ESC Cardiovascular Round Table

27 March 2017, Amsterdam

Anticoagulation in Specific Populations: Biological Heart Valves, TAVI

Stephan Windecker

Department of Cardiology

Swiss Cardiovascular Center

Bern University Hospital, Switzerland

What do these Gentlemen have in common?

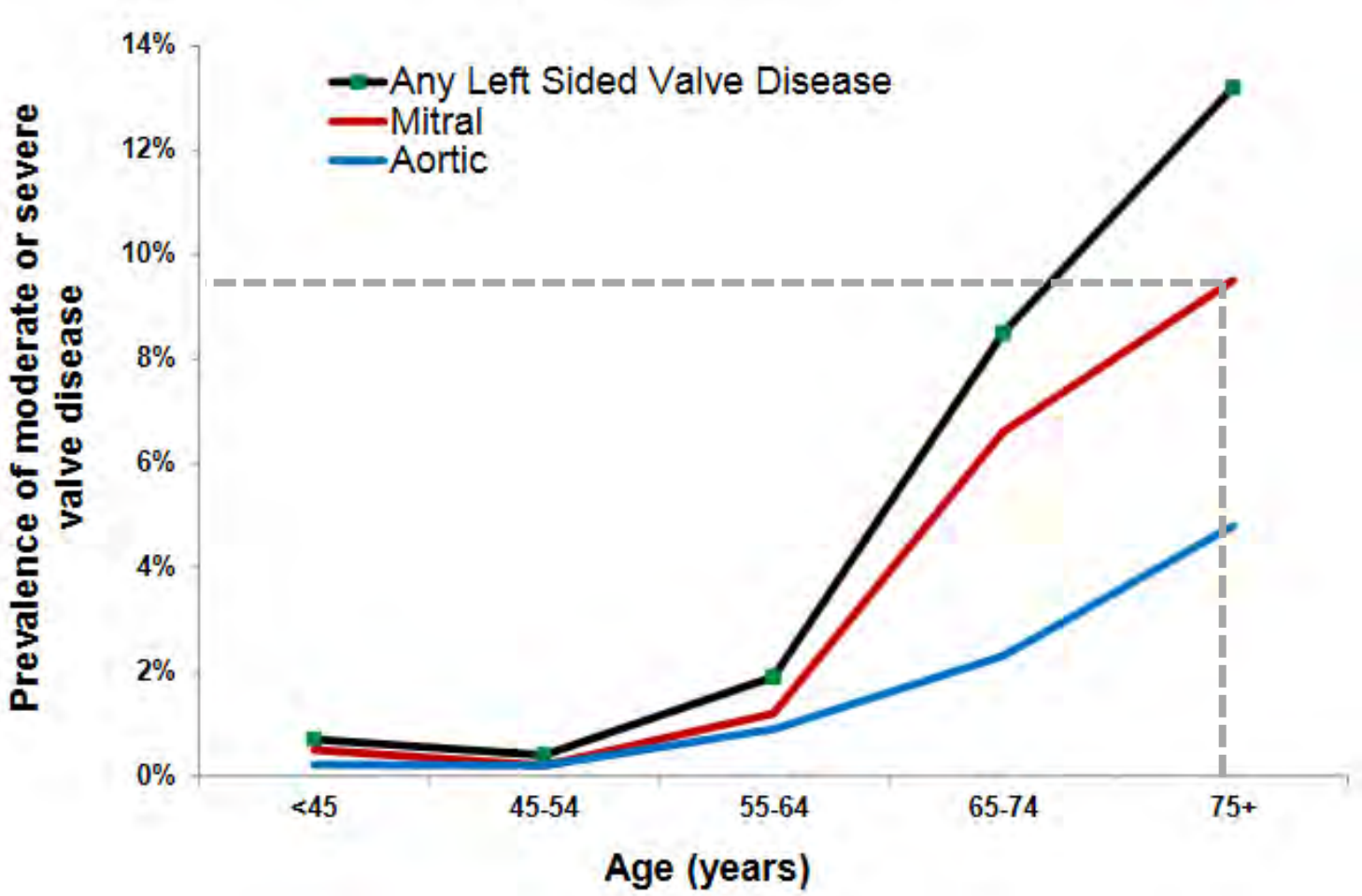
Foreign Minister of Germany
1974-1992

TAVI 2012

US Secretary of State
1973-1977

TAVI 2014

Left-sided valvular heart disease



Nkomo VT et al., Lancet 2006

15 Years of TAVI (2002 – 2017)

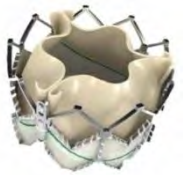
Prosthesis with CE – Mark Approval

2007 2010 2011 2012 2013 2014 2015 2017

Edwards Sapien THV

TF, TA

Edwards Sapien XT



TF, TA

Symetis Acurate TA

TA

SJM Portico

TF

Direct Flow Medical

TF

BSC Lotus

TF

Edwards Sapien 3

TF, TA

Medtronic Evolut R

TF

Medtronic CoreValve

TF, TS, DA

JenaValve

TA

Medtronic Engager

TA

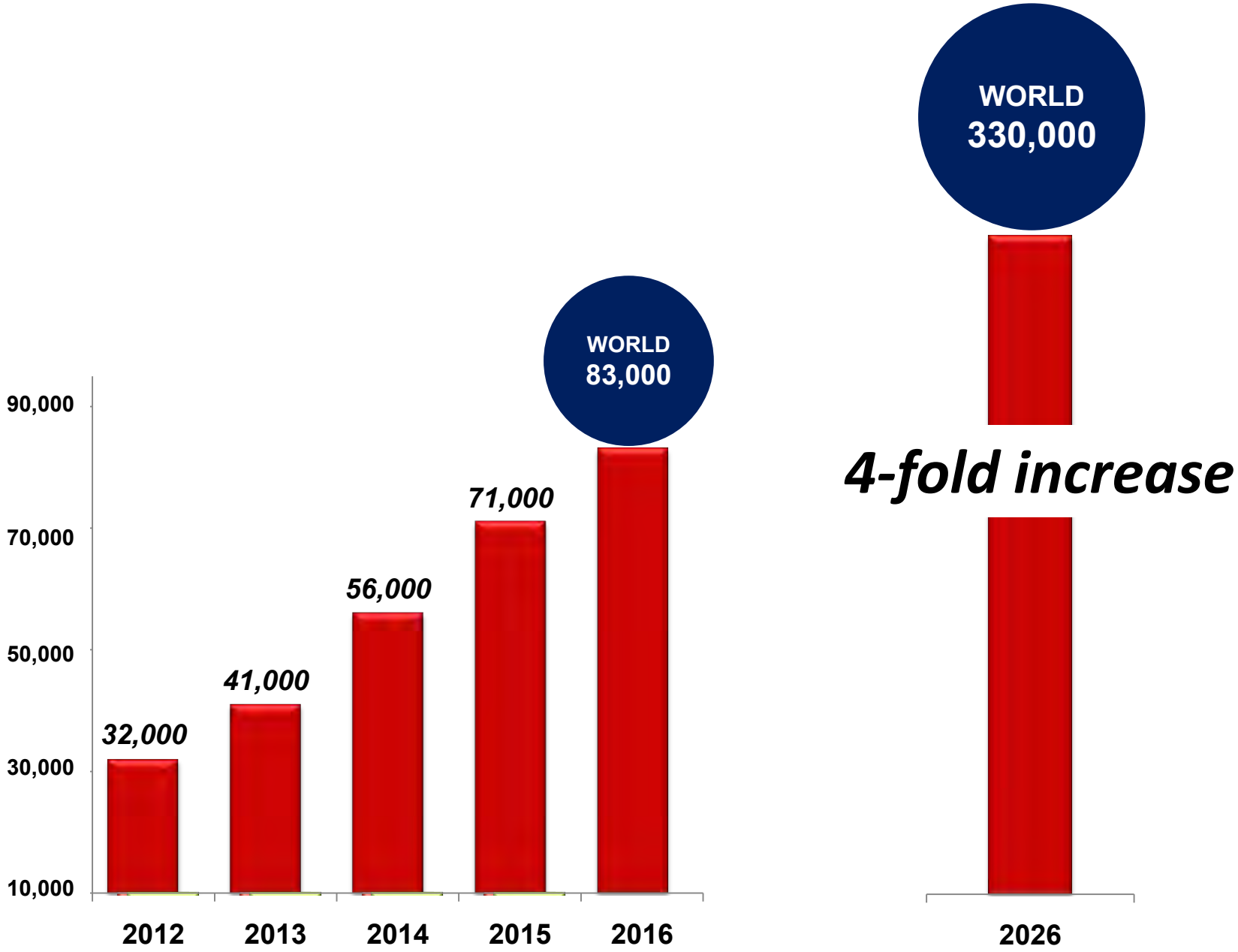
Symetis Acurate Neo

TF

Lotus Edge

TF

GLOBAL TAVI ADOPTION

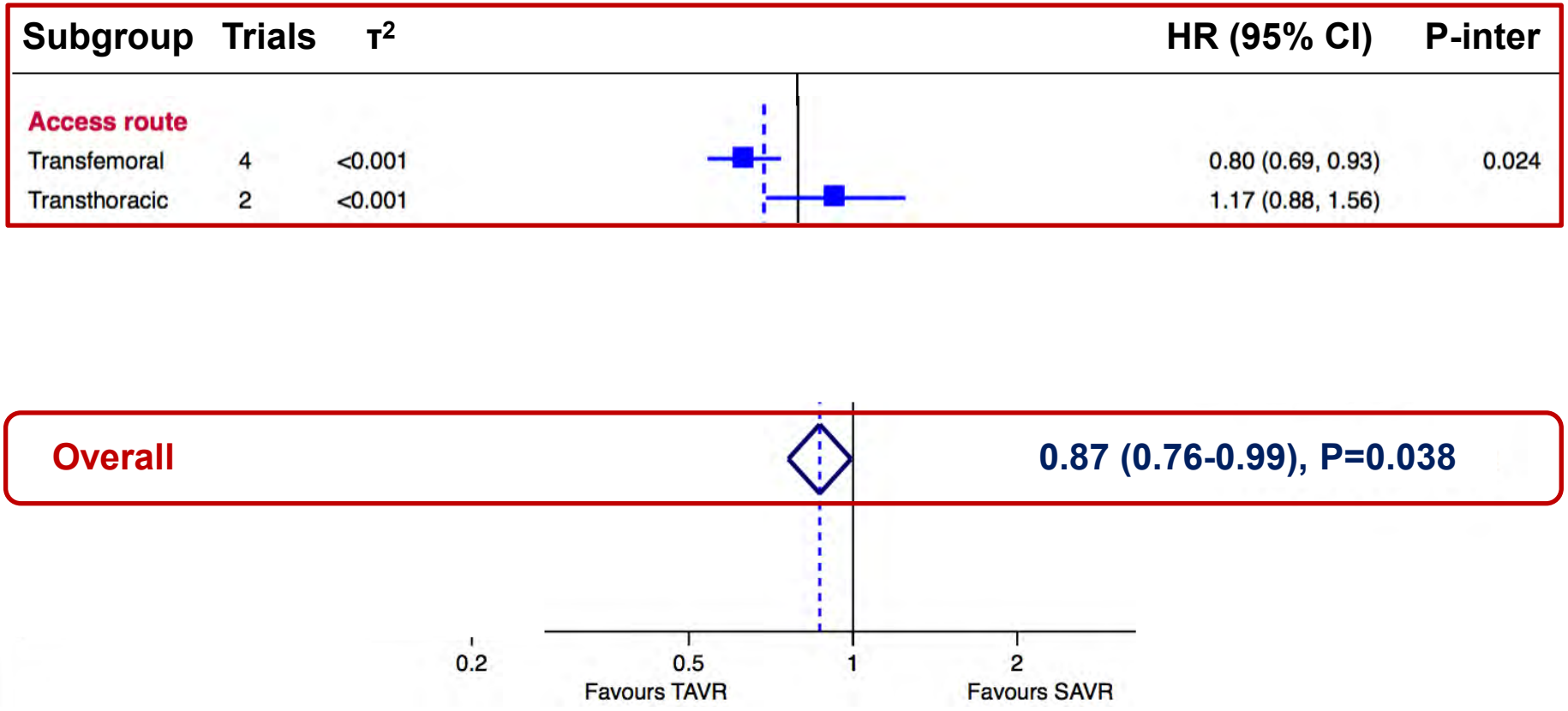


SOURCE: Credit Suisse TAVI Comment - January 8, 2015

TAVI vs SAVR: Meta-Analysis Of 4 Randomized Trials

Siontis et al, *Eur Heart J* 2016 Dec 14;37(47):3503-3512

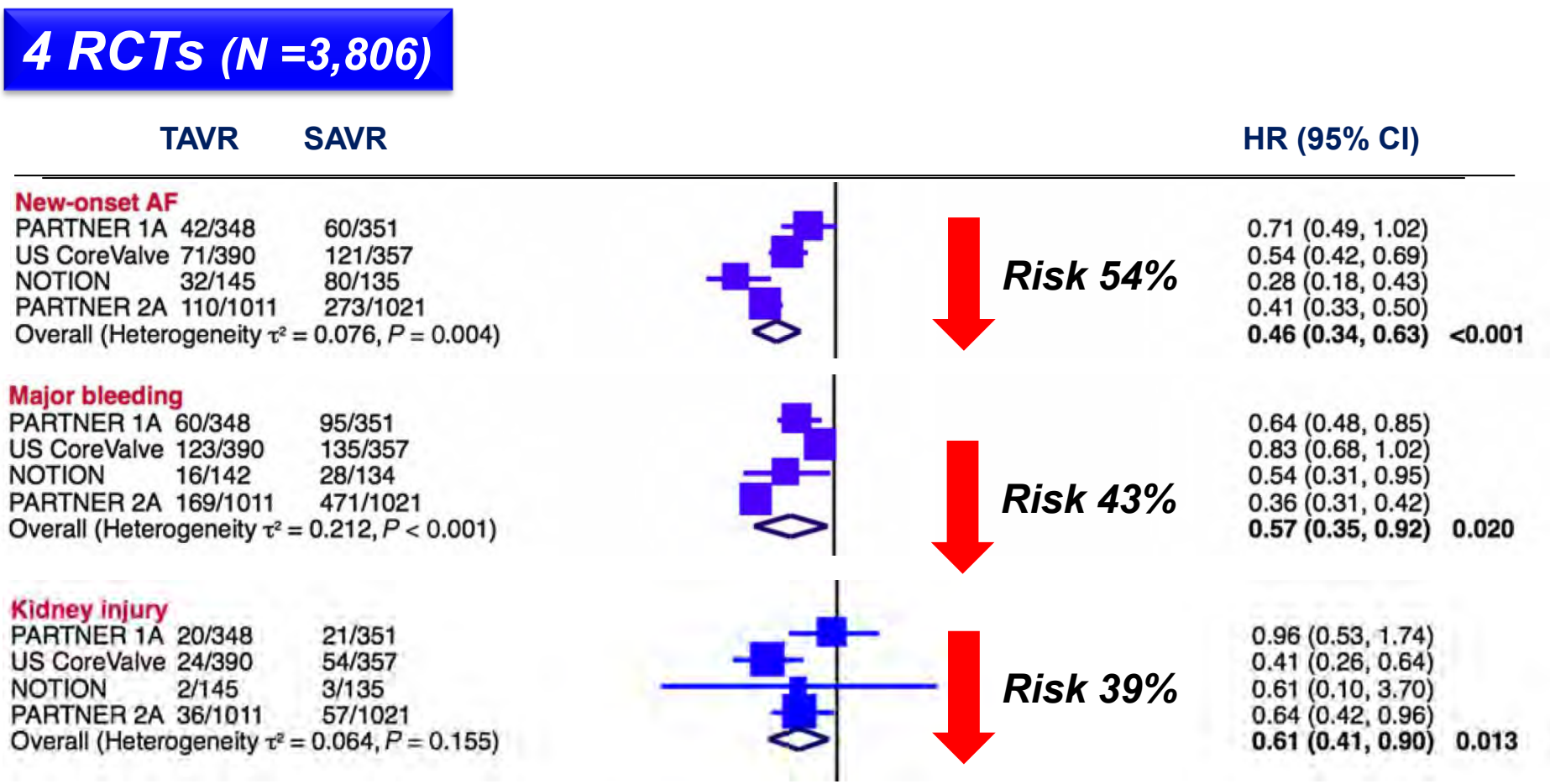
All-cause Mortality at 2 years (N =3,806)

