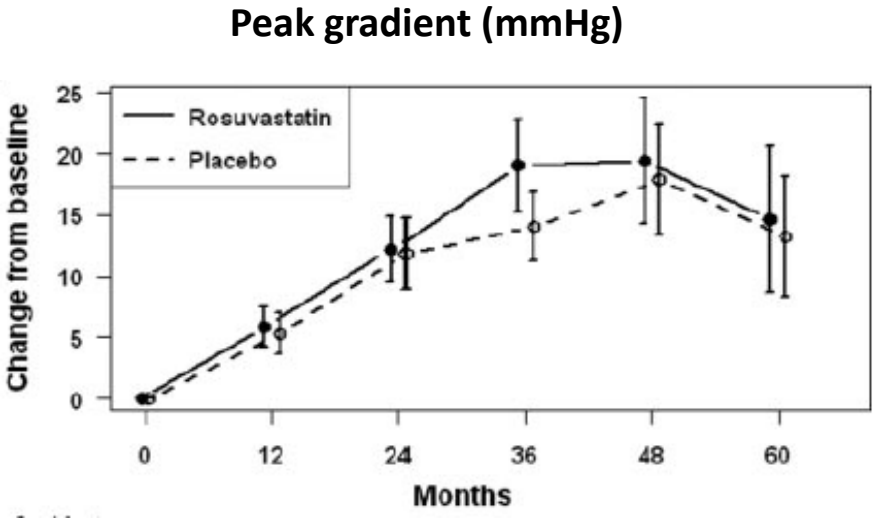
N = 1,873 pts



Rossebo et al, NEJM, 359:1343-56, 2008

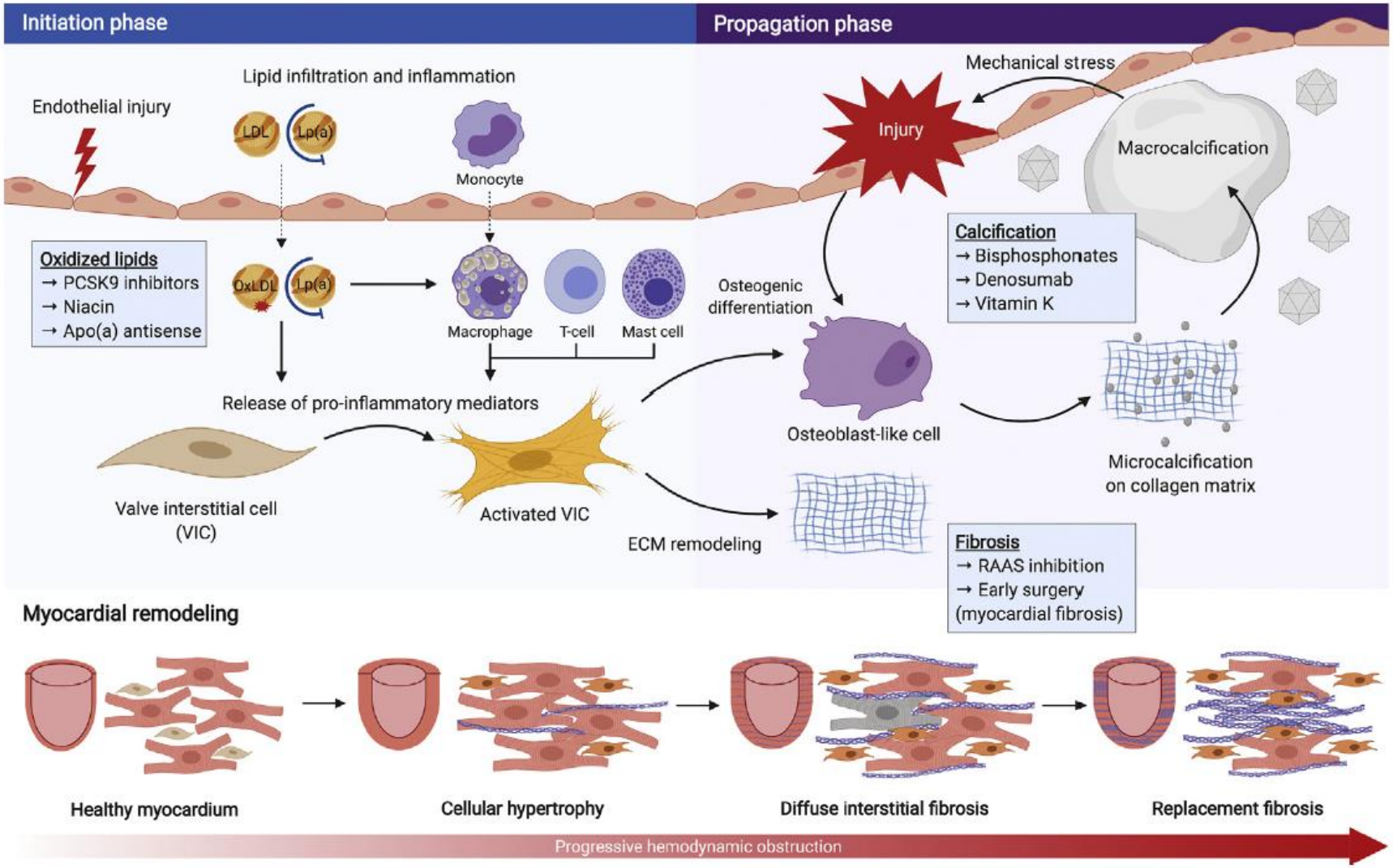
ASTRONOMER (2010)

