TCTAP

Seoul, April 27-29, 2018

Rapidly Changing TAVR Story: Predicting the Future from Ongoing Clinical Trials

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Physician Name	Company/Relationship
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Key

G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
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SB – Speaker´s Bureau O – Ownership OF – Other Financial Benefits‘

TAVR Success

TAVR has proven success in extreme, high, and intermediate risk patients with symptomatic, severe aortic stenosis.

Extreme Risk → **High Risk** → **Intermediate Risk**


The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 21, 2010

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery


The NEW ENGLAND JOURNAL of MEDICINE

JUNE 9, 2011

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients

M.J. Reardon, N.M. Van Mieghem, J.J. Popma, N.S. Kleiman, L. Søndergaard, M. Mumtaz, D.H. Adams, G.M. Deeb, B. Maini, H. Gada, S. Chetcuti, T. Gleason, J. Heiser, R. Lange, W. Merhi, J.K. Oh, P.S. Olsen, N. Piazza, M. Williams, S. Windecker, S.J. Yakubov, E. Grube, R. Makkar, J.S. Lee, J. Conte, E. Vang, H. Nguyen, Y. Chang, A.S. Mugglin, P.W.J.C. Serruys, and A.P. Kappetein, for the SURTAVI Investigators*


Transcatheter Aortic Valve Replacement Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery


ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis

David H. Adams, M.D., Jeffrey J. Popma, M.D., Michael J. Reardon, M.D., Steven J. Yakubov, M.D., Joseph S. Coselli, M.D., G. Michael Deeb, M.D., Thomas G. Gleason, M.D., Maurice Buchbinder, M.D., James Hermiller, Jr., M.D., Neal S. Kleiman, M.D., Stan Chetcuti, M.D., John Heiser, M.D., William Merhi, D.O., George Zorn, M.D., Peter Tadros, M.D., Newell Robinson, M.D., George Petrossian, M.D., G. Chad Hughes, M.D., J. Kevin Harrison, M.D., John Conte, M.D., Brijeshwar Maini, M.D., Mubashir Mumtaz, M.D., Sharla Chenoweth, M.S., and Jae K. Oh, M.D., for the U.S. CoreValve Clinical Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

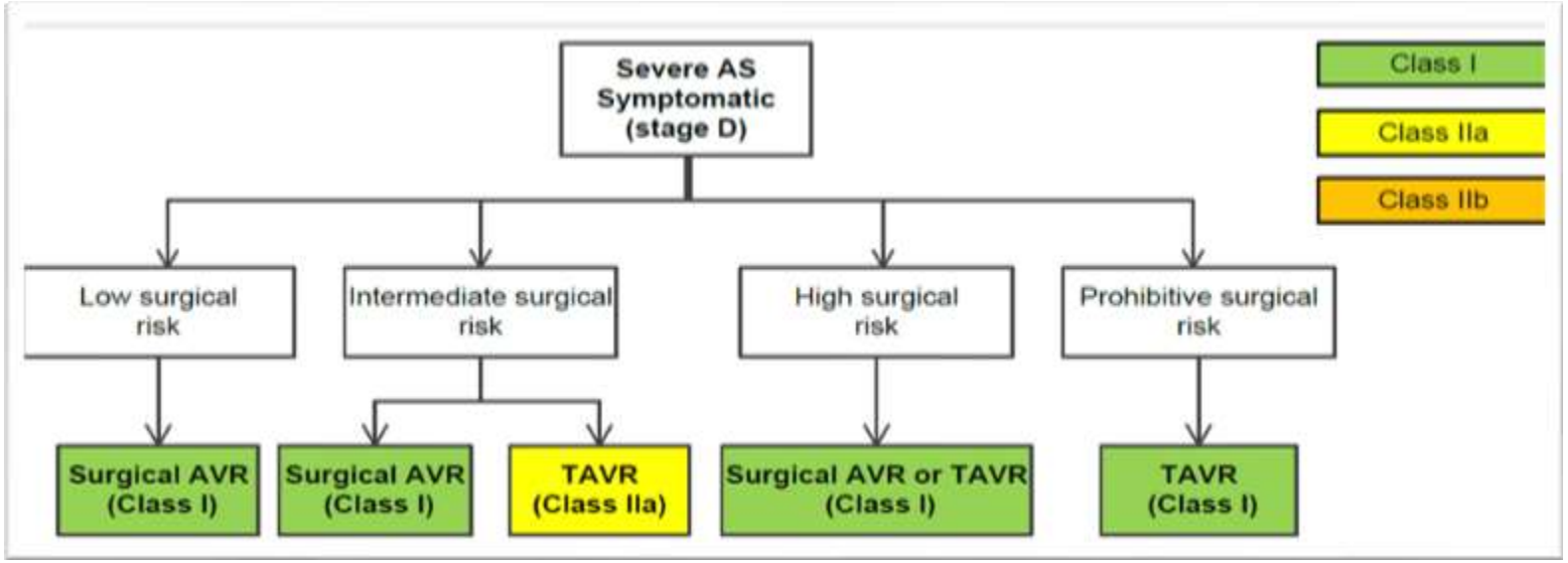
Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D., Raj R. Makkar, M.D., Lars G. Svensson, M.D., Ph.D., Susheel K. Kodali, M.D., Vinod H. Thourani, M.D., E. Murat Tuzcu, M.D., D. Craig Miller, M.D., Howard C. Herrmann, M.D., Darshan Doshi, M.D., David J. Cohen, M.D., Augusto D. Pichard, M.D., Samir Kapadia, M.D., Todd Dewey, M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators*

TAVR Success

The ACC/AHA and ESC/EACTS guidelines reflect the success TAVR has demonstrated, and ***TAVR is now recommended in extreme risk patients, and considered for both high and intermediate risk*** patients.

ACC/AHA 2017 Update



ESC/EACTS 2017 Update

The choice for intervention must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each modality (aspects to be considered are listed in *Table 7*). In addition, the local expertise and outcomes data for the given intervention must be taken into account.	I	C
SAVR is recommended in patients at low surgical risk (STS or EuroSCORE II < 4% or logistic EuroSCORE I < 10%[d] and no other risk factors not included in these scores, such as frailty, porcelain aorta, sequelae of chest radiation).[93]	I	B
TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team.[91,94]	I	B
In patients who are at increased surgical risk (STS or EuroSCORE II ≥ 4% or logistic EuroSCORE I ≥ 10%[d] or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics (see *Table 7*), with TAVI being favoured in elderly patients suitable for transfemoral access.[91,94–102]	I	B

Prediction #1:
TAVR will be the treatment of choice for all isolated AVR patients

Low Risk

Current Status | LRT Trial

Interim results from the multicenter, investigator sponsored, Low-Risk TVR (LRT) Trial were reported earlier this year. The study propensity matched low-risk TAVR patients to isolated SAVR patients from the STS database.