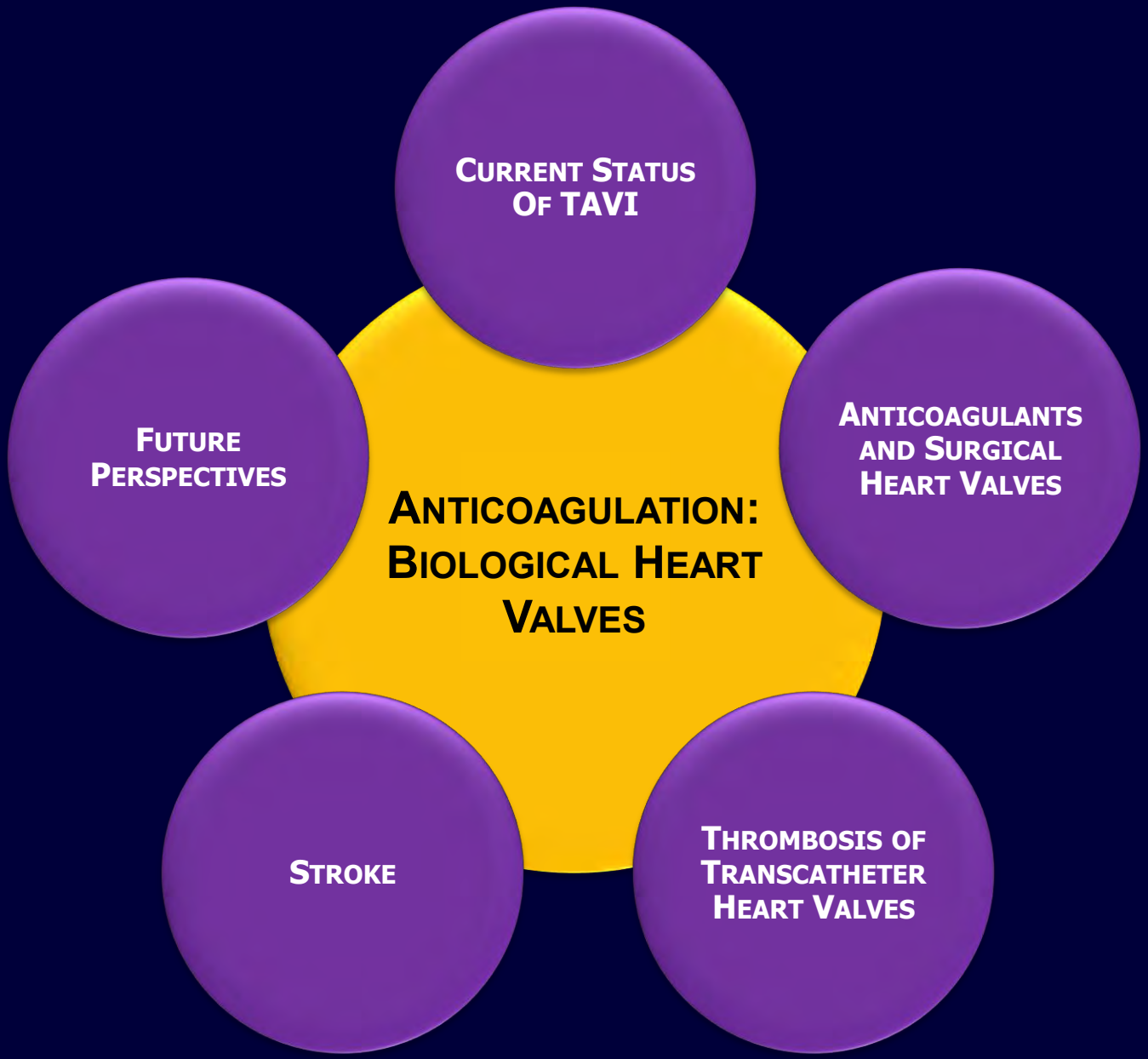


TAVI vs. SAVR
Peri-Procedural Adverse Events

Siontis et al, *Eur Heart J* 2016 Dec 14;37(47):3503-3512

4 RCTs (N =3,806)




Current Status Of TAVI
Anticoagulants and Surgical Heart Valves
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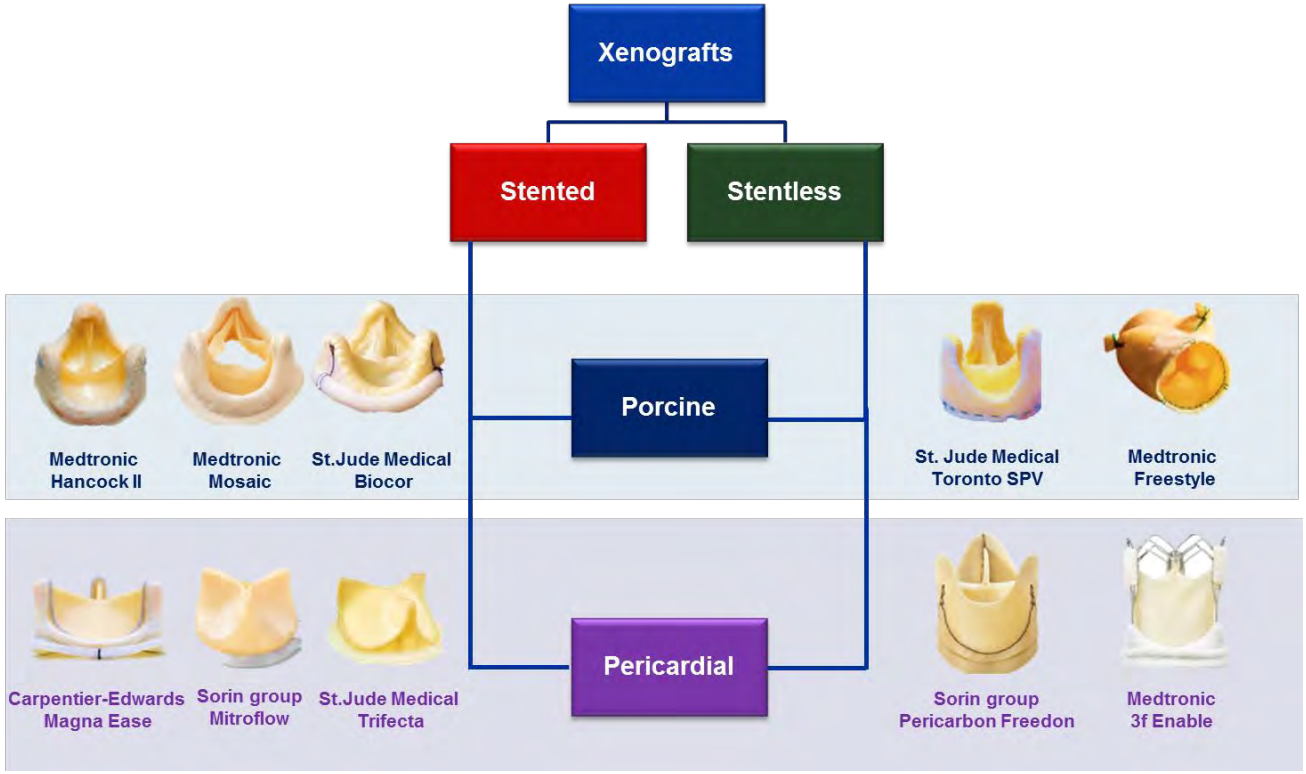
Anticoagulation: Biological Heart Valves

SURGICAL HEART VALVES

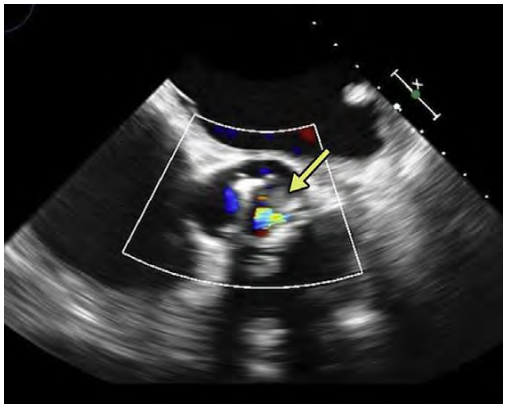
BIOLOGICAL

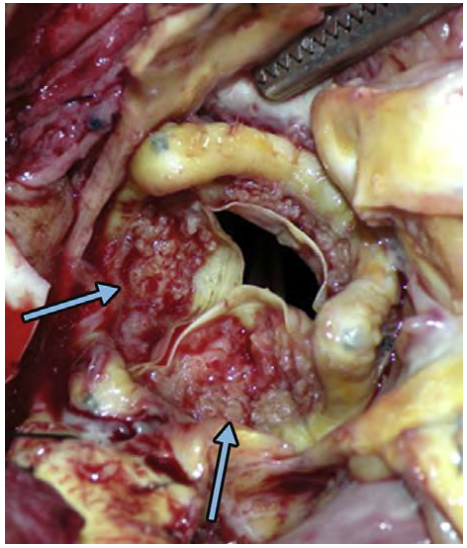


MECHANICAL

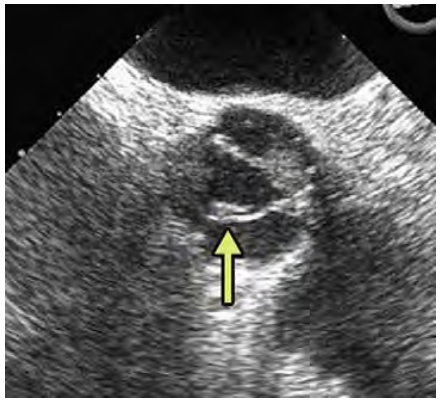
PATHOLOGY OF BIOPROSTHETIC VALVES THROMBOSIS

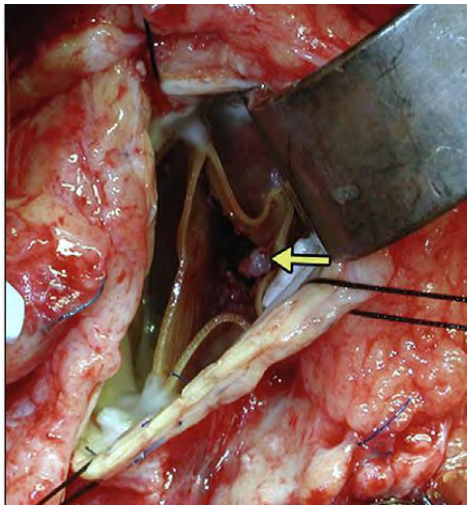
Thrombi on the nonflow surface of the valve

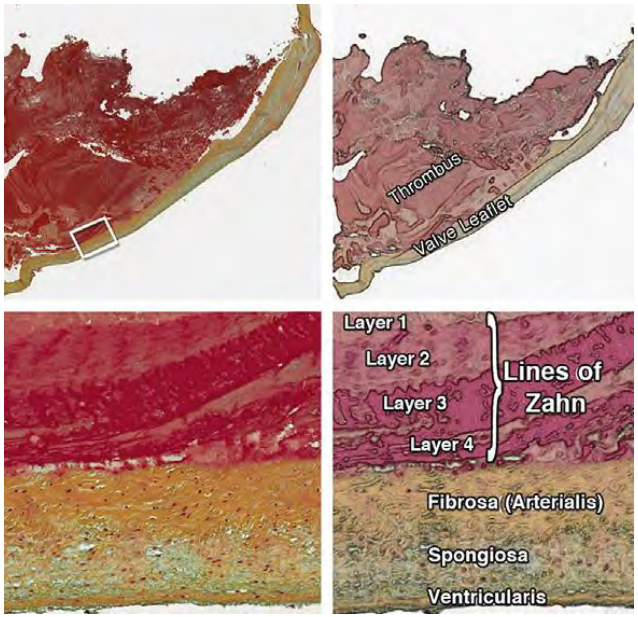


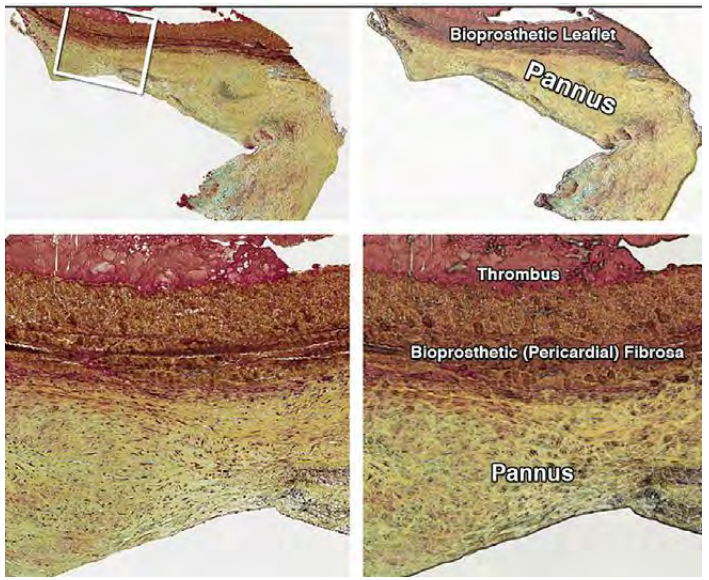


Thrombus and Subvalvular Pannus









PREVALENCE, TIMING AND PREDICTORS

Mayo Clinic matched case–control study

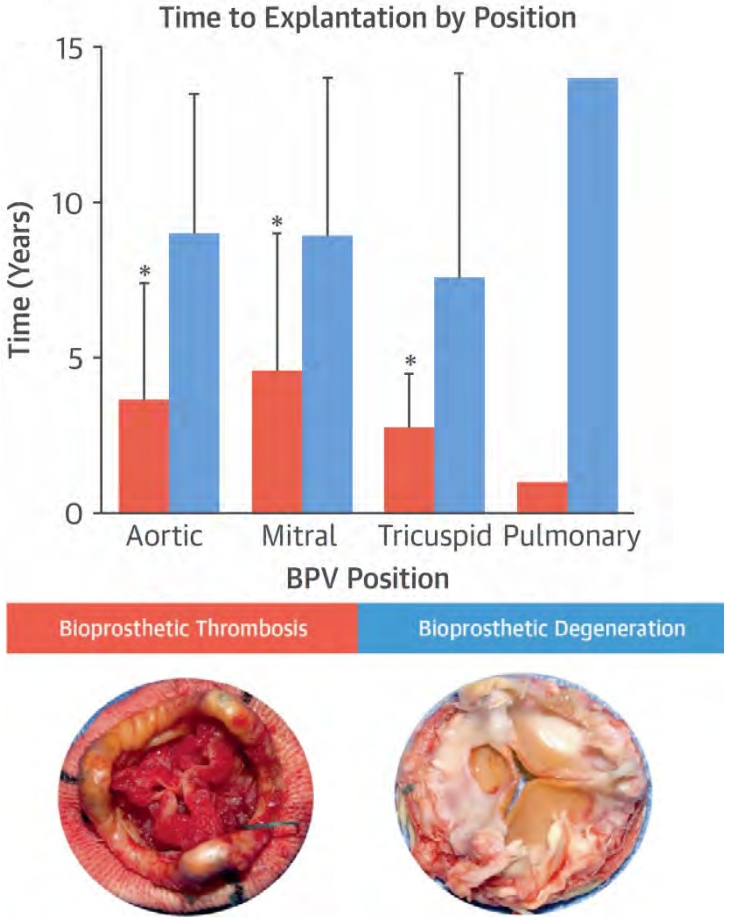
Between 1997 and 2013, 397 consecutive explanted bioprostheses

	BPV Explanted (n)	BPVT (n)	BPVT Prevalence (%)
Aortic	265	29	10.9
Mitral	71	9	12.7
Tricuspid	58	7	12.1
Pulmonary	3	1	
Total	397	46	11.6

			Estimated BPVT Incidence* (%)
Aortic	3,843	29	0.57
Mitral	1,395	9	0.64
Tricuspid	722	7	1.0
Pulmonary	218	1	0.5
Total	6,178	3	0.74

- ***Prevalence 11.6%***
- ***Incidence 0.74%***
- ***Predictors***
  - ***AF, ↑gradient, ↑cusp thickness, subtherapeutic INR***

BPVT occurred earlier than structural deterioration, after a median of 24 months and regardless of position



Egbe et al. J Am Coll Cardiol 2015;66:2285–94

RECOMMENDATIONS FOR ANTICOAGULANT THERAPY

BIOLOGICAL

EUROPEAN SOCIETY OF CARDIOLOGY

Recommendations	Class	Level
Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indication for anticoagulation	I	B
Oral anticoagulation should be considered for the first three months after implantation of a mitral- or tricuspid bioprosthesis	IIa	C
Oral anticoagulation may be considered for the first three months after implantation of an aortic bioprosthesis	IIb	C
Low-dose aspirin should be considered for the first three months after implantation of an aortic bioprosthesis	IIa	C

Vahanian et al. European Heart Journal (2012) 33, 2451–2496

American Heart Association.