N = 269 pts



Chan et al, Circulation 121:306-314, 2010

Pathophysiology of Aortic Stenosis



KH Zheng, E Tzolos, MR Dweck. Cardiol Clin 38 (2020) 1-12

JACC STATE-OF-THE-ART REVIEW

Evaluating Medical Therapy for Calcific Aortic Stenosis

JACC State-of-the-Art Review

Brian R. Lindman, MD, MSc,[a] Devraj Sukul, MD, MS,[b] Marc R. Dweck, MD,[c] Mahesh V. Madhavan, MD,[d] Benoit J. Arsenault, PhD,[e] Megan Coylewright, MD,[f] W. David Merryman, PhD,[g] David E. Newby, MD,[c] John Lewis, MA,[h] Frank E. Harrell, Jr, PhD,[i] Michael J. Mack, MD,[j] Martin B. Leon, MD,[d] Catherine M. Otto, MD,[k] Philippe Pibarot, DVM, PhD[e]

JACC 2021

A Anatomical Progression of Calcific Aortic Stenosis

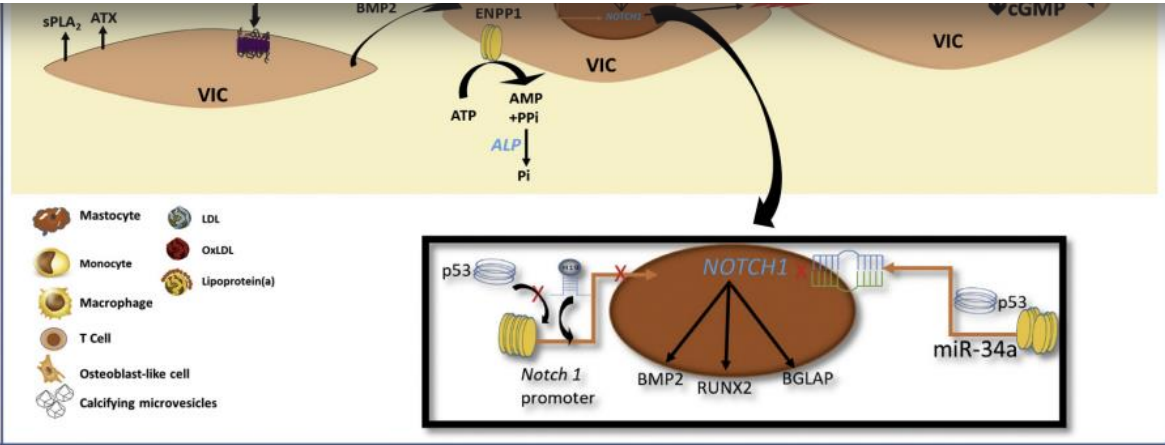
Normal Aortic Valve | Aortic Sclerosis | Mild-Moderate Stenosis | Severe Stenosis