Low Surgical Risk
STS ≤ 3

- Heart Team Evaluation
  - -Eligible for transfemoral
  - -No high-risk surgical criteria independent of STS score
- Transfemoral
  - 200 patients

1:1 Matched SAVR Patients

- Propensity matched based on likelihood to receive or SAVR
- Outcomes extracted from STS for mortality through 30 days from the STS data

Bicuspid aortic valve

- - Low surgical risk
  - - Eligible for transfemoral
- 100 patients

[1]Waksmen et al., presented at CRT 2018

Low Risk

Current Status |LRT Trial

Early outcomes were excellent with no mortality or disabling stroke out to 30 days

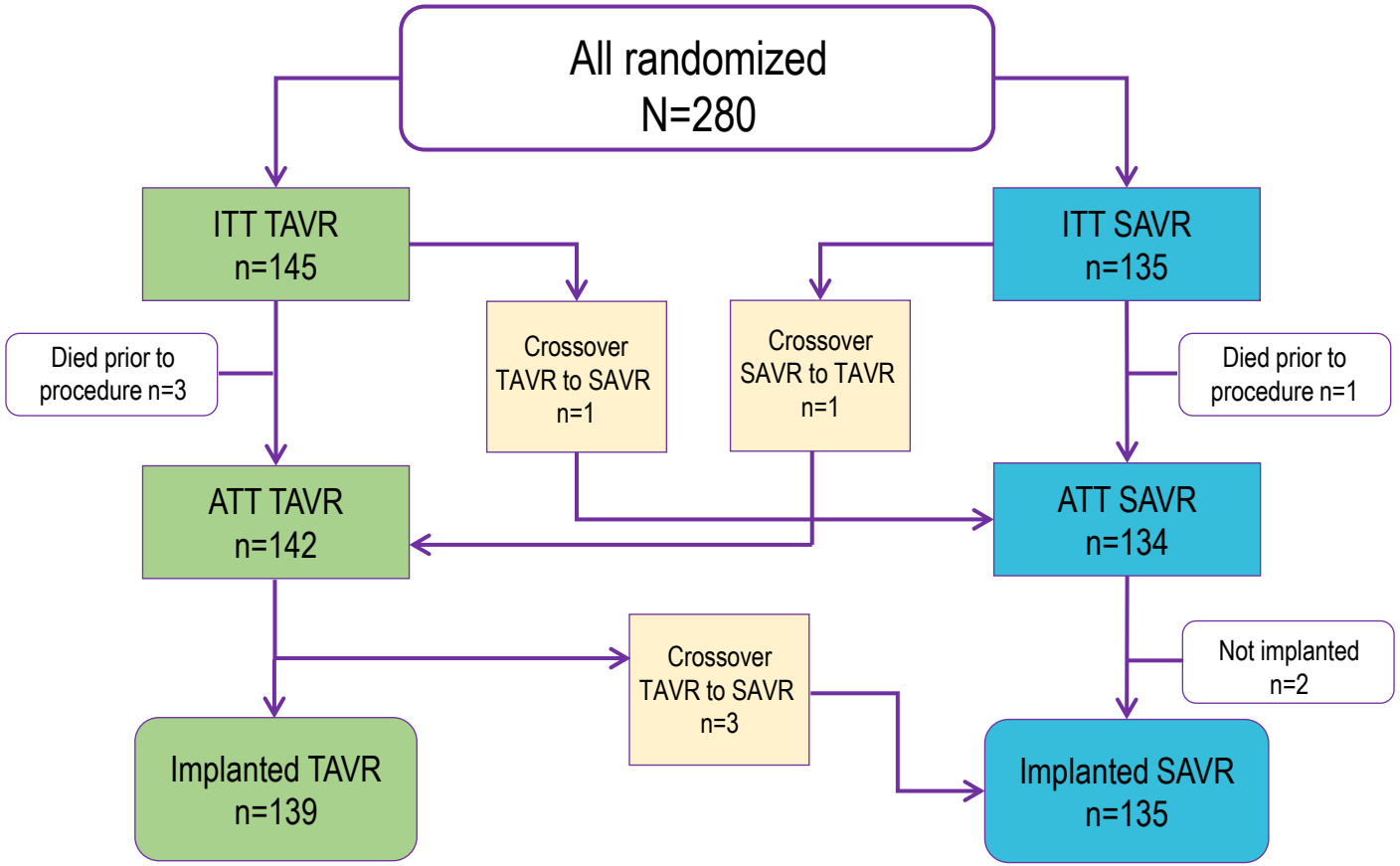
Outcome, %	In Hospital n=125	30 days n=125
Death, any cause	0%	0%
Bleeding, Life-threatening or Major	3.2%	0.8%
Paravalvular leak (≥ moderate)	0.8%	0%
Vascular Complication, Major	3.2%	0.8%
Acute kidney injury (stage II+III)	0%	0%
Disabling Stroke	0%	0%
Non-disabling Stoke	0%	0.8%
TIA	0%	0%
Myocardial infarction	0%	0%
Coronary Obstruction*	0.8%	0%
Atrial fibrillation, New Onset	3.2%	1.6%
Pacemaker	4.0%	0.8%

[1]Waksmen, presented at CRT 2018

Low Risk

Current Status |NOTION

The 5 year outcomes from the randomized, all-comers NOTION trial with TAVR in lower risk patients were also reported earlier this year.



[1]Thyregod, presented at ACC 2018

Low Risk

Current Status

The NOTION clinical outcomes demonstrated outstanding results with TAVR in lower risk patients. Both death from any cause and cardiovascular death were similar to SAVR out to 5 years.

	TAVR	SAVR	p-value
Death, any cause	27.7	27.7	0.90
Death, cardiovascular	21.0	22.5	0.75
Stroke	10.5	8.2	0.67
TIA	6.8	4.1	0.35
Atrial fibrillation	25.2	62.2	<0.001
Pacemaker	41.8	8.4	<0.001
Aortic re-intervention	2.5	0.0	0.09
Valve endocarditis	11.3	5.8	0.10

[1]Thyregod, presented at ACC 2018

Low Risk

Ongoing Trials

Low-risk trials are currently underway and results of the Medtronic and PARTNER trials are expected in early 2019. ***I predict results will show TAVR is non-inferior or superior to SAVR.***

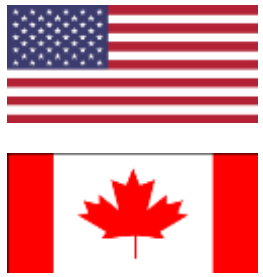
Medtronic Low Risk

N = ~1200

Up to 80 centers
Evolut R, all routes

Industry-sponsored
10-year follow-up

PARTNER 3



N = 1228

Up to 64 centers
SAPIEN 3, transfemoral

Industry-sponsored
10-year follow-up

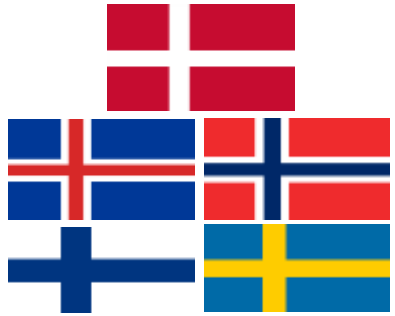
UK TAVR

N = 808

All UK TAVR centers
All valves, all routes

Publically funded
5-year follow-up

NOTION-2



N = 992

All Nordic countries
All valves, transfemoral

Physician and industry-sponsored
5-year follow-up

[1]Popma, presented at TCT 2016; [2]Mack, presented at TCT 2016; [3]Moat, presented at TCT 2016; [4]Sondergaard, presented at TCT 2016