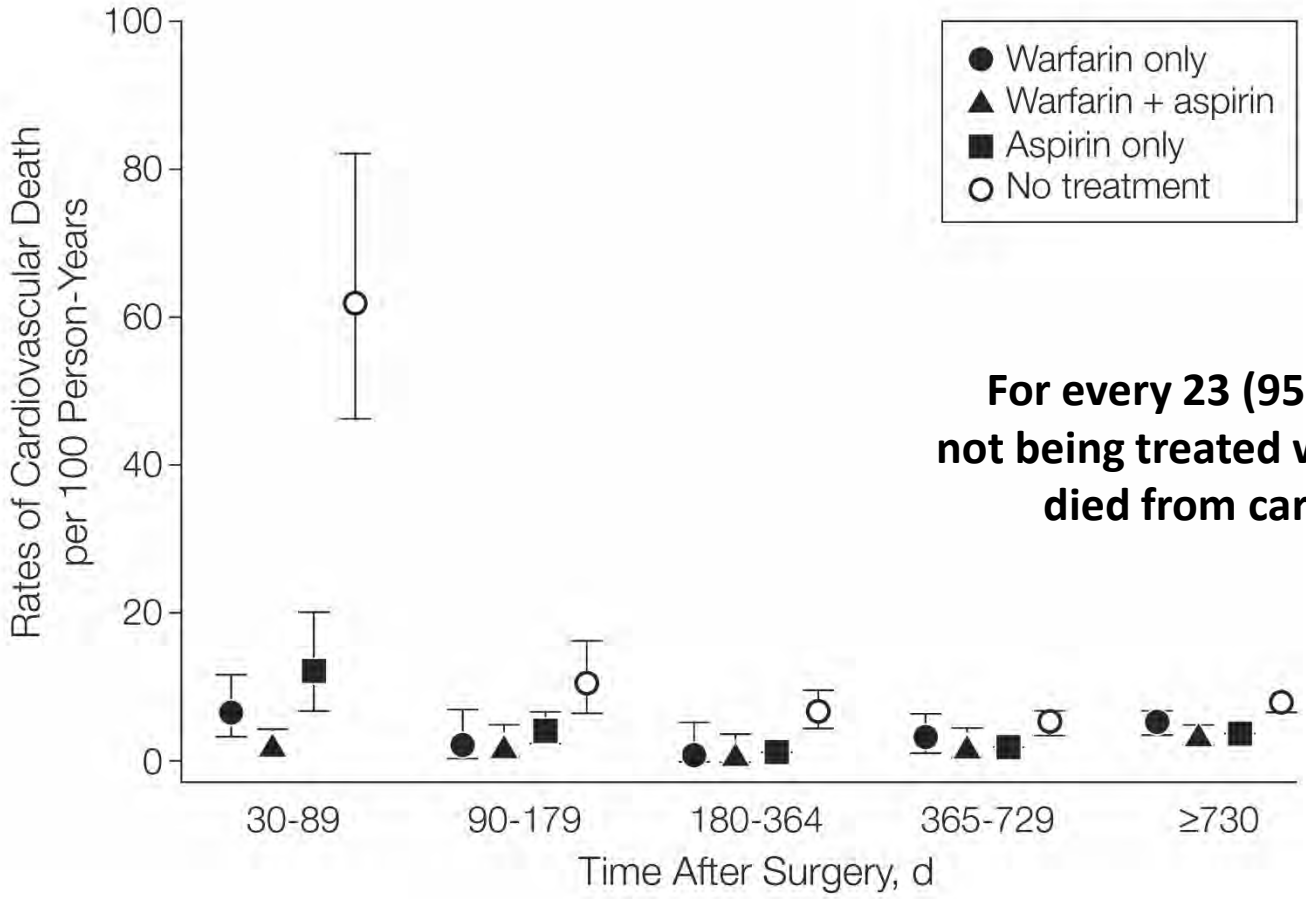
AMERICAN COLLEGE of CARDIOLOGY

Recommendations	Class	Level
Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve	IIa	B
Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical bioprosthetic MVR or AVR in patients at low risk of bleeding	IIa	B

Nishimura et al. Circulation. 2017 Mar 15

DURATION OF ANTICOAGULANT THERAPY

4,075 patients who had bioprosthetic AVR in the Danish National Patient Registry



For every 23 (95% CI, 14-54) patients not being treated with warfarin, 1 patient died from cardiovascular cause

Me´rie et al. JAMA. 2012;308(20):2118-212585–94

RECOMMENDATIONS FOR ANTICOAGULANT THERAPY

MECHANICAL

EUROPEAN SOCIETY OF CARDIOLOGY

Vahanian et al.
European Heart Journal 2012

Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.	I	B
Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.[d]	I	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease.	IIa	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.	IIa	C

American Heart Association.

AMERICAN COLLEGE of CARDIOLOGY

Nishimura et al.
Circulation. 2017

I	A	**Anticoagulation with a VKA and INR monitoring is recommended in patients with a mechanical prosthetic valve (178-183).**
I	B	**Anticoagulation with a VKA to achieve an INR of 2.5 is recommended for patients with a mechanical bileaflet or current-generation single-tilting disc AVR and no risk factors for thromboembolism (178,184-186).**
I	B	**Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage) (178).**
I	B	**Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR (178,187,188).**
I	A	**Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis (178,189,190).**

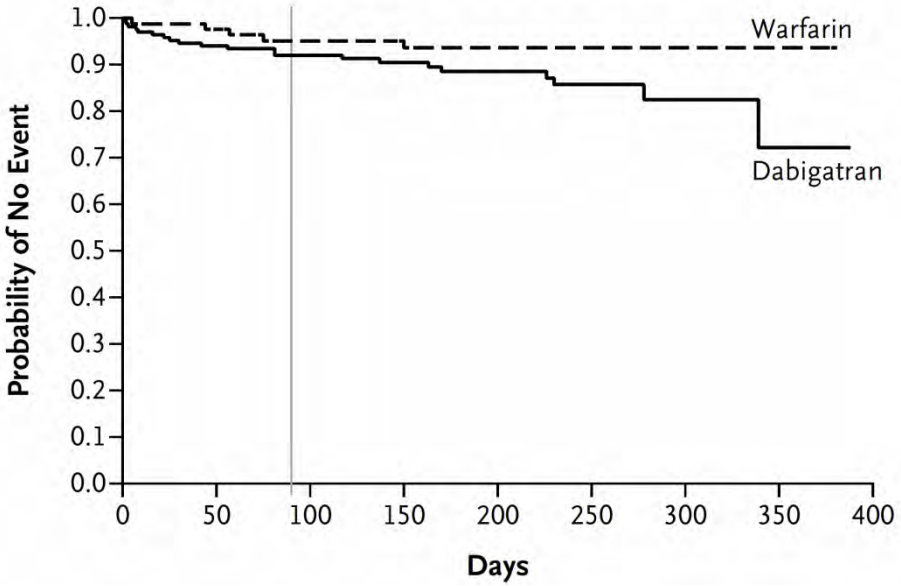
NOAC AND MECHANICAL HEART VALVES

The Re-ALIGN Trial

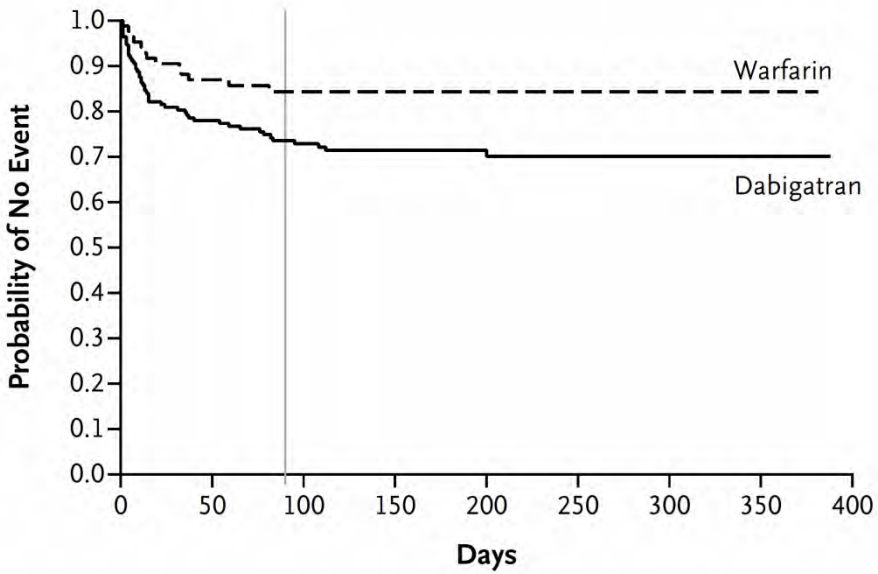
Dabigatran vs. warfarin (2:1) after aortic- or mitral-valve replacement

Prematurely interrupted after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group

First thromboembolic event



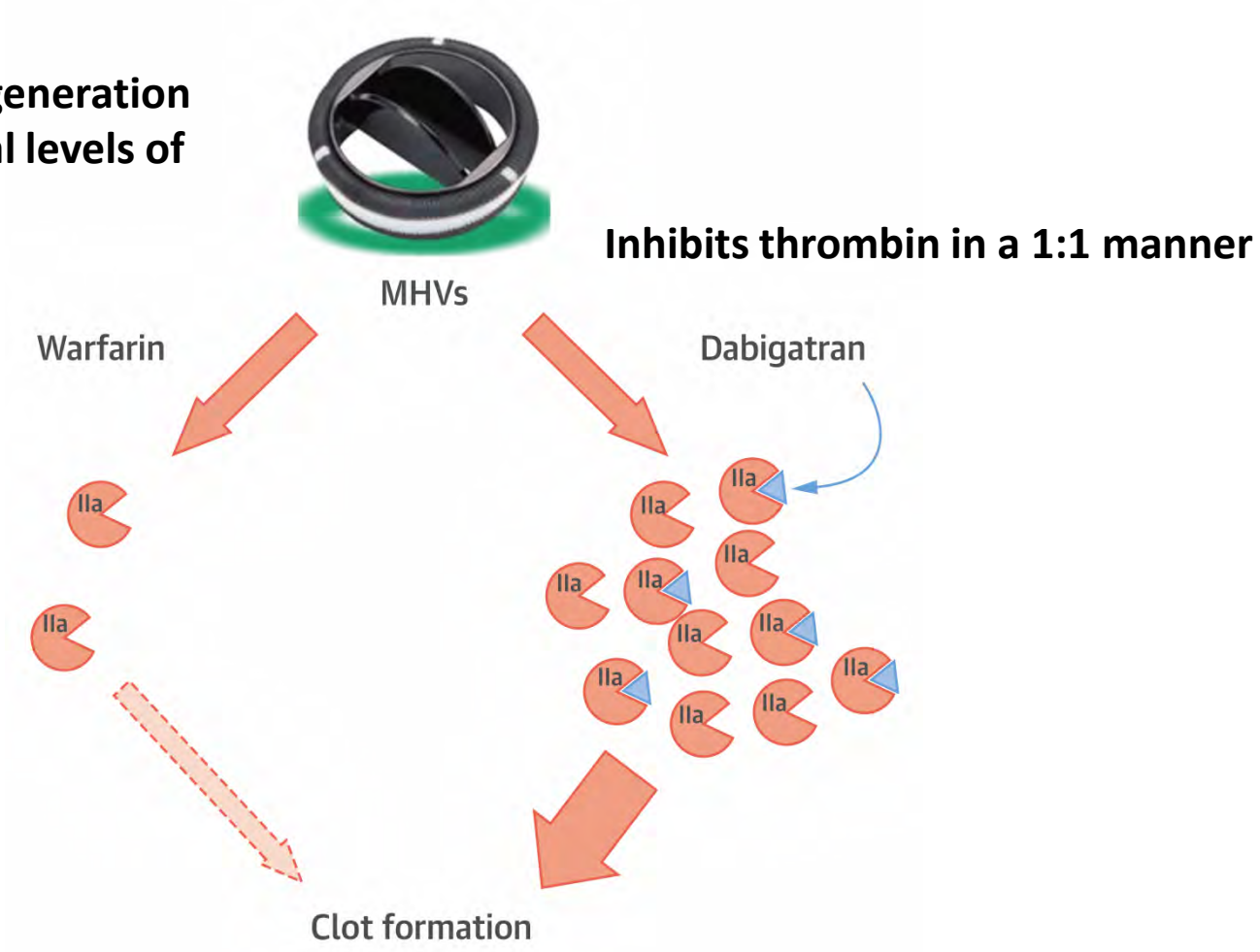
First bleeding event



Eikelboom et al. N Engl J Med 2013;369:1206-14

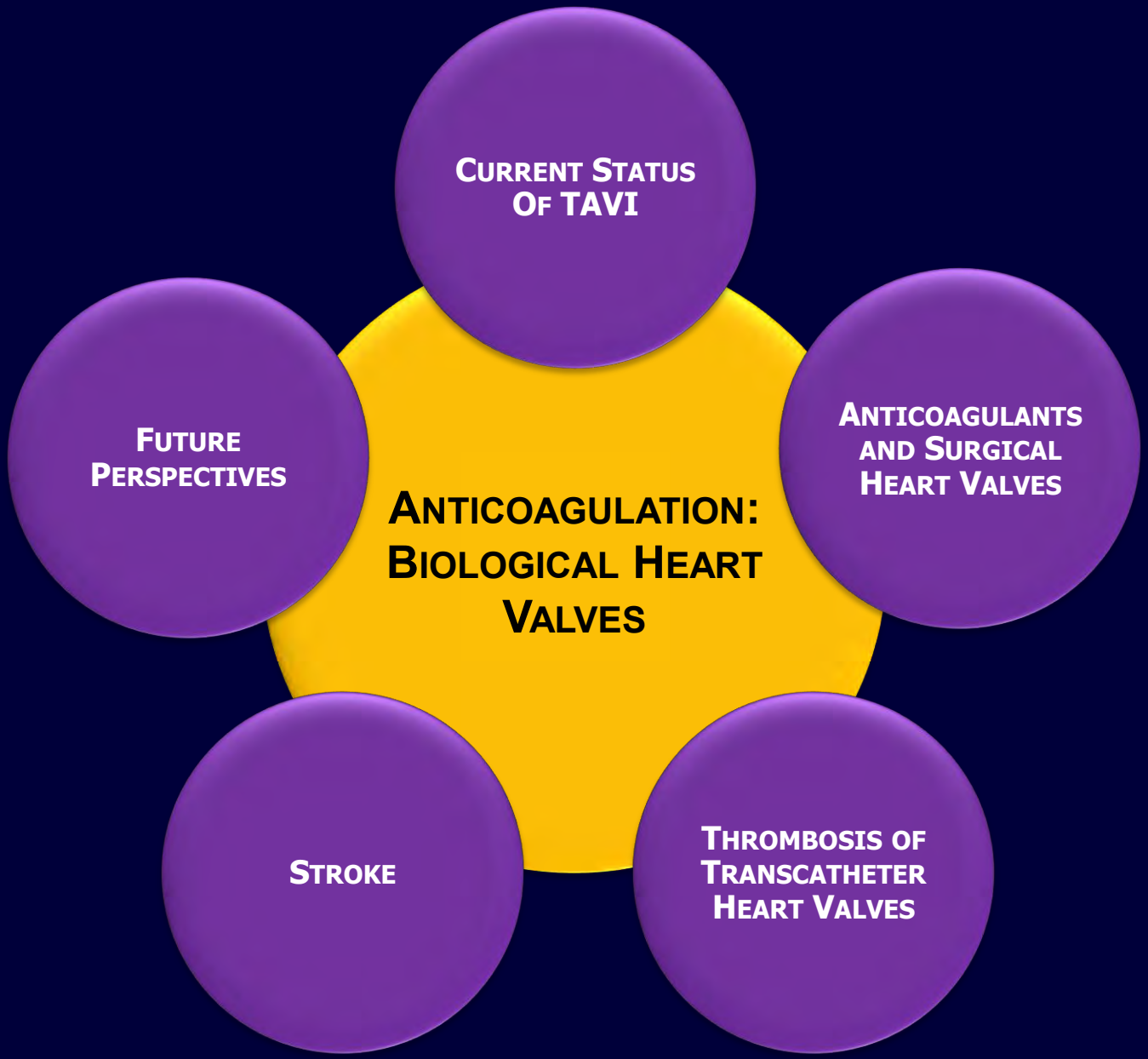
NOAC and Mechanical Heart Valves

Attenuates thombin generation by reducing functional levels of fIX, fX, and fII



Inhibits thrombin in a 1:1 manner

Dangas G et al. J Am Coll Cardiol 2016;68:2670–89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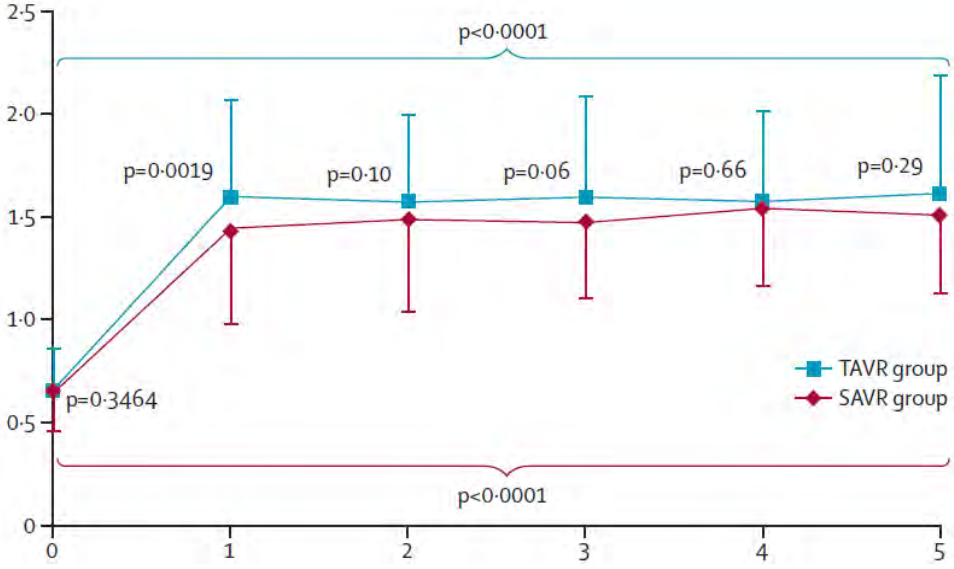
DURABILITY OF TRANSCATHETER HEART VALVES