B Pathophysiology of Calcific Aortic Stenosis

Initiation Phase	Propagation Phase
Genetic variants	VIC activation
Mechanical stress	Osteoblast differentiation
Valve morphology	Fibrosis
Inflammation	Calcification
Dyslipidemia (LDL-c, Lp(a))	

C Therapeutic Targets for Calcific Aortic Stenosis

Targeting lipid infiltration	Targeting Notch1-CDH11 axis	Targeting fibro-calcific response
PCSK9i, LPAi, DPP4i and TZDs	microRNA-34a, H19 and CDH11	RAAS inhibitors, Vitamin K, PALMD, Inositol phosphate analogs, upregulating NO-cGMP signaling



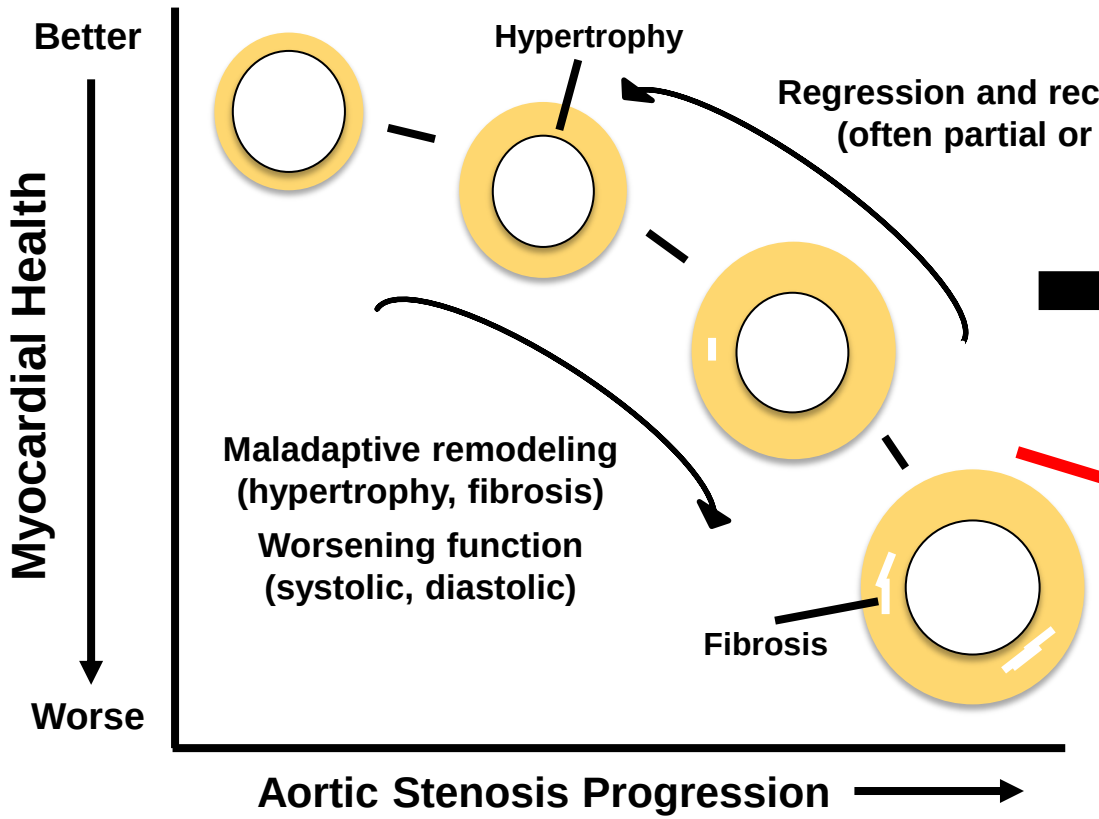
VIEWPOINT

Prevention and Mitigation of Heart Failure in the Treatment of Calcific Aortic Stenosis
A Unifying Therapeutic Principle

RAAS inhibition?

Entresto?

SGLT2i?