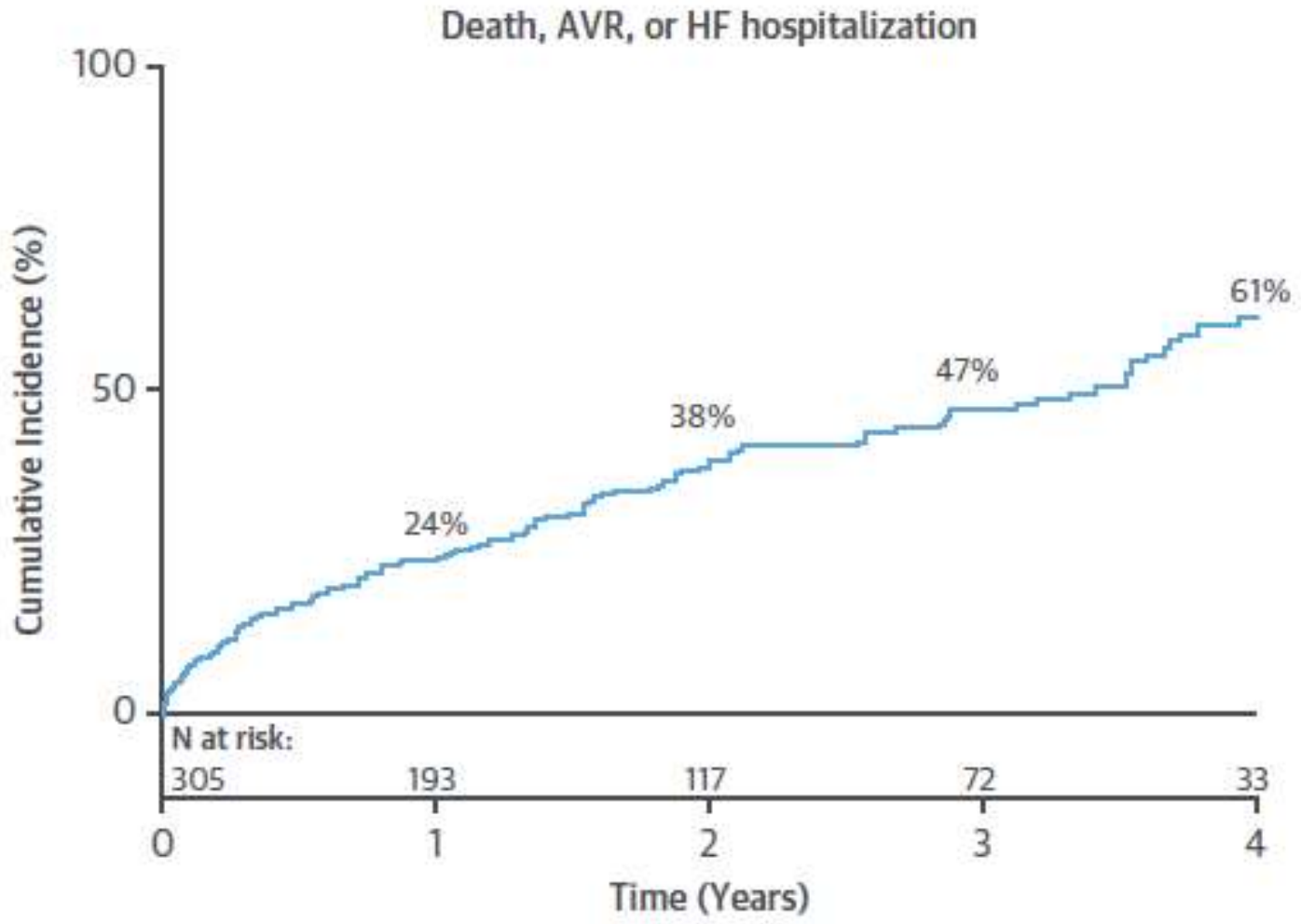
Prediction #2:

TAVR will be a reasonable treatment option for patients with asymptomatic and moderate AS

Moderate Aortic Stenosis

Current State

Clinical events are common in patients with moderate AS. A recent study found 61% of patients with moderate AS and left ventricular systolic dysfunction experienced a clinical event at 4 years.