PARTNER 1A

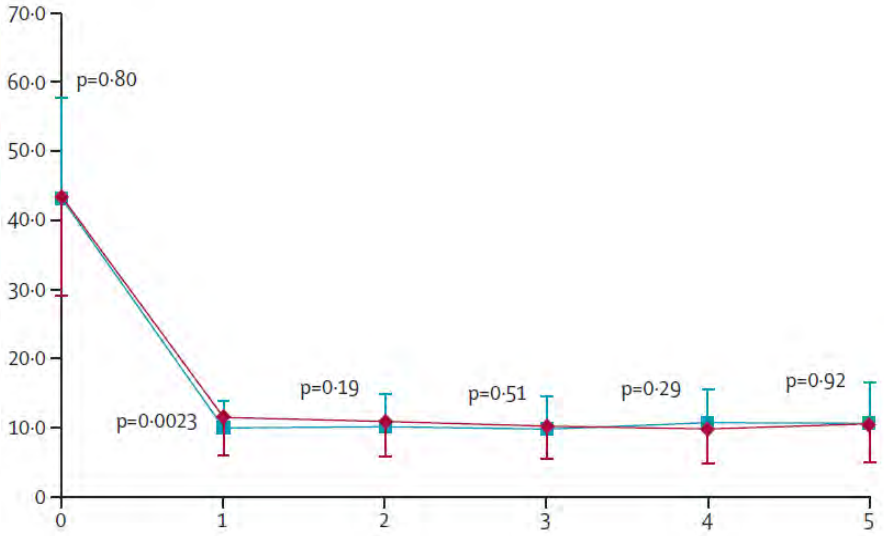
MACK MJ ET AL. *LANCET* 2015

5-Years Follow-up

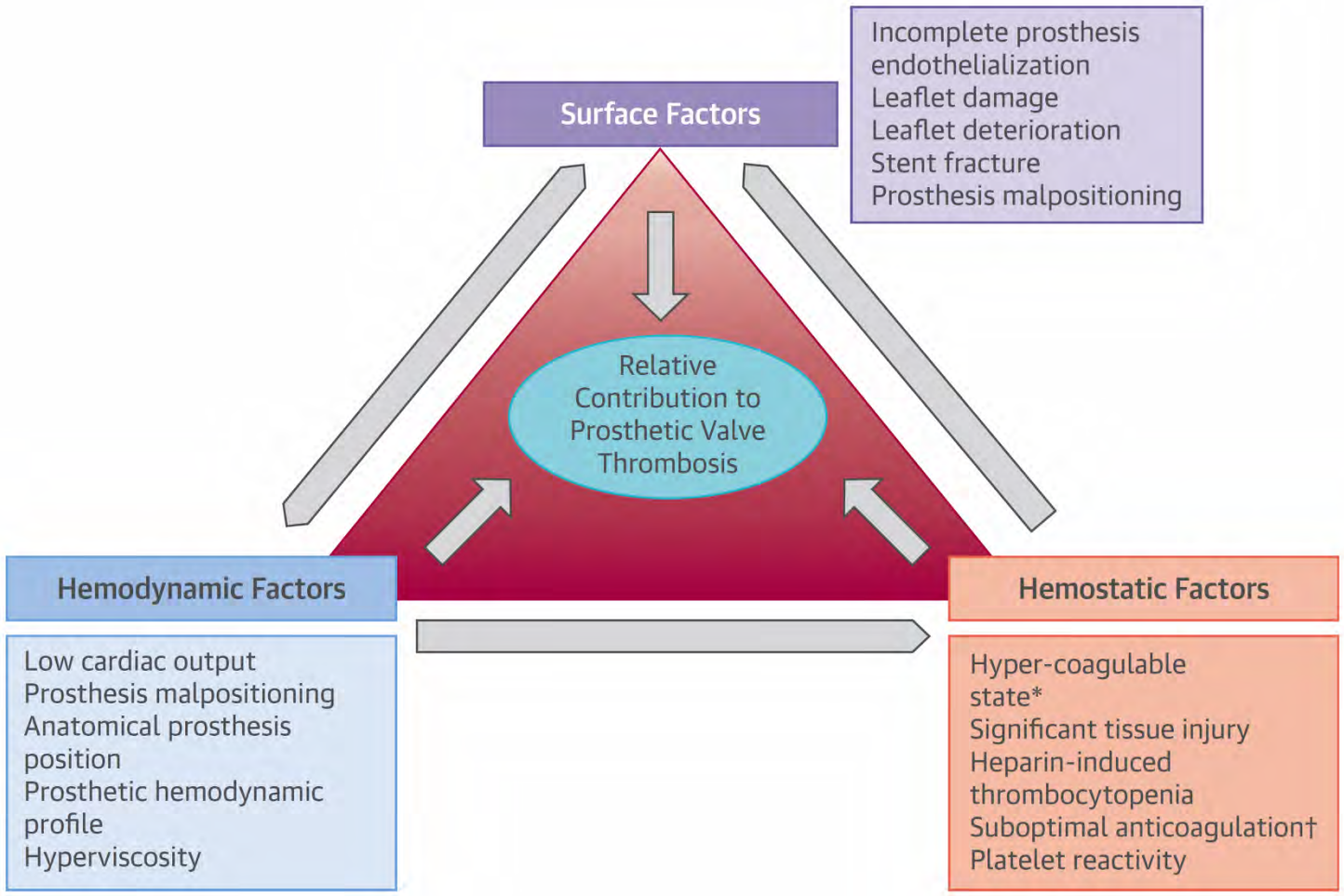
Mean valve area (cm²)



Mean gradient (mm Hg)



Mechanisms of Bioprosthetic Valve Thrombosis



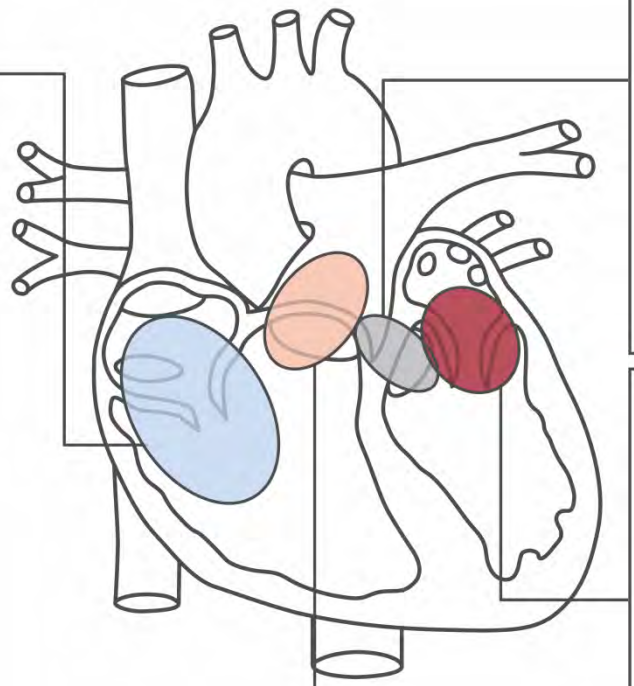
Dangas G et al. J Am Coll Cardiol 2016;68:2670–89

Anatomic Location and Bioprosthetic Valve Thrombosis

≈ 20 times more frequent than with the mitral valve

Right-sided heart valves
clotting pathway > platelet pathway

Left-sided heart valves
platelet pathway > clotting pathway



TRICUSPID VALVE

1. Hemodynamic factors
   - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
2. Hemostatic factors
   - Hypercoagulability
   - Tissue injury
3. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning

PULMONIC VALVE

1. Hemodynamic factors
   - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
2. Hemostatic factors
   - Hypercoagulability
3. Surface factors
   - Valve frame fracture

AORTIC VALVE

1. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning
2. Hemostatic factors
   - Tissue injury
   - Prosthesis malpositioning
3. Hemodynamic factors
   - Local blood flow turbulences
   - Incomplete apposition

MITRAL VALVE

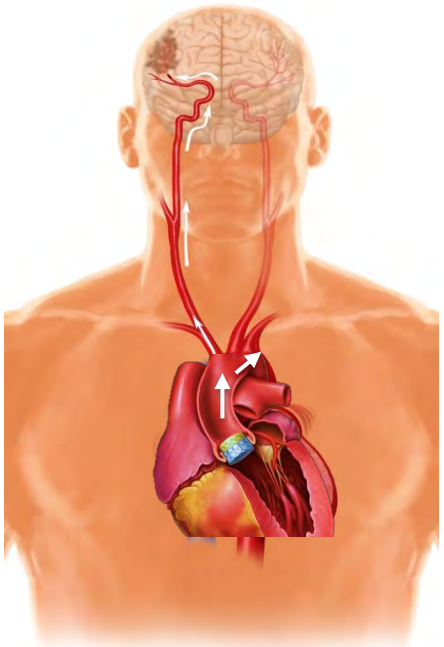
1. Hemodynamic factors
   - Relatively slow blood flow in case of AF, atrial dilation or low LV output.
   - Local blood flow turbulences
   - Incomplete apposition
2. Hemostatic factors
   - Tissue injury
3. Surface factors
   - Incomplete prosthesis endothelialization.
   - Prosthesis malpositioning
   - Leaflet injury

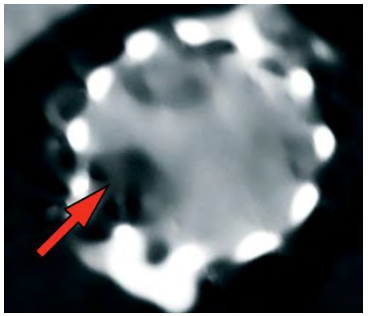
≈ 2-3 times more frequent than with the aortic valve

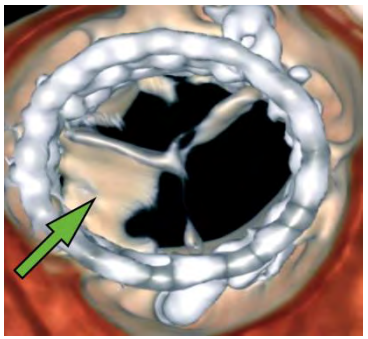
Dangas G et al. J Am Coll Cardiol 2016;68:2670–89

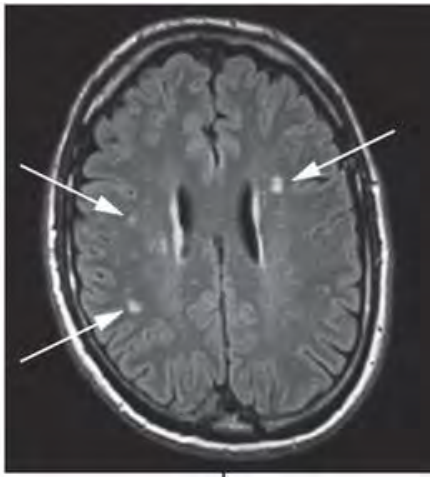
Clinical Spectrum of Prosthetic Valve Thrombosis

Clinically Apparent	Subclinical	Silent
Valve dysfunction	Hypoattenuating opacities	Silent Brain Infarction
Stroke/TIA	Reduced leaflet motion	
Systemic embolism		









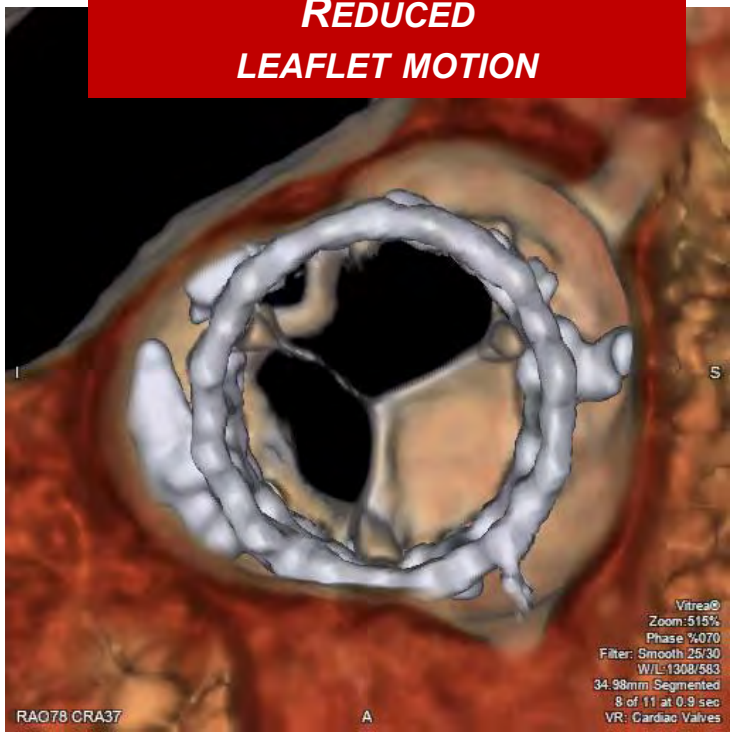
SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

Makkar RR et al. *N Engl J Med* 2015

- ***Incidence: 17 of 132 patients (13%)***
- ***Reduced incidence with oral anticoagulation (0% vs 29%, p=0.04)***
  Restoration of leaflet motion in all 11 patients who received oral anticoagulation
- ***Higher incidence of stroke/TIA in patients with leaflet motion abnormality (18% vs 1%, p=0.007)***

HYPOATTENUATING OPACITIES

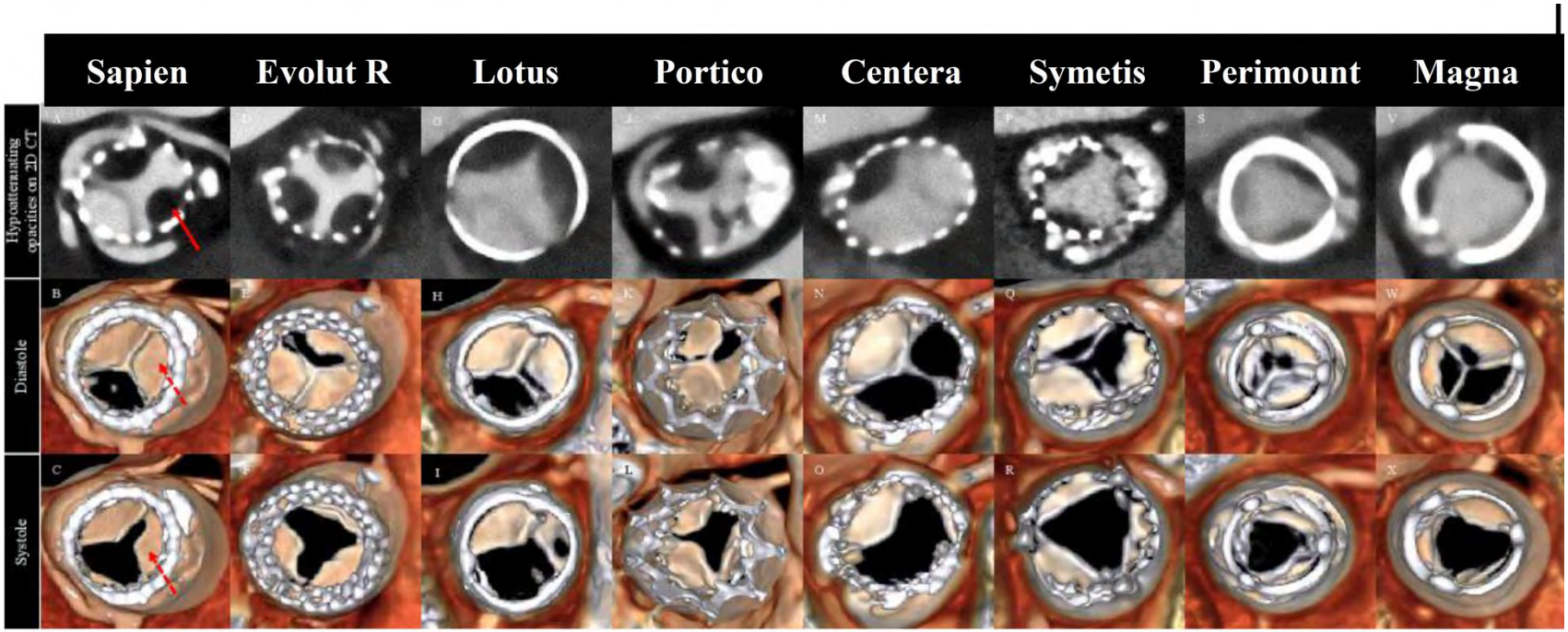
REDUCED LEAFLET MOTION



Subclinical Leaflet Thrombosis in Bioprosthetic Valves

Chakravarty et al. Lancet 2017

- *890 patients with interpretable CT scans were included (RESOLVE registry, n=626; SAVOR Registry, n=264)*
- *Incidence: 12%: 4% after SAVR and 13% after TAVR (p<0.001)*