Myocardial Health Impacts Post-AVR Clinical Outcomes

High residual risk
(early death, heart failure, poor quality of life)

Adjunctive medical therapy to protect the heart during progressive AS and augment its recovery after AVR

Asymptomatic

Symptomatic

Symptom-based trigger for AVR (too late)

Increased mortality, residual heart failure, poor QoL

Brian R. Lindman, MD, MSc and JoAnn Lindenfeld, MD; JAMA Cardiology 2021

Lp (a)

The NEW ENGLAND JOURNAL of MEDICINE

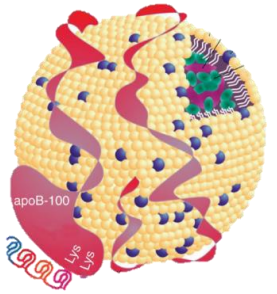
ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6

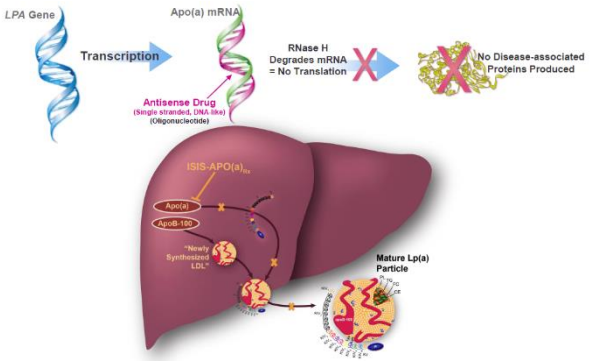
Genetic Associations with Valvular Calcification and Aortic Stenosis

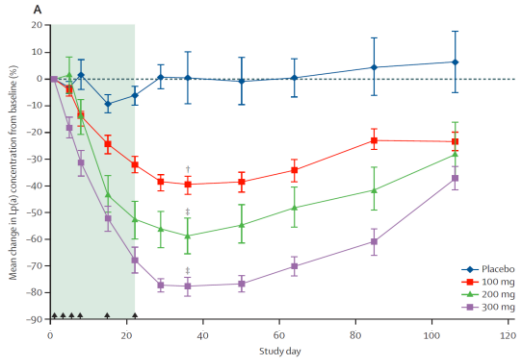
George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Kerr, Ph.D., Sonali Pechlivanis, Ph.D., Matthew J. Budoff, M.D., Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevin D. O'Brien, M.D., Pia R. Kamstrup, M.D., Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Hansen, M.D., D.M.Sc., Matthew A. Allison, M.D., M.P.H., Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., Susan R. Heckbert, M.D., Ph.D., Shih-Jen Hwang, Ph.D., Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jesper van der Pals, M.D., Ph.D., Hagen Kälsch, M.D., Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D., L. Adrienne Cupples, Ph.D., Muriel Caslake, Ph.D., Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R.C.P., Jerome I. Rotter, M.D., Sigurdur Sigurdsson, M.Sc., Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Vilmundur Gudnason, M.D., Ph.D., Christopher J. O'Donnell, M.D., M.P.H., and Wendy S. Post, M.D., for the CHARGE Extracoronary Calcium Working Group

Lp (a)

- **About 20% of the general population (65 Million people in North America) have elevated Lp(a)**
- **Lp(a) circulating levels are determined genetically and currently available drugs (Niacin) only achieve modest reduction in Lp(a)**
- **Phase I and II trials report that oligonucleotide antisense directed to Apo(a), reduces Lp(a) levels by >80%**