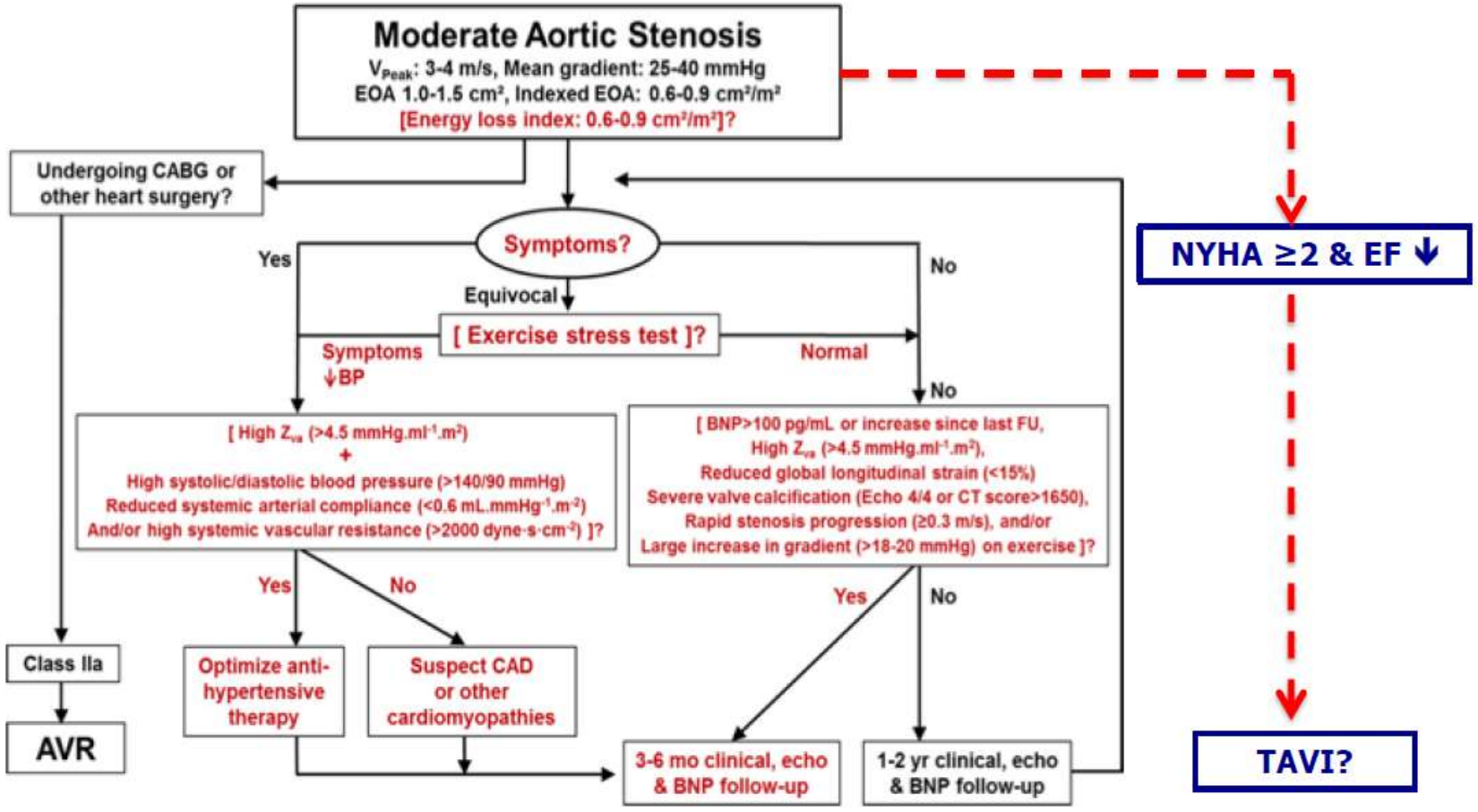


[1]Van Gils et al., JACC 2017;69:2383-92

Moderate Aortic Stenosis

Current State

Guidelines, including recent updates from ESC/EACTS and ACC/AHA, are lacking evidence. Randomized trial results are needed as outcomes of TAVR in moderate AS patients is mostly limited to case studies.

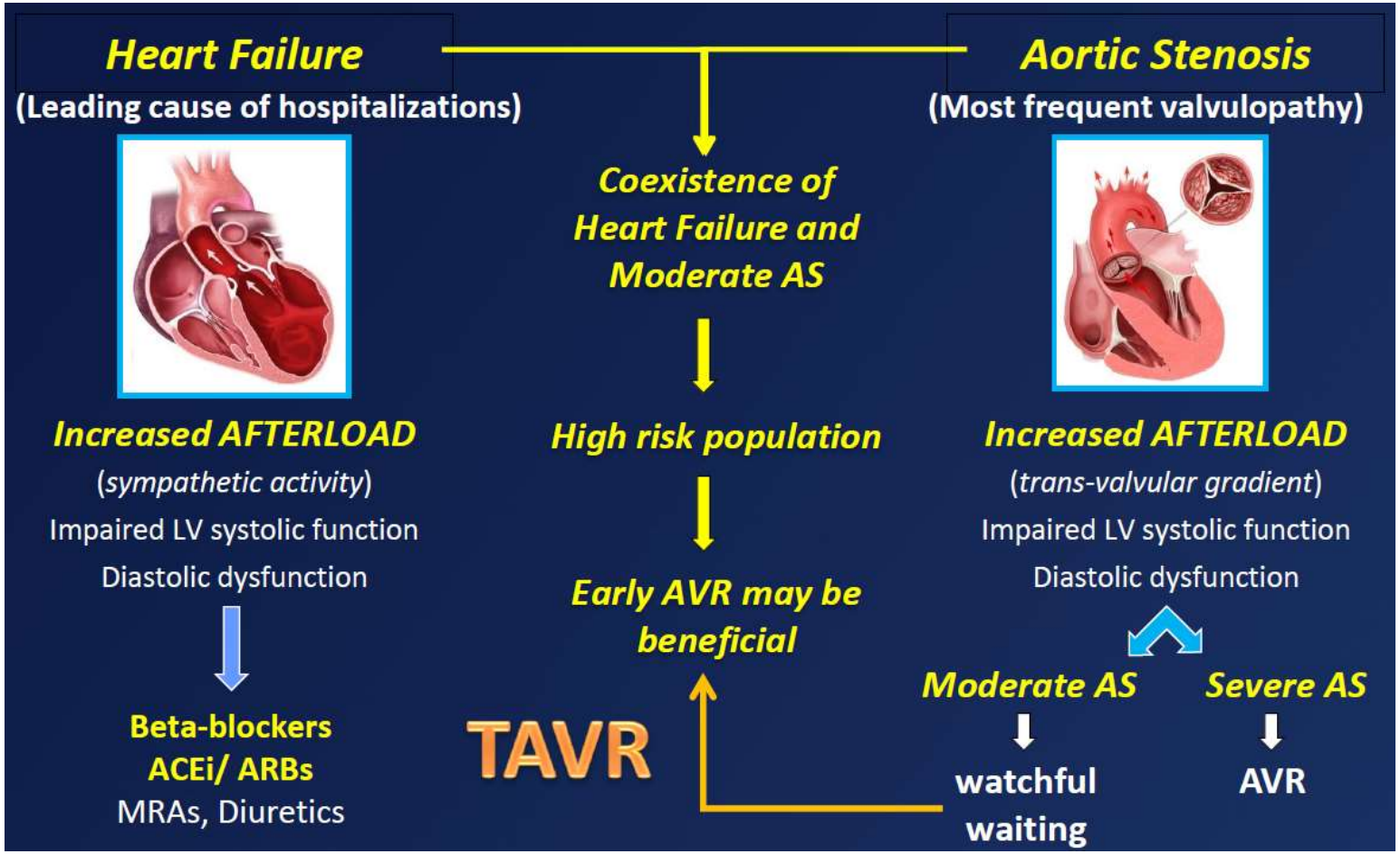


[1]Van Mieghem et al., presented at TVT 2017; [2]Nishimura, et al., K Am Coll Cardiol. 2017 Jul 11;70(2):252-289; [3]Baumgartner et al., Eur Heart J. (2017) 00, 1-53; Pibarot et al., J Am Coll Cardiol 2012;60:169-80

Moderate Aortic Stenosis

Current State

The less-invasive TAVR procedure may be a better option for earlier intervention in patients with moderate AS.