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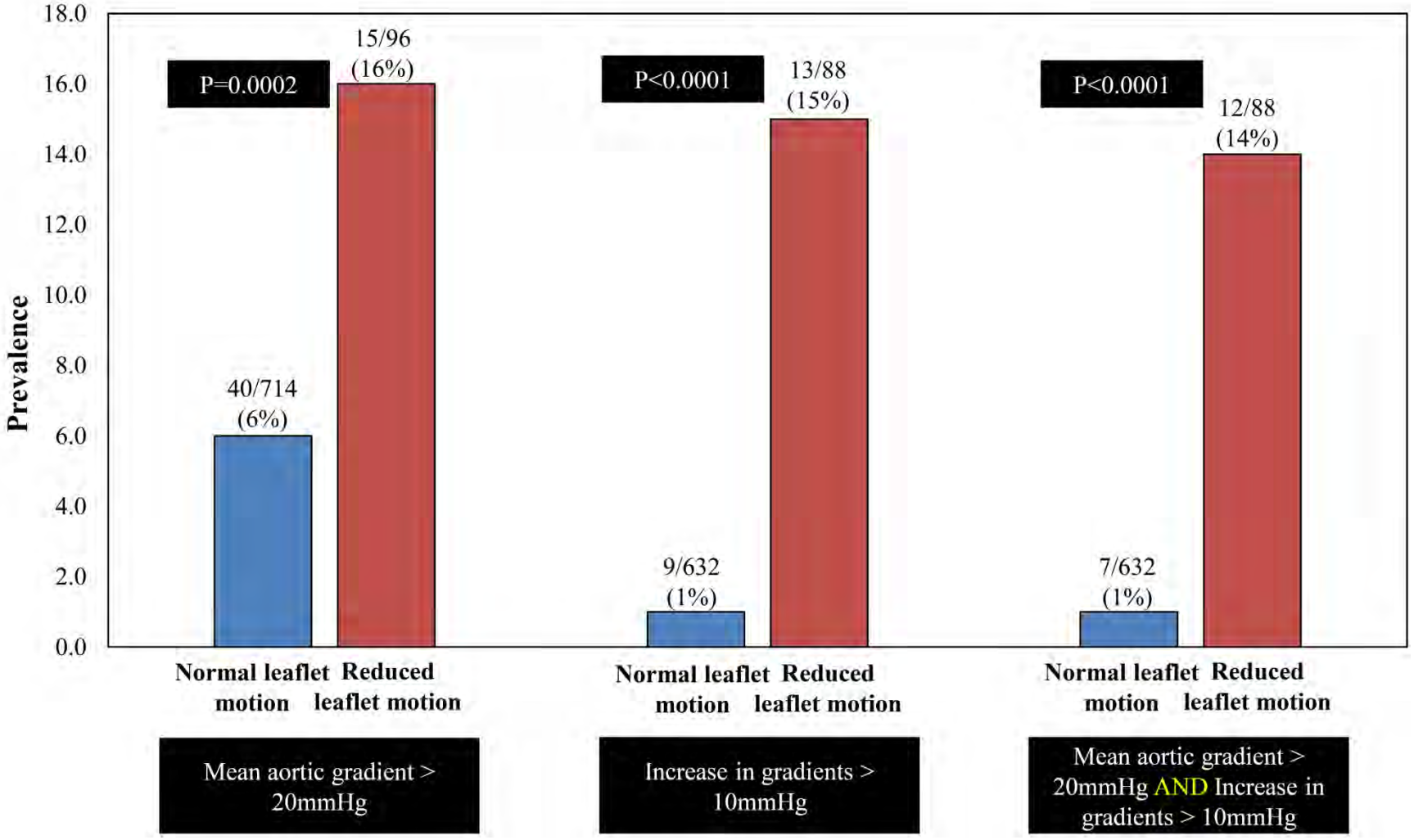
Chakravarty et al. *Lancet* 2017



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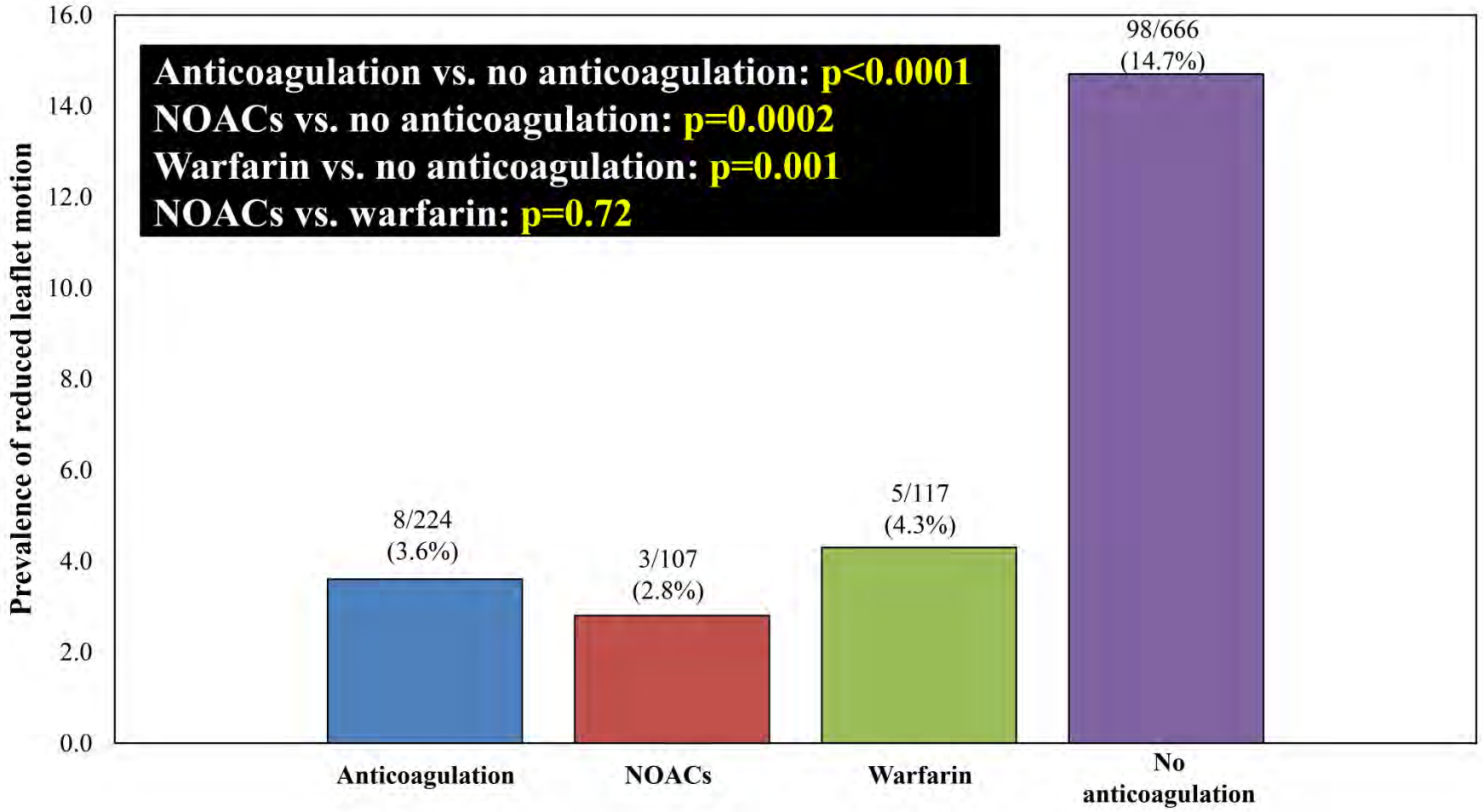
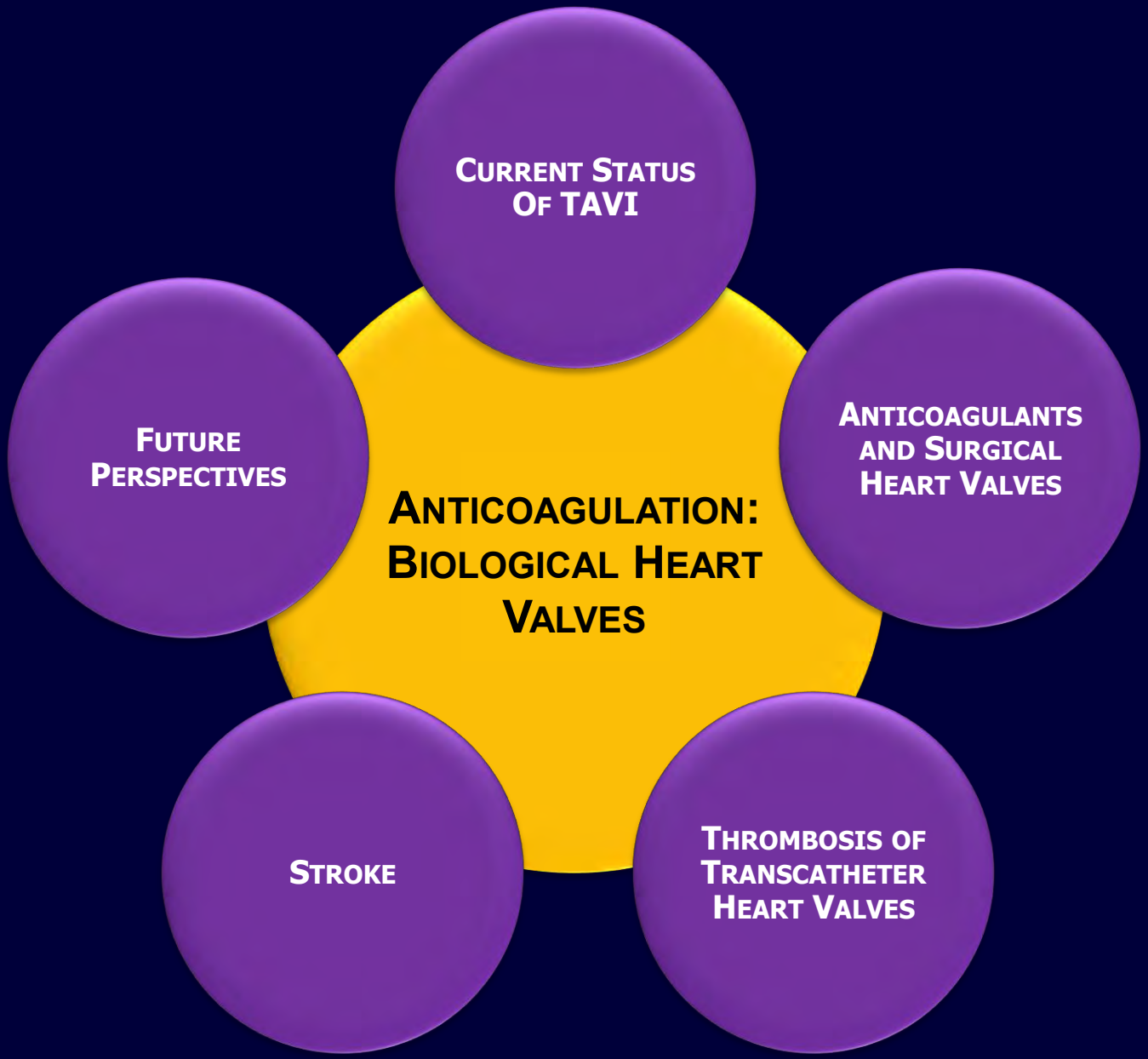
Chakravarty et al. Lancet 2017

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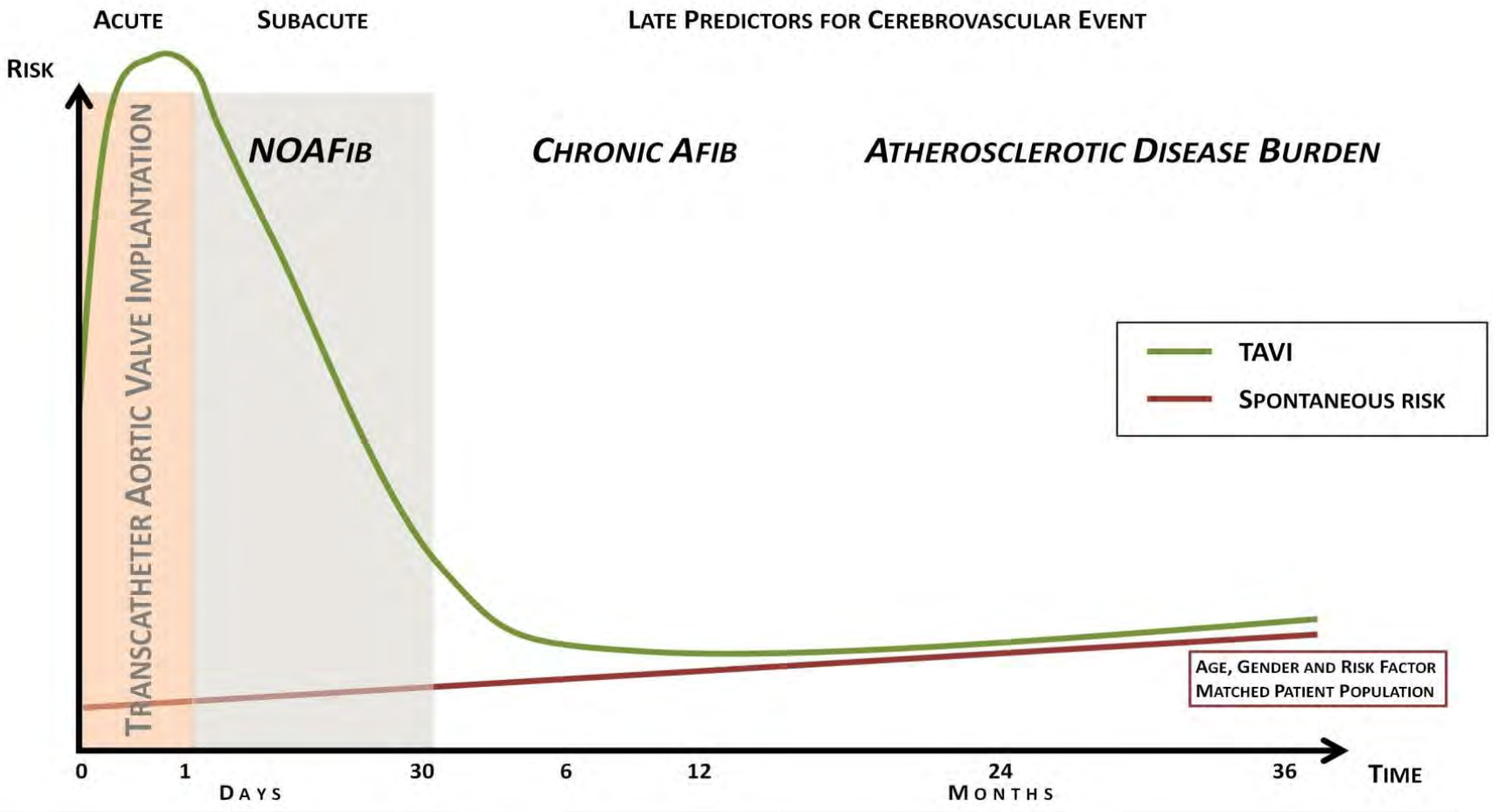
TAVI and Cerebrovascular Events