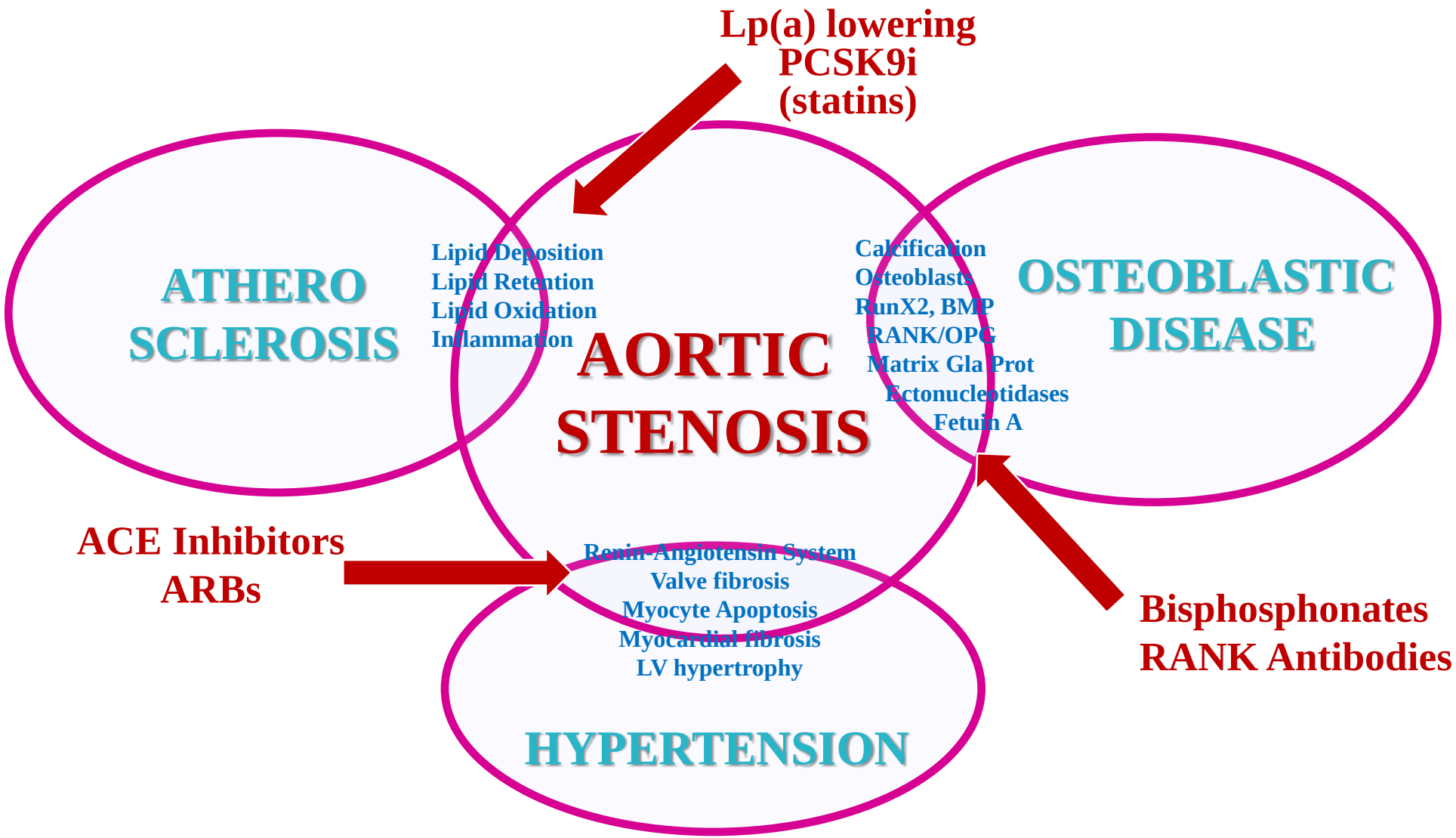






Tsimikas et al. Lancet 2015

Modern Thinking – Medical Rx for CAVD



Candidates For Medical Rx for CAVD

Lp(a) lowering
PCSK9i

Young age
BAV
Mild/moderate AS

ARBs
Antifibrotic therapy

Young/ old age
TAV/ BAV
Women

Bisphosphonates
RANK Ab, Vit K

Old age
TAV/ BAV
Mild/Moderate AS

Summary of Medical Therapy for CAVD

Aortic stenosis is a disease of both the valve and the myocardium.

Currently, there are no medical therapies that have been proven to slow the progression in aortic stenosis.

Numerous possible targets related to oxidized lipids, calcification, and fibrosis,

A multi-drug approach to precisely target disease stage and patient phenotype is the most realistic and promising.

Clinical trials should be started using non-invasive imaging modalities such as CT calcium scoring, 18F-NaF PET, and MRI to assist in risk stratification and as surrogate clinical endpoints .

Courtesy Martin Leon

The TAVR train has long ago left the station

TAVR
Final Thoughts

- To be able to experience the transformation of the treatment of a disease over less than two decades is truly remarkable
- ¾ patients with AS will be treated by TAVR (same as PCI/CABG for CAD)
- TAVR seems like “the answer” for everything right now; but there will be disappointments and TAVR will not meet all expectations
- As transformative as TAVR is, the creation of the “heart team” is arguably even bigger

Hvala Vam