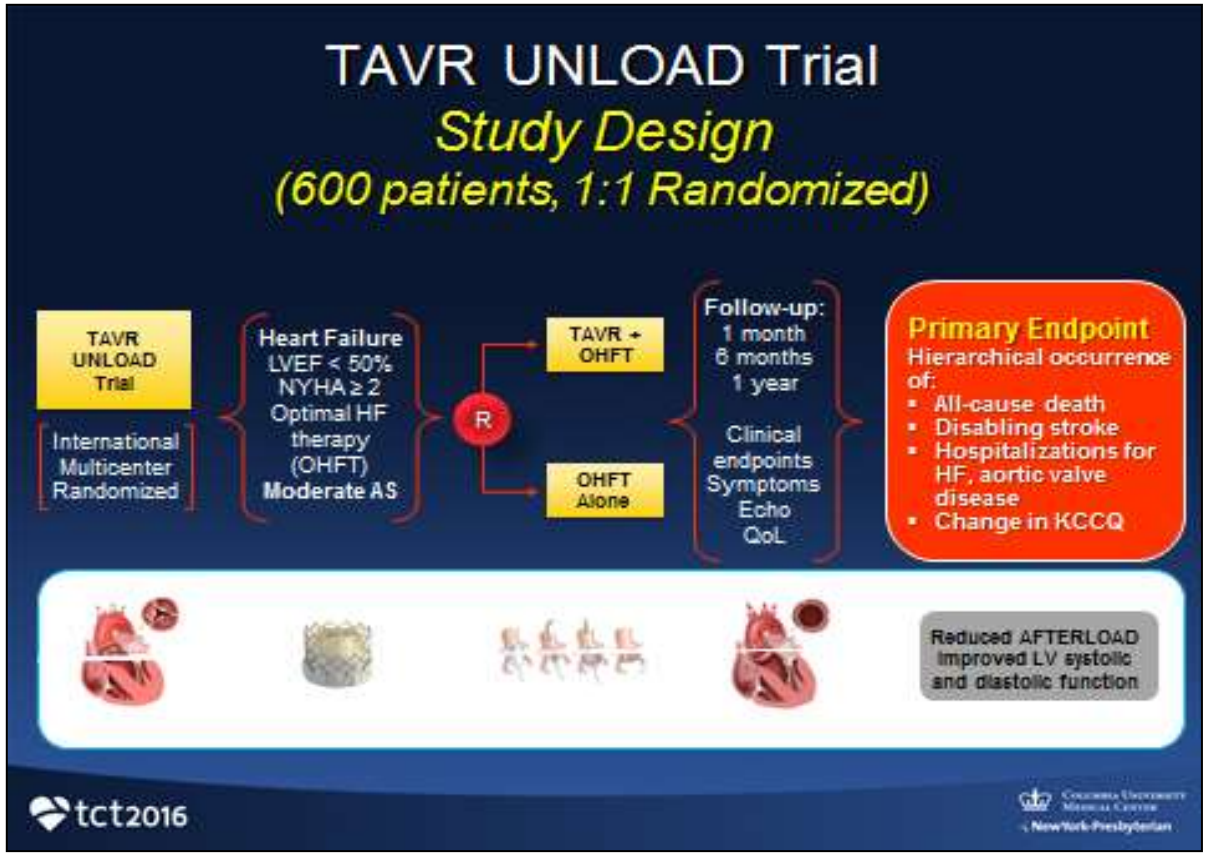


[1]Schwartz, presented at TCT 2017

Moderate Aortic Stenosis

TAVR UNLOAD

The TAVR UNLOAD Trial will compare TAVR to medical therapy in patients with moderate AS, symptoms of heart failure, and reduced ejection fraction. ***I predict this study will show TAVR outcomes are superior to medical therapy.***



[1]Leon, presented at TCT 2016

Asymptomatic Aortic Stenosis

Current State

Early SAVR is rarely performed in severe asymptomatic AS patients due to risk of peri-operative mortality.

Sudden Death	Peri-operative Mortality
Severe Asymptomatic AS	***SAVR***
~1-2%/year	***~1-5%***

TAVR may be a better option for Asymptomatic patients

30-day Mortality SURTAVI Intermediate risk	
Core Valve TAVR	SAVR
2.2%	1.7%

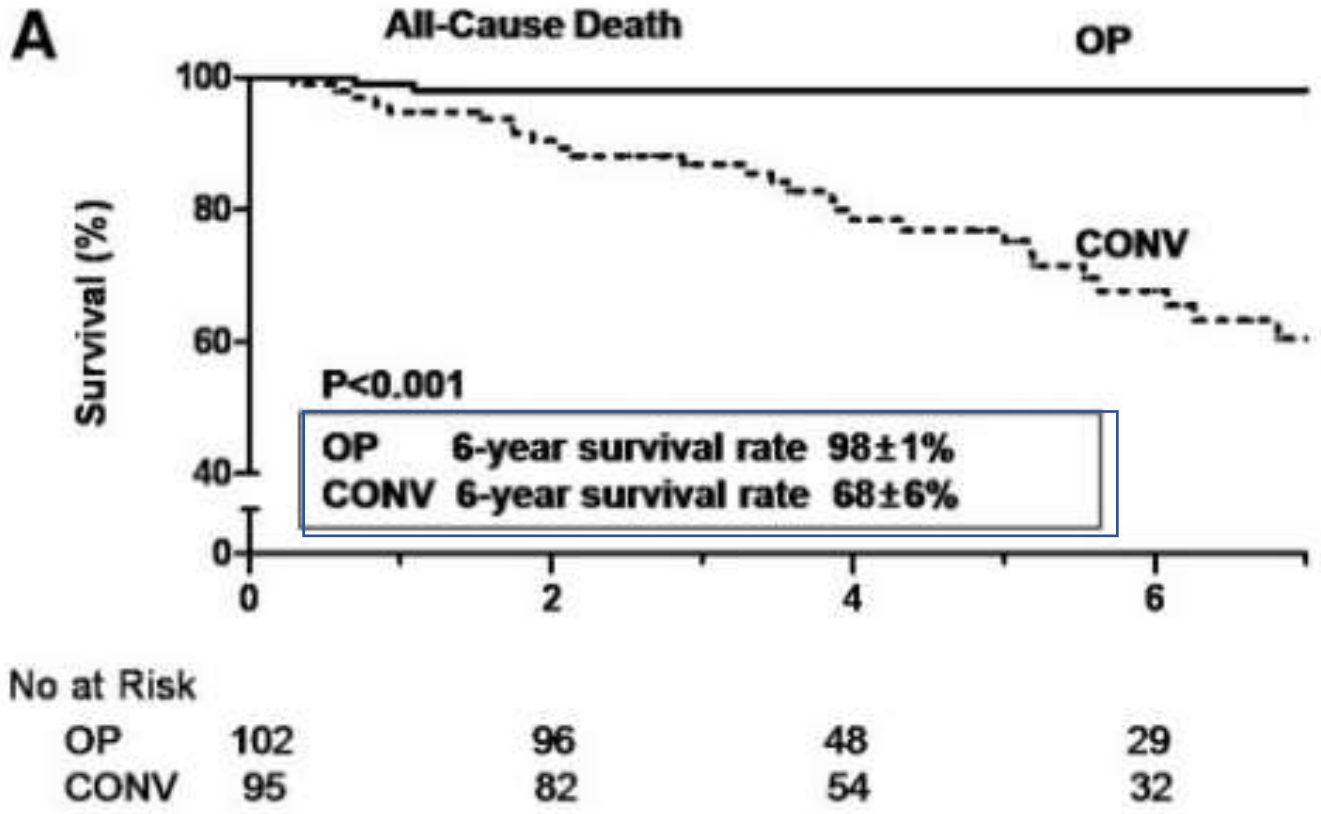
30-day Mortality PARTNER trial 2A Intermediate PM	
Sapien 3 TAVR	SAVR
1.1%	4.0%

[1]Genereux, presented at TCT 2017; [2]Genereux et al., J Am Coll Cardiol. 2016;67:2263-88; [3]Reardon et al., NEJM 2017; [4]Thourani et al. Lancet 2016; 387:2218-25

Asymptomatic Aortic Stenosis

Current State

Although patients rarely undergo surgery for asymptomatic AS, early treatment has shown improved outcomes when compared to symptom driven aortic valve replacement.



OP = early surgery
CONV = conventional treatment

[1]Kang et al., circulation 2010:121;1502-1509

Asymptomatic Aortic Stenosis

Current State

Similar to moderate AS, guidelines are lacking evidence and randomized trial results are needed. Outcomes of TAVR in asymptomatic AS patients is mostly limited to case studies.