Stortecky, Windecker. *Circulation* 2012;126:2921-4

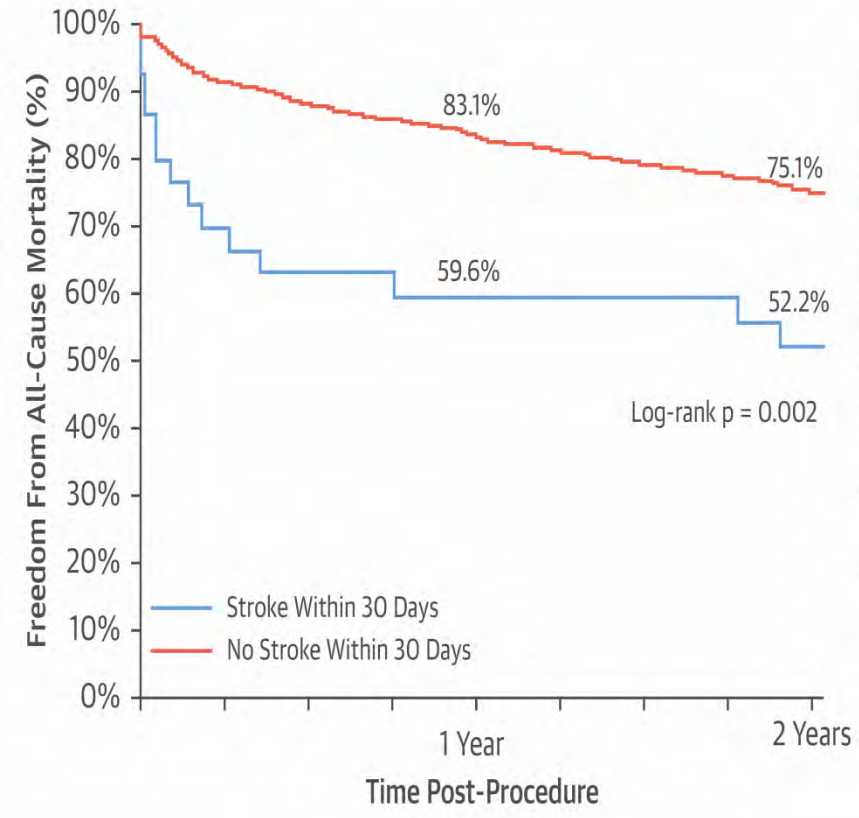


Effect Of Cerebrovascular Events On Mortality

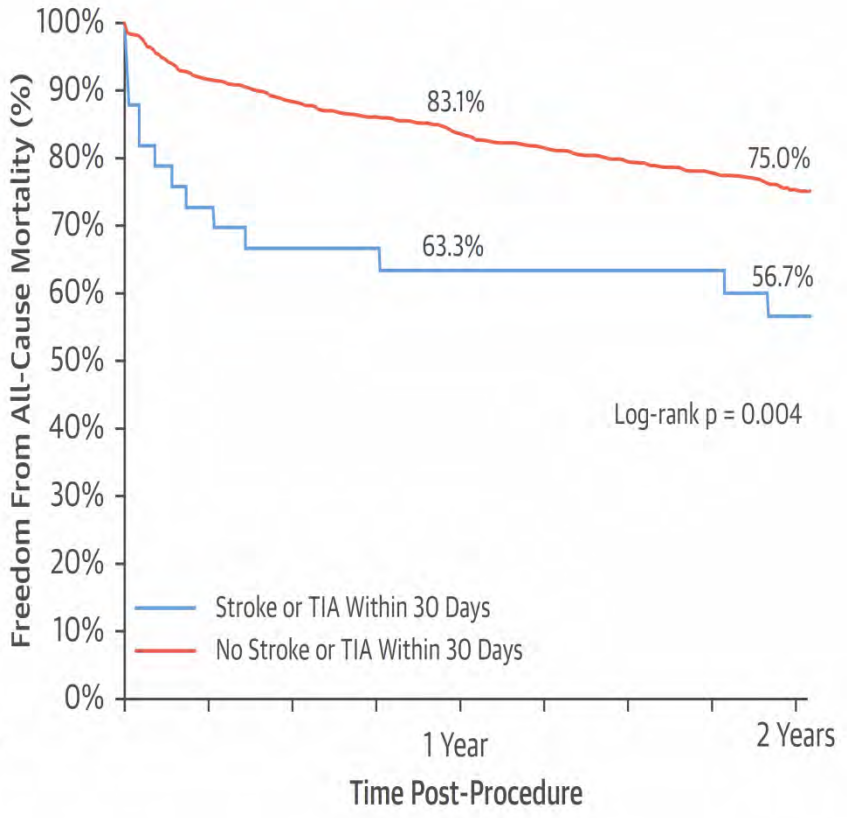
Bosmans et al. *J Am Coll Cardiol* 2015; 66:209-17

ADVANCE (N=1,015)

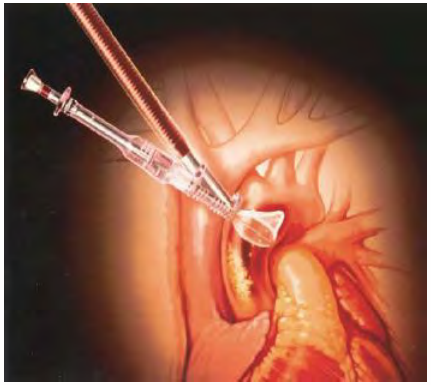
Stroke

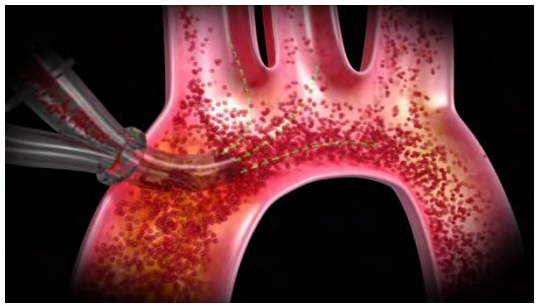


Stroke or TIA



EMBOLIC PROTECTION DEVICES AND SAVR





Randomized
(n=383)

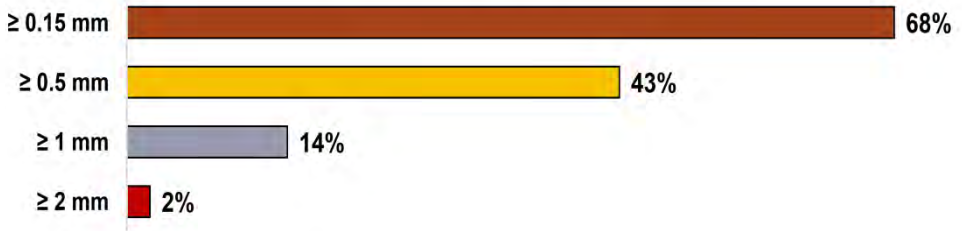
Embol-X
(n=133)

Shared
Control
(n=132)

CardioGard
(n=118)

Percent of Embol-X Patients with at Least One Particle of a Given Size

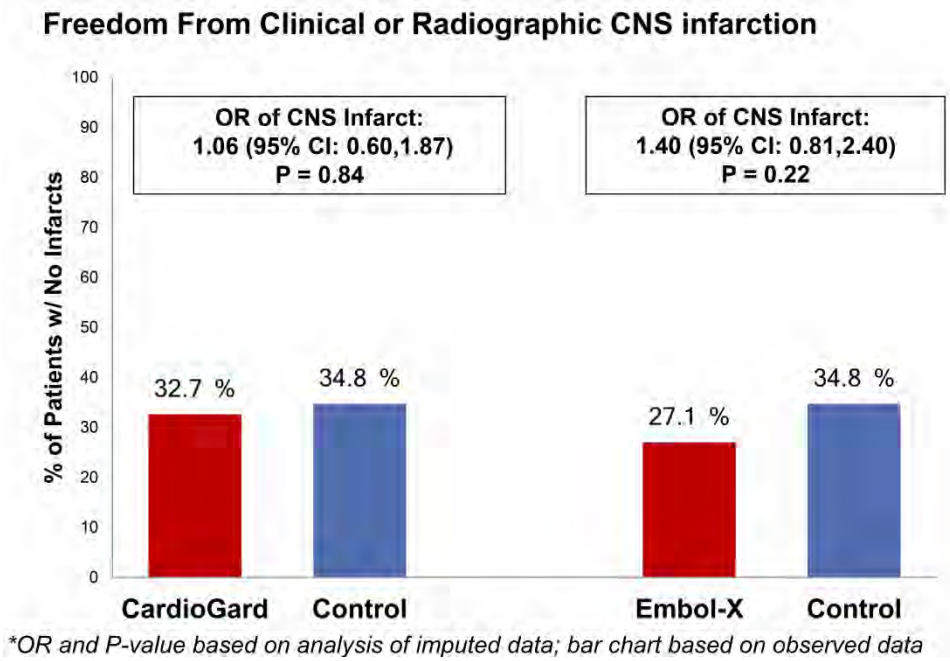
Percent of Cardiogard Patients with at Least One Particle of a Given Size



Mack M . ACC 2017

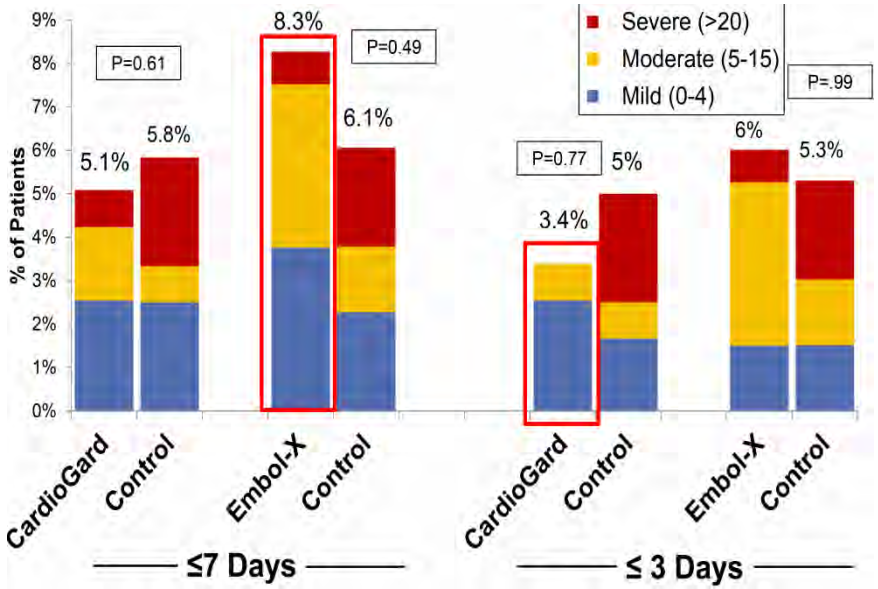
EMBOLIC PROTECTION DEVICES AND SAVR

Primary Endpoint



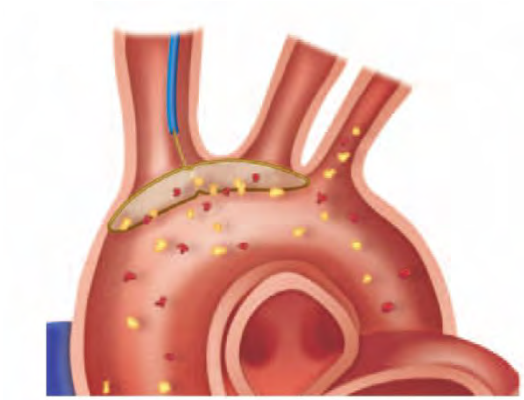
*OR and P-value based on analysis of imputed data; bar chart based on observed data

Stroke

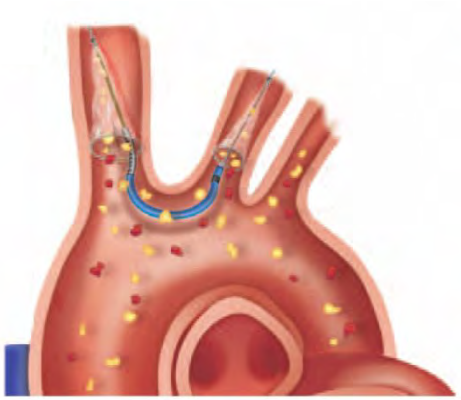


Mack M . ACC 2017

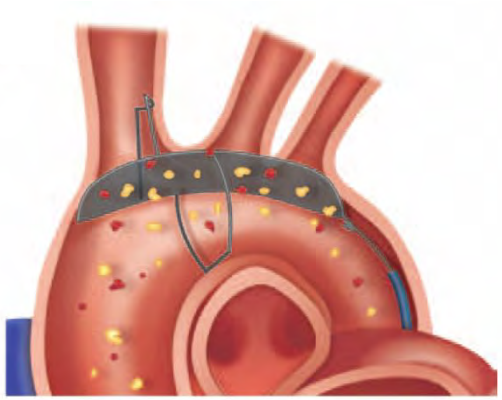
EMBOLIC PROTECTION DEVICES AND TAVI



Embrella Deflector (Edwards LifeSciences)



Montage 2 Capture Device (Claret Medical)



Triguard Cerebral Deflector (Keystone Heart)

EVIDENCE FROM RANDOMIZED TRIALS

PROTAVI-C

RODÉS-CABAU ET AL JACC CARDIOVASC INTERV. 2014

41 patients

↓ **average volume of ischemic lesion**

CLEAN-TAVI

HAUSSIG ET AL JAMA 2016

100 patients

↓ **frequency of ischemic cerebral lesions**

SENTINEL

KAPADIA ET AL JACC 2017

363 patients

No significant reduction of lesion volume on MRI

DEFLECT III TRIAL

LANSKY ET AL EUROPEAN HEART JOURNAL 2015

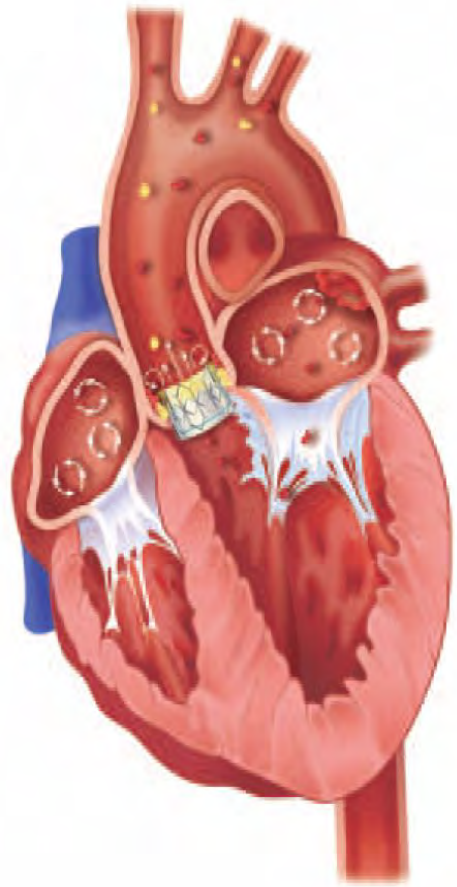
85 patients

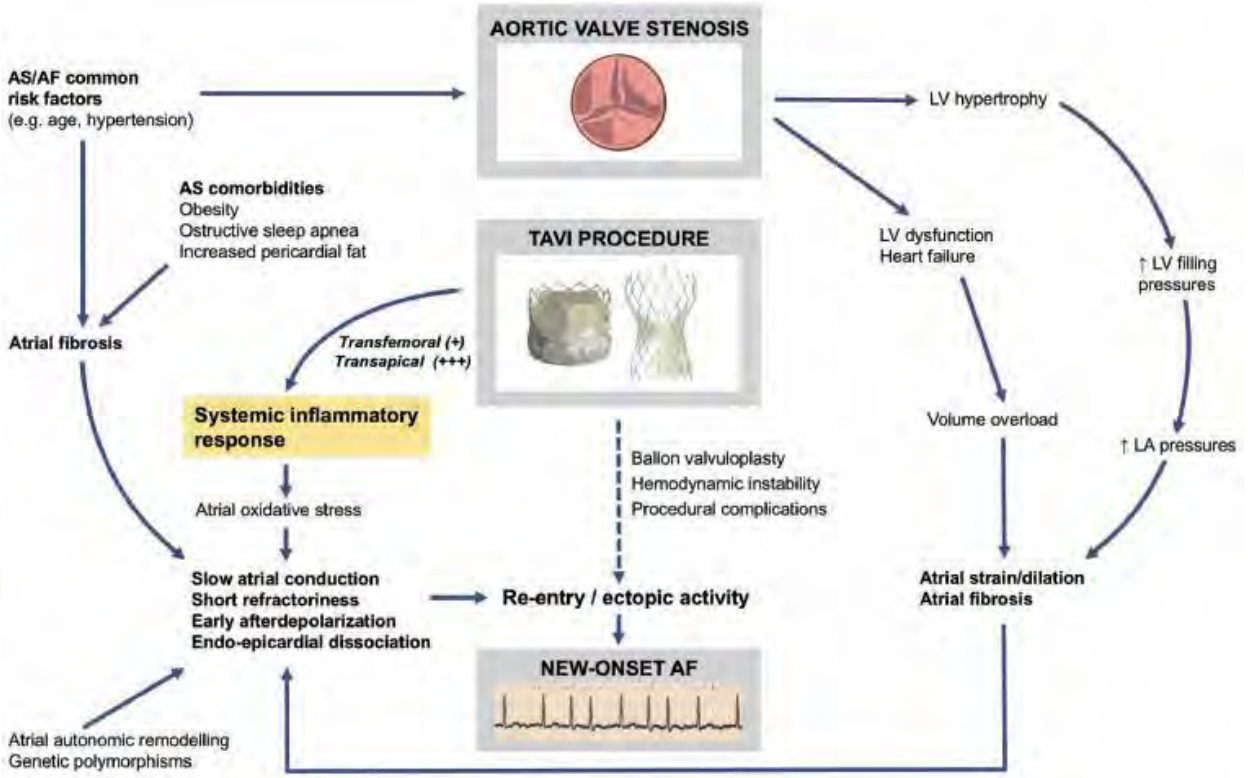
↓ **new ischemic brain lesions and neurologic deficits**