Recommendations and Levels of Evidence for Diagnosis, Follow-up, and Timing of Aortic Valve Replacement in Patients With Asymptomatic Severe Aortic Stenosis

	ACC/AHA	ESC/EACTS
Indications for aortic valve replacement		
Left ventricular ejection fraction <50%	I, B	I, C
Undergoing other cardiac surgery	I, B	I, C
Symptoms on exercise test clearly related to aortic stenosis	I, B	I, C
Repeatedly markedly elevated natriuretic peptide and low surgical risk	-	IIa, C
Severe pulmonary hypertension (>60mmhg) and low surgical risk	-	IIa, C

ACC = American College of Cardiology; AHA = American Heart Association; EACTS = European Association for Cardio-Thoracic Surgery; European ESC = European Society of Cardiology

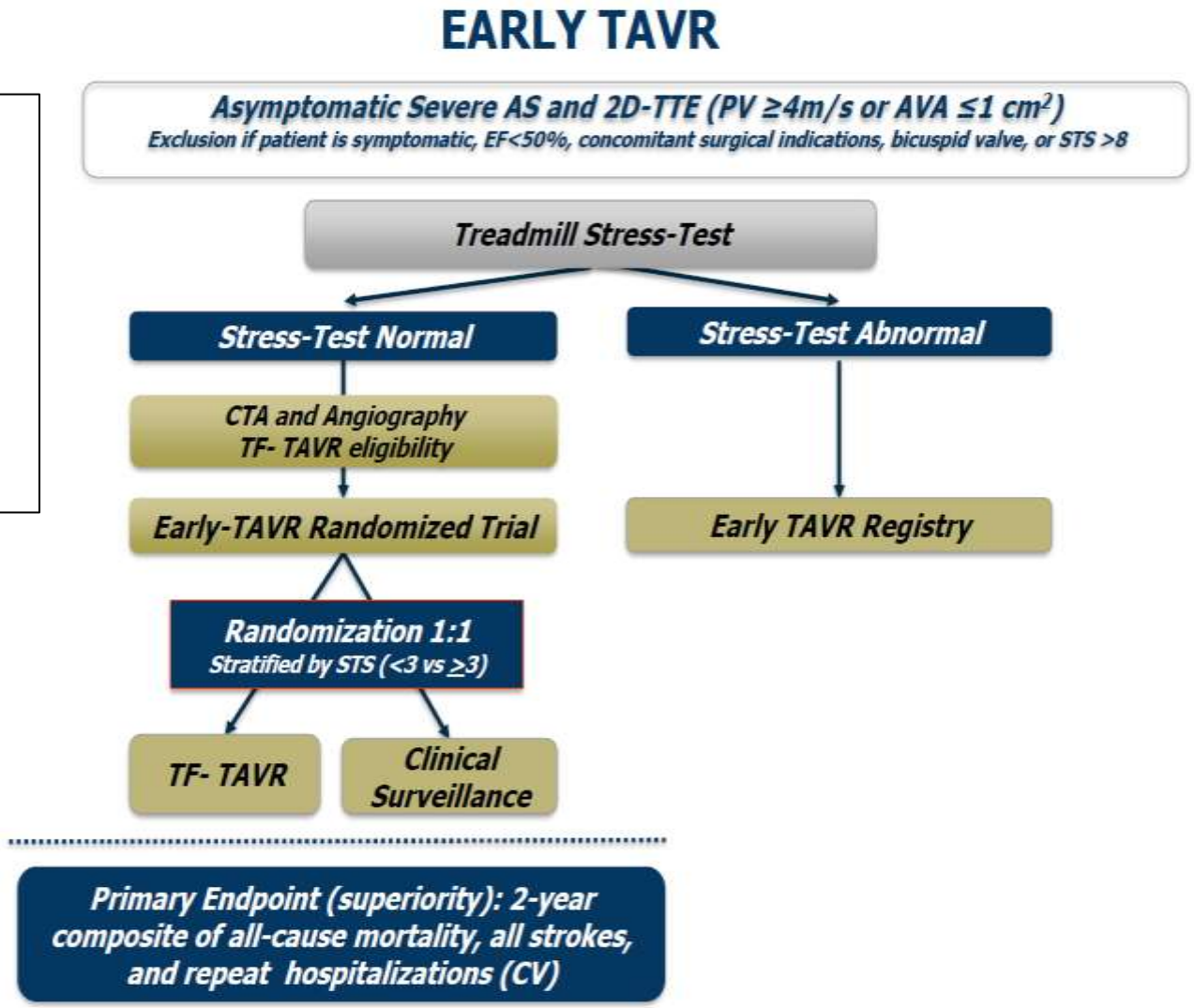
3 Class I indications…6 Class IIa indications…
Level of evidence B or C
No Randomized trial

[1]Genereux, presented at TCT 2017; [2]Nishimura, et al., K Am Coll Cardiol. 2017 Jul 11;70(2):252-289; [3]Baumgartner et al., Eur Heart J. (2017) 00, 1-53

Moderate and Asymptomatic Aortic Stenosis

Current State

The EARLY TAVR clinical trial is currently underway to evaluate the use of TAVR for asymptomatic aortic stenosis. ***I predict earlier intervention with TAVR will prevent myocardial damage and functional decline.***



[1]Van Mieghem et al, presented at TCT 2017

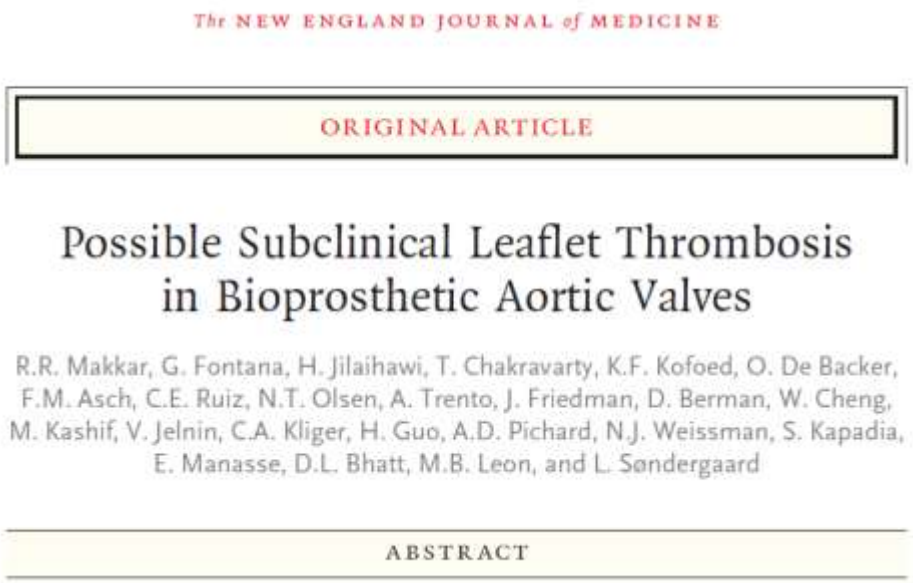
Prediction #3:
TAVR pharmacology will be optimized

Lifetime Management

Anticoagulation | Valve Thrombosis

Valve thrombosis has come to the forefront with studies reporting

- Reduced leaflet motion in 22 of 55 (40%) patients analyzed from the PORTICO IDE Cohort (16 of 37 (40%) Portico patients, 6 of 14 (43%) Sapien XT patients, and 0 of 4 (0%) CoreValve patients).
- ***In the pooled RESOLVE and SAVORY registry patients, reduced leaflet motion was found in 14% of patients and 7% of SAVR patients***



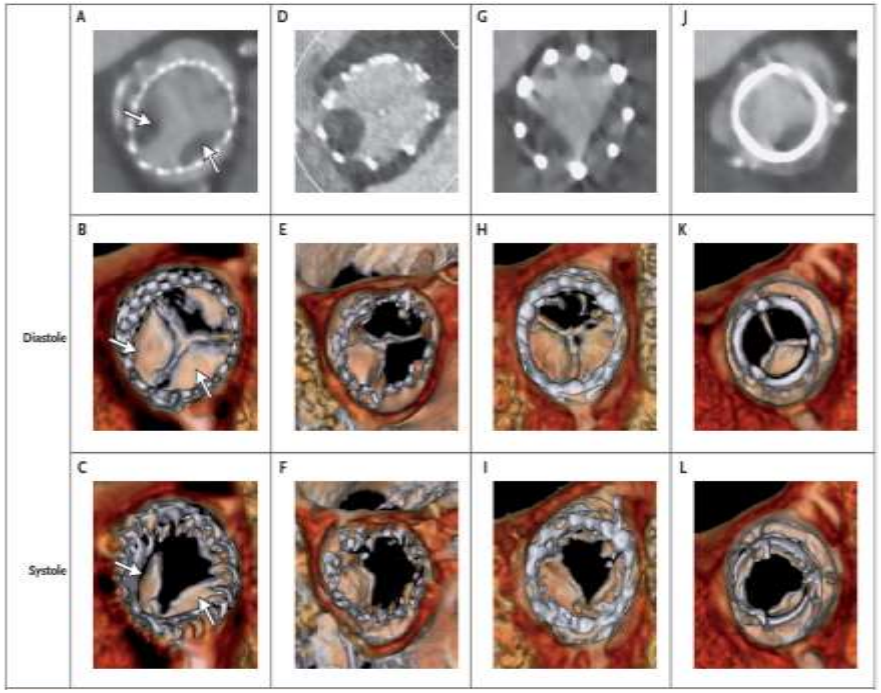
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

R.R. Makkar, G. Fontana, H. Jilaihawi, T. Chakravarty, K.F. Kofoed, O. De Backer, F.M. Asch, C.E. Ruiz, N.T. Olsen, A. Trento, J. Friedman, D. Berman, W. Cheng, M. Kashif, V. Jelnin, C.A. Kliger, H. Guo, A.D. Pichard, N.J. Weissman, S. Kapadia, E. Manasse, D.L. Bhatt, M.B. Leon, and L. Søndergaard

ABSTRACT



[1]Makkar, et al., *N Engl J Med.* 2015 Nov 19;373(21):2015-24

Lifetime Management

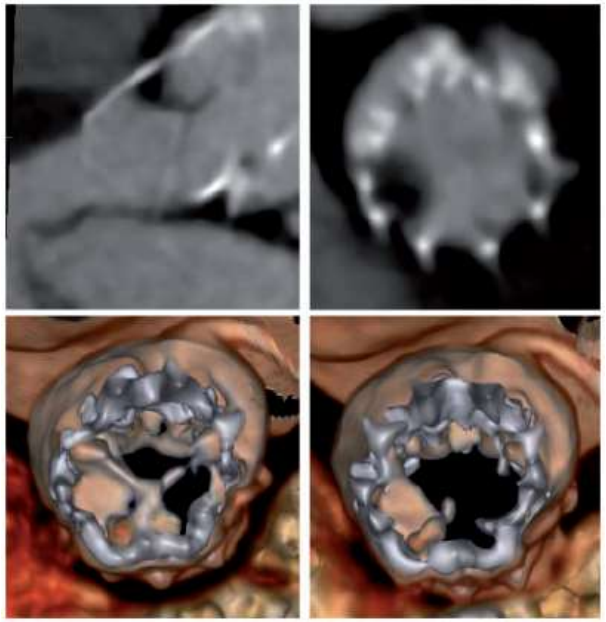
Anticoagulation | Subclinical Leaflet Thrombosis Affecting Motion

- **84 patients (61 TAVR and 23 SAVR) undergoing 2 consecutive 4D-CTs, without change in pharmacotherapy between the 2 scans, included in the analysis**
- Hypo-attenuating leaflet thickening ***(HALT)***, was found in 32 patients ***(38%)***
- Hypo-attenuation affecting motion ***(HAM)***, defined as a leaflet excursion reduced by more than ***50%*** in relation to the bioprosthetic frame radius, in 17 patients (20%)

Table I Evolution pattern of leaflet status between the first and second computed tomography scan

HALT/HAM at first CT	HALT/HAM at second CT			
	HALT− HAM−	HALT+ HAM−	HALT+ HAM+	Total
HALT-HAM-	53	7	4	64
HALT+HAM-	5	3	2	10
HALT+HAM+	2	2	7	11
Total	60	12	13	85

HALT, hypo-attenuating leaflet thickening, HAM, hypo-attenuation affecting motion; Green, regression; orange, progression; CT, computed tomography.