↑ **cognitive function**

LATE THROMBOEMBOLIC EVENTS AFTER TAVI

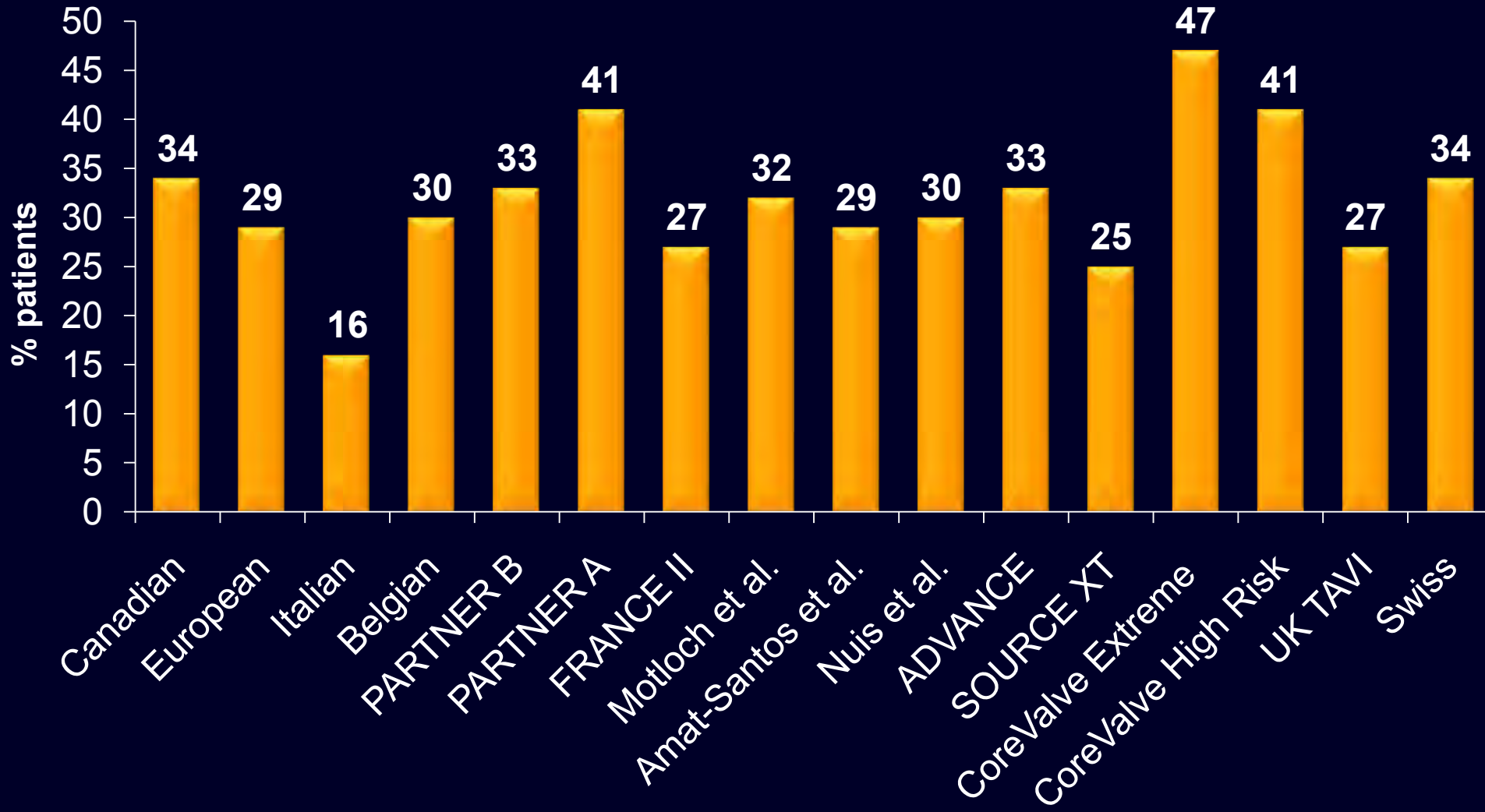
Subacute Embolization → **Atrial fibrillation**





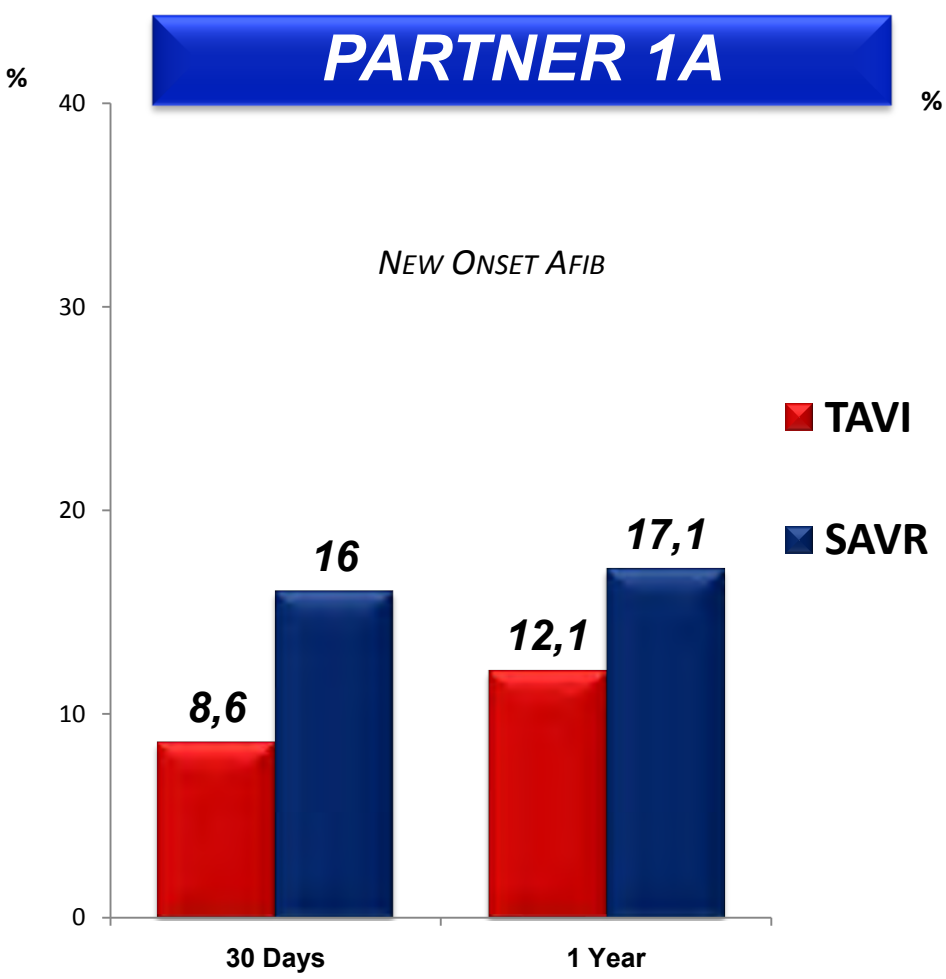
Tarantini et al. European Heart Journal (2016) 0, 1–12

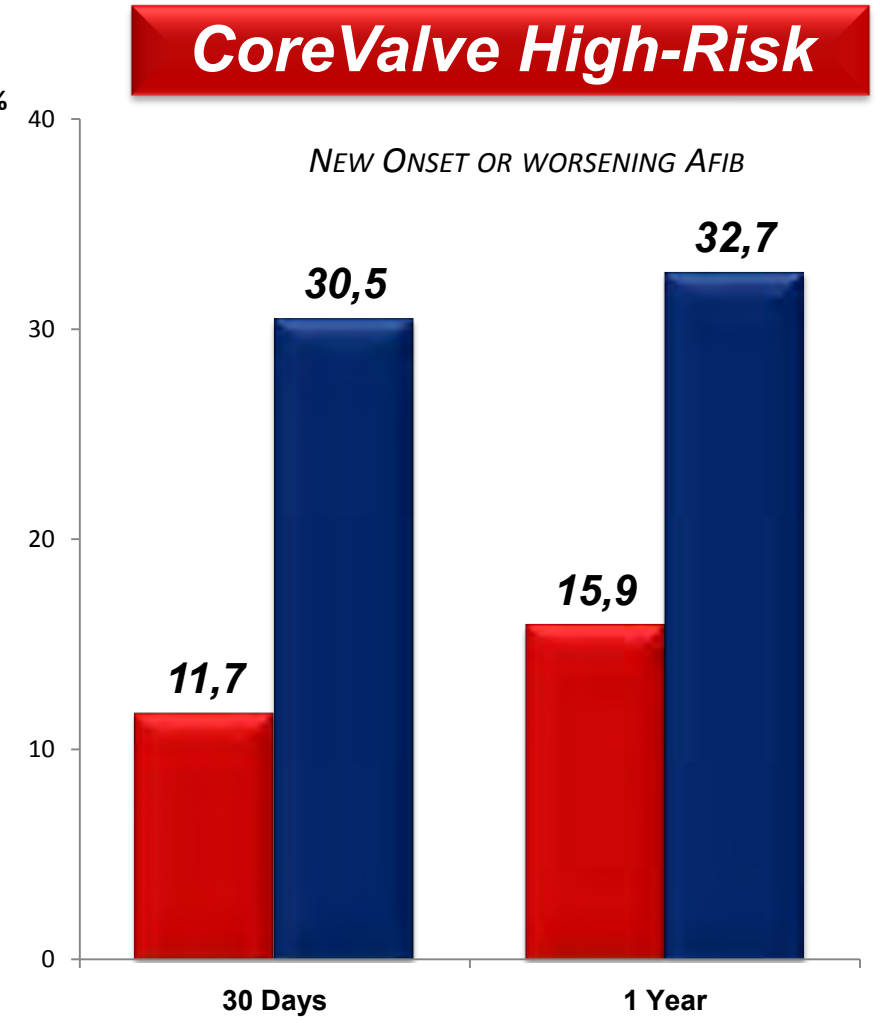
Baseline AFib in TAVI Candidates



1-Rodes-Cabau et al, JACC 2010
2-Piazza et al, EuroInterv 2008
3-Tamburino et al, Circulation, 2011
4- Bosmans et al, Inter Cardiovasc and Thor Surg, 2011
5-Leon et al, NEJM 2010
6-Smith et al, NEJM 2011
7-Gilard et al, NEJM 2012
8-Motloch et al, Ann Thorac Surg 2011
9-Amat-Santos et al, JACC 2012
10-Nuis et al, Am J Cardiol 2012
11-Linke at al, TVT 2012
12-Wendler et al, EuroPCR 2012
13-Popma et al, JACC 2014
14-Adams et al, NEJM 2014
15-Ludman. Circulation 2015
16-Stortecky. Circ Cardiov Intv 2013

New Onset Atrial Fibrillation





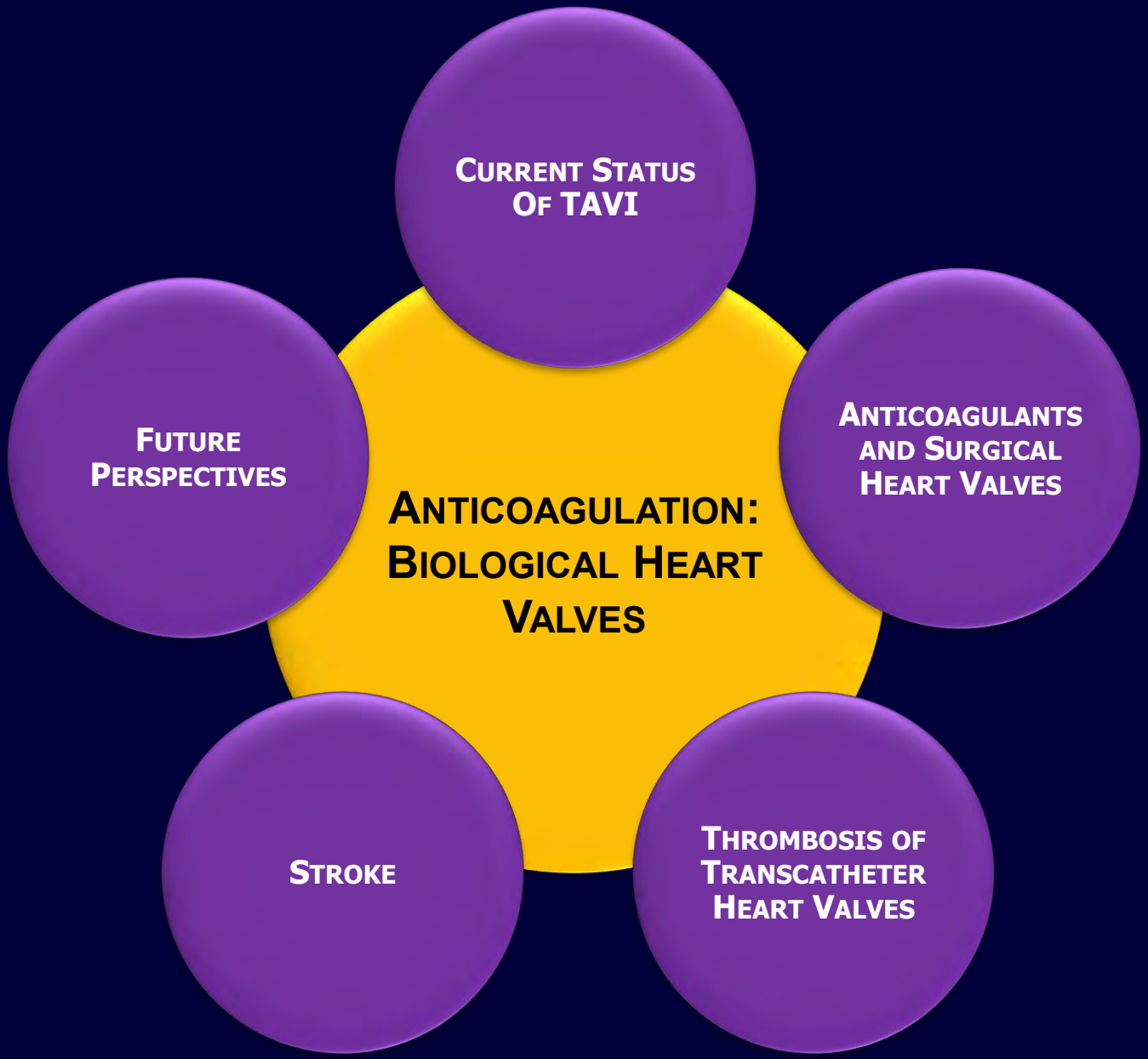
SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

Chakravarty et al. *Lancet* 2017

	Normal leaflet motion (N=784)		Reduced leaflet motion (N=106)			
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years	Hazard ratio (95% CI)	p-value
All events						
Death	34/784 (4.3%)	2.91	4/106 (3.8%)	2.66	0.96 (0.34-2.72)	0.94
Myocardial infarction	4/784 (0.5%)	0.34	1/106 (0.9%)	0.67	1.91 (0.21-17.08)	0.56
Strokes/TIAs	27/784 (3.4%)	2.36	11/106 (10.4%)	7.85	3.27 (1.62-6.59)	0.001
All strokes*	22/784 (2.8%)	1.92	6/106 (5.7%)	4.12	2.13 (0.86-5.25)	0.10
Ischemic strokes	21/784 (2.7%)	1.83	6/106 (5.7%)	4.12	2.23 (0.90-5.53)	0.08
TIAs	7/784 (0.9%)	0.60	6/106 (5.7%)	4.18	7.02 (2.35-20.91)	0.0005