[1]Sondergaard, et al., *Eur Heart J.* 2017 Jul 21;38(28):2201-2207

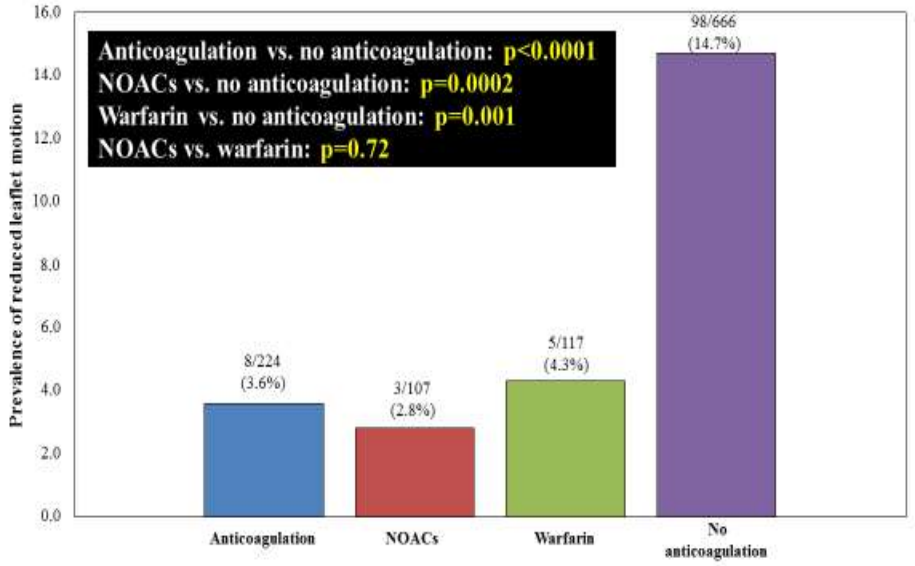
Lifetime Management

Anticoagulation | Possible Factors Affecting Leaflet Motion

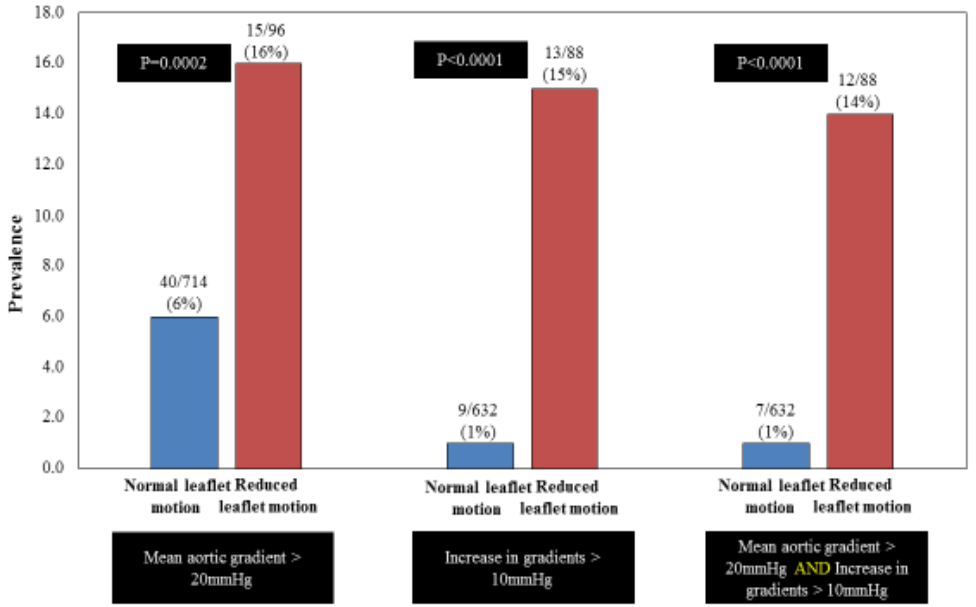
No anticoagulation and increased gradients have been associated with decreased leaflet motion

Anticoagulation and reduced leaflet motion

Anticoagulation vs. no anticoagulation



Increased gradients in patients with reduced leaflet motion

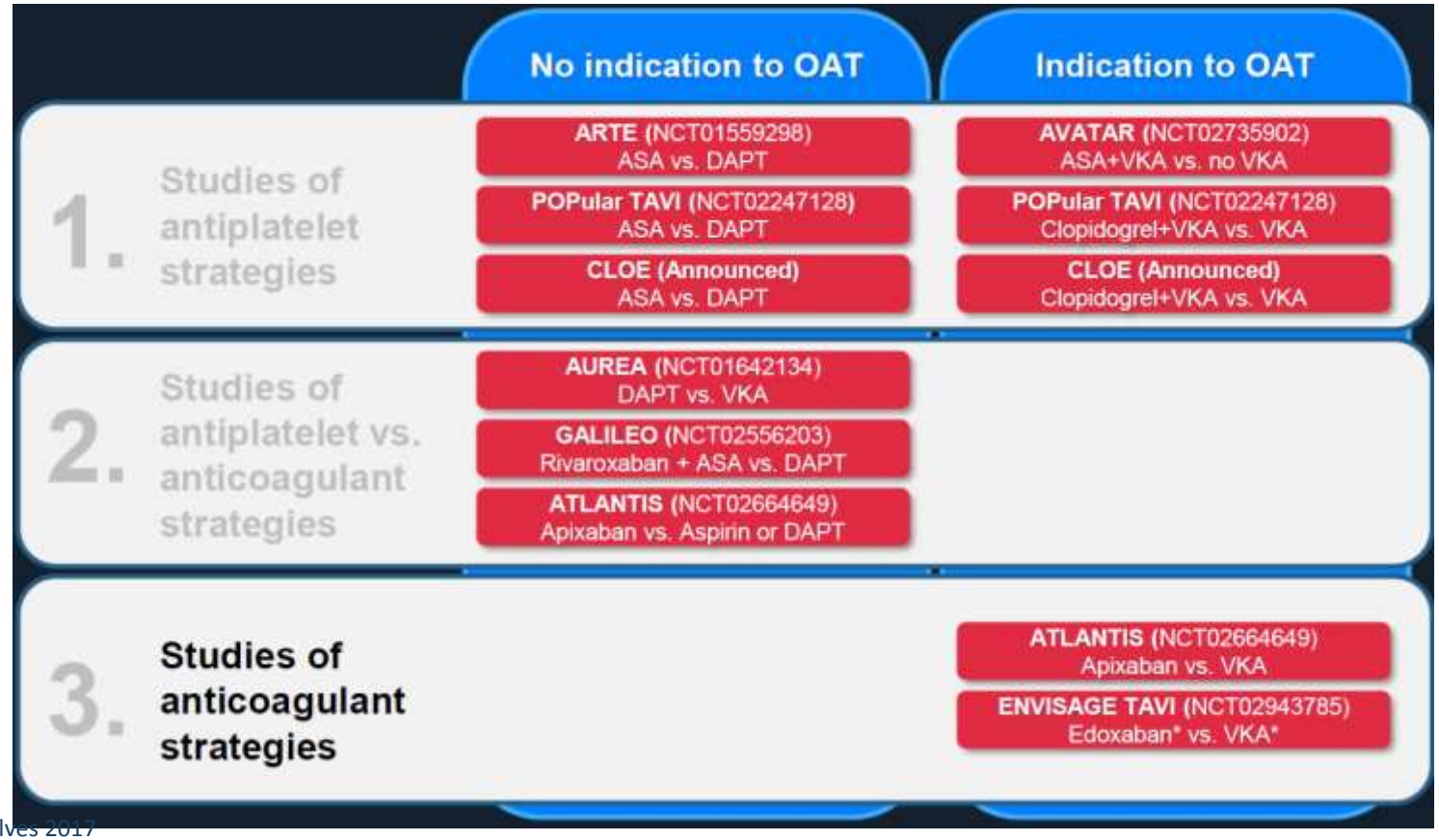


[1]Makkar et al., presented at TCT 2017

Lifetime Management

Anticoagulation

Current clinical antithrombotic therapy post-TAVR is mostly empirical and practice variation is quite high. Clinical trials are currently underway and will bring clarity and guidance on this important topic. ***I predict the post TAVR Implant strategy will change and Anticoagulation will be recommended***



[1]Capodanno, et al., presented at London Valves 2017

Summary

- TAVR has seen great success and become the gold standard in extreme- and high-risk aortic stenosis patients.
- Recent results from the LRT and NOTION Trials show excellent outcomes in low-risk patients, and I predict results from ongoing low-risk clinical trials will show TAVR is as good or better than SAVR.
- Currently, TAVR data on moderate and asymptomatic AS patients is limited. Ongoing clinical trials will provide valuable information and show TAVR is a reasonable treatment option for early intervention.
- Many clinical trials are underway to determine the optimal antithrombotic regimen post-TAVR. This will be essential in reducing post-procedure bleeds, strokes, and thrombosis, as well as increasing the durability of transcatheter valves.

Thank You!