TIA=Transient ischemic attack

* All strokes include hemorrhagic and ischemic strokes


Current Status Of TAVI
Anticoagulants and Surgical Heart Valves
Thrombosis of Transcatheter Heart Valves
Stroke
Future Perspectives
Anticoagulation: Biological Heart Valves

Current Recommendations for Management of Antiplatelet Therapy after TAVI

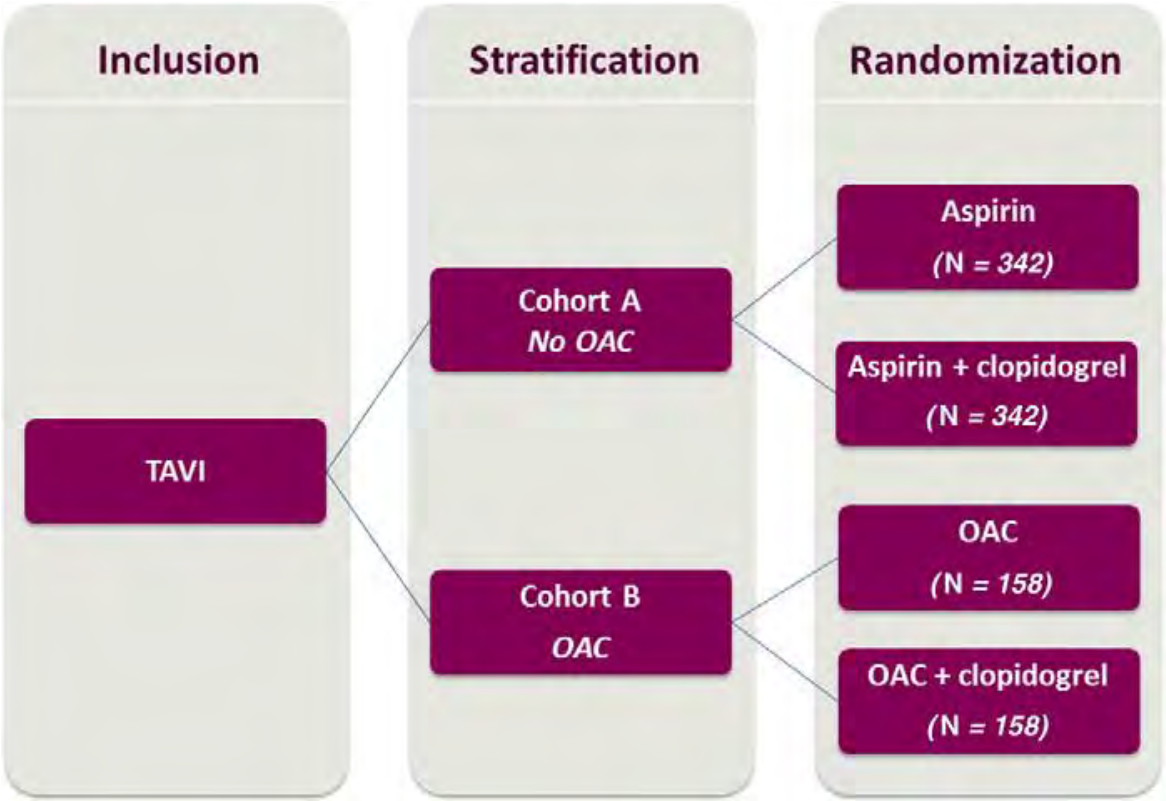
ESC[1]	ACC/AHA[2]	ACCP Consesus[3]
Low-dose aspirin and a thienopyridine early after the procedure followed by aspirin or a thienopyridine alone	Clopidogrel 75 mg plus aspirin 75–100 mg for 6 months followed by aspirin 75–100 mg daily alone (Class IIb)	Aspirin 50–100 mg plus clopidogrel 75 mg/dl for the first 3 months (Grade 2C) followed by aspirin lifelong

[1]Eur Heart J 2012;33:2451–96; [2]Circulation 2014;129:e521–643; [3]Chest 2012;141:e576S–600S

POPULAR-TAVI

Nijenhuis et al. *Am Heart J* 2016;173:77-85

Study Hypothsis: Monotherapy with Aspirin or OAC monotherapy is safer (non-procedure-related bleeding) than the addition of clopidogrel for 3 months



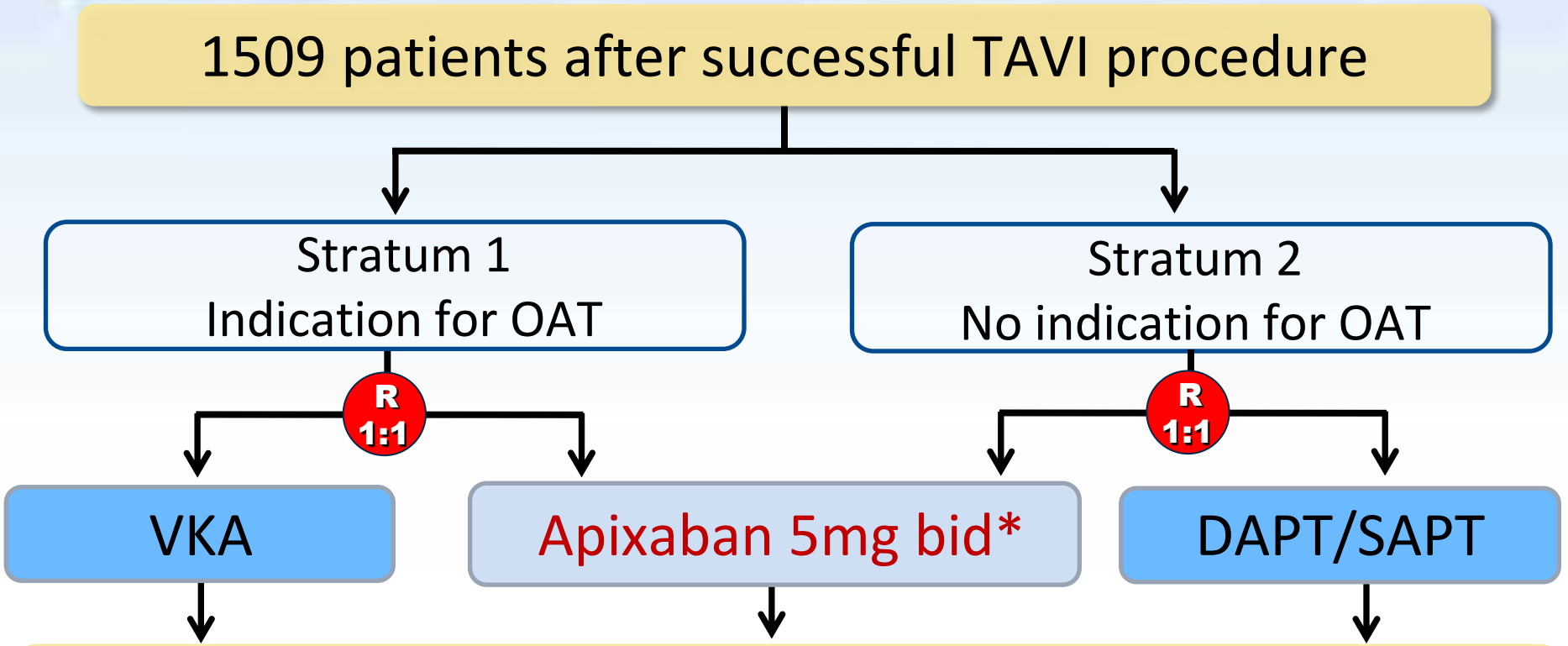
POPular TAVI

ZIEKENHUIS ST ANTONIUS

UMC Utrecht

Recruitment began in February 2014, and the trial will continue until a total of 1,000 patients (684 expected in cohort A and 316 in cohort B) are included and followed up for 1 year.

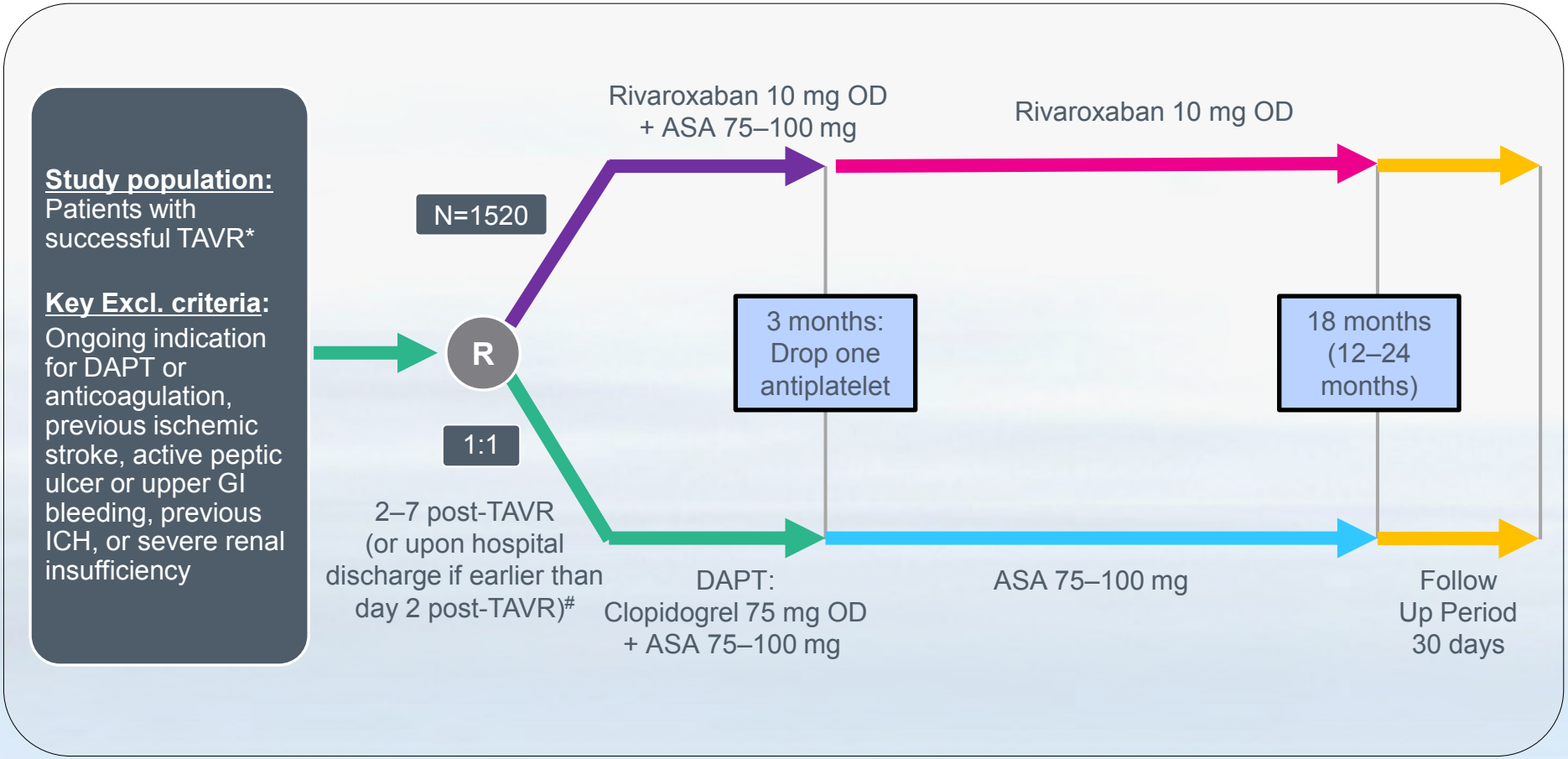
ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis)



Primary end-point is a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism,major bleedings *over one year follow-up*.

*2.5mg bid if creatinine clearance 15-29mL/min or if two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1,5mg/dL (133µMol).

Design overview



*~110 sites in Europe & North America (15 countries); # Majority of patients will be on DAPT after TAVR gastric protection recommended throughout study.
ASA=Acetylsalicylic acid; DAPT=Dual antiplatelet therapy; GI=Gastrointestinal; ICH=Intracranial haemorrhage; OD=Once daily; TAVR=Transcatheter aortic valve replacement.
www.ClinicalTrials.gov Identifier: NCT02556203.

Treatment after new onset of AF (NOAF)

15% of patients develop NOAF after randomisation

1 **Randomised to rivaroxaban**

- Switch to 20 mg OD
- Switch to 15 mg OD for moderate renal impairment*

2 **Randomised to clopidogrel**

- Switch to VKA (target INR: 2–3)

- Follow-up until end of study
  - Included in primary efficacy analysis (ITT)
  - Censoring in secondary analysis

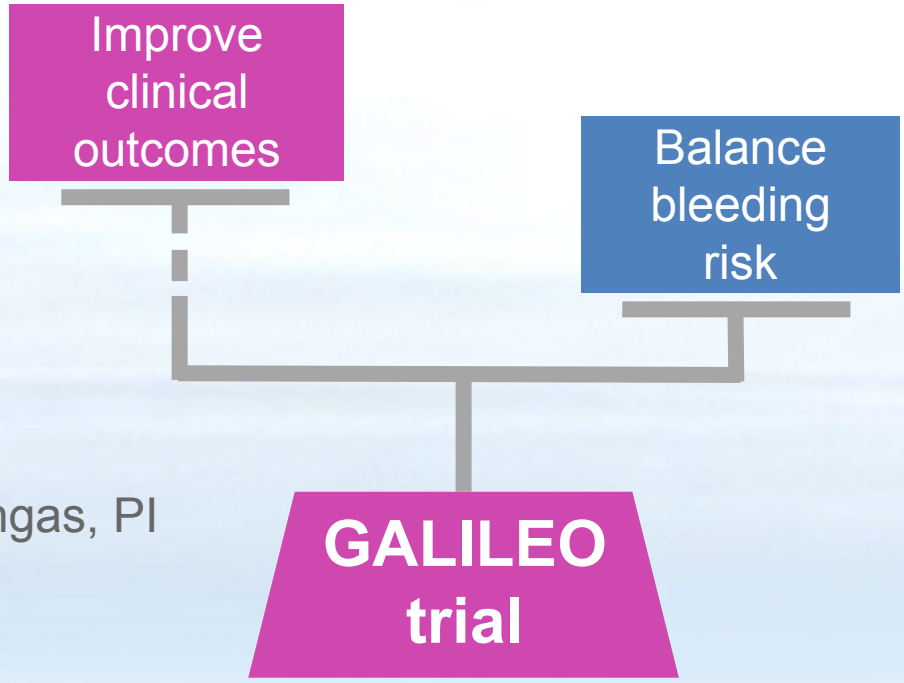
* i.e. CrCl=30–49 mL/min.
CrCl=Creatinine clearance; INR=International normalised ratio; ITT=Intention to treat; NOAF=New onset atrial fibrillation; OD=Once daily; VKA=Vitamin K antagonist.
Unpublished data.

The GALILEO trial: Study design

Global study comparing a riv**A**roxaban-based antithrombotic strategy to an antip**L**atelet-based strategy after transcatheter aort**I**c va**L**ve r**E**placement to **O**ptimize clinical outcomes

Objective

To assess a rivaroxaban-based anticoagulation regimen following successful TAVR balancing ischaemic and bleeding outcome measures



- Stephan Windecker, PI, George Dangas, PI
- Roxana Mehran, Marco Valgimigli
- Pascal Vranckx, Robert Welsh

PI=Principal investigator; TAVR=Transcatheter aortic valve replacement.
www.ClinicalTrials.gov Identifier: NCT02556203.

Conclusions

- **Severe aortic stenosis is associated with increased thrombogenicity;**
- **Increased thrombogenicity may explain in part the risk of CVEs, systemic thromboembolism and valve thrombosis observed in SAVR and TAVR patients;**
- **The use of dual antiplatelet therapy is currently empirical and may be not optimal in targeting mechanisms of thrombus formation;**
- **Oral anticoagulation may represent a valid alternative and its use is supported by indirect proof of effectiveness;**
- **Ongoing randomized trials will improve current limited knowledge on optimal antithrombotic treatment after TAVI.**

TAVI

The New York Times

Henry Kissinger, 92, the former secretary of state, has had the procedure (TAVI).
“I was getting out of breath more easily, and my cardiologist said something had to happen,” he said in a telephone interview. “He said I would be in a wheelchair if I didn’t have it, and my survival rate in a year would be only 50–50.”
“I am more energetic, people tell me I look better, and I feel much less tired,” Mr. Kissinger said. He described the procedure as **easier** and **less debilitating than** the **open-heart bypass surgery** he had previously. “**There’s no comparison**.”