Overview on ongoing RCLs in TAVI ?

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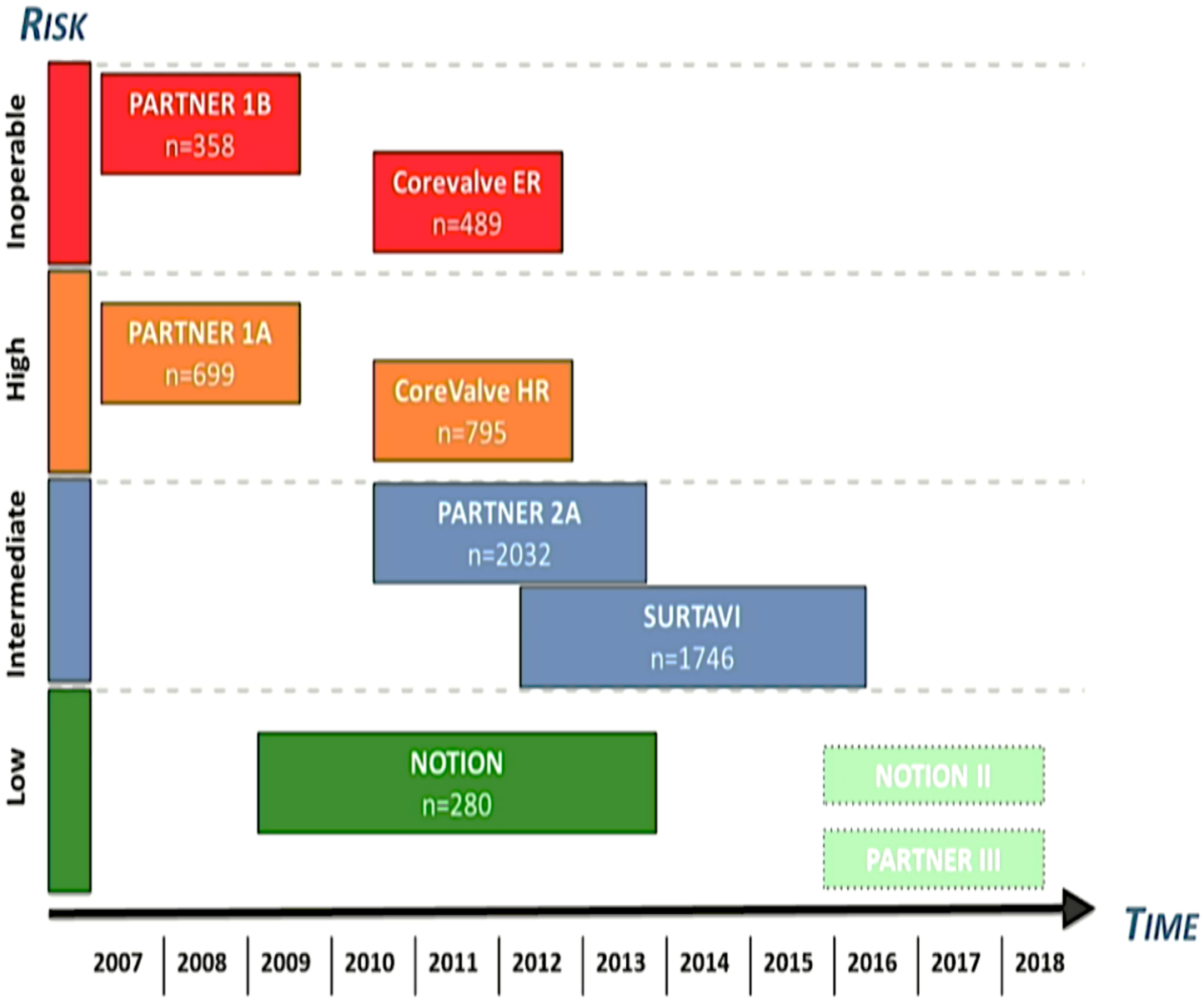
Disclosure related to this presentation: None

Evidence Base Derived From Clinical Trials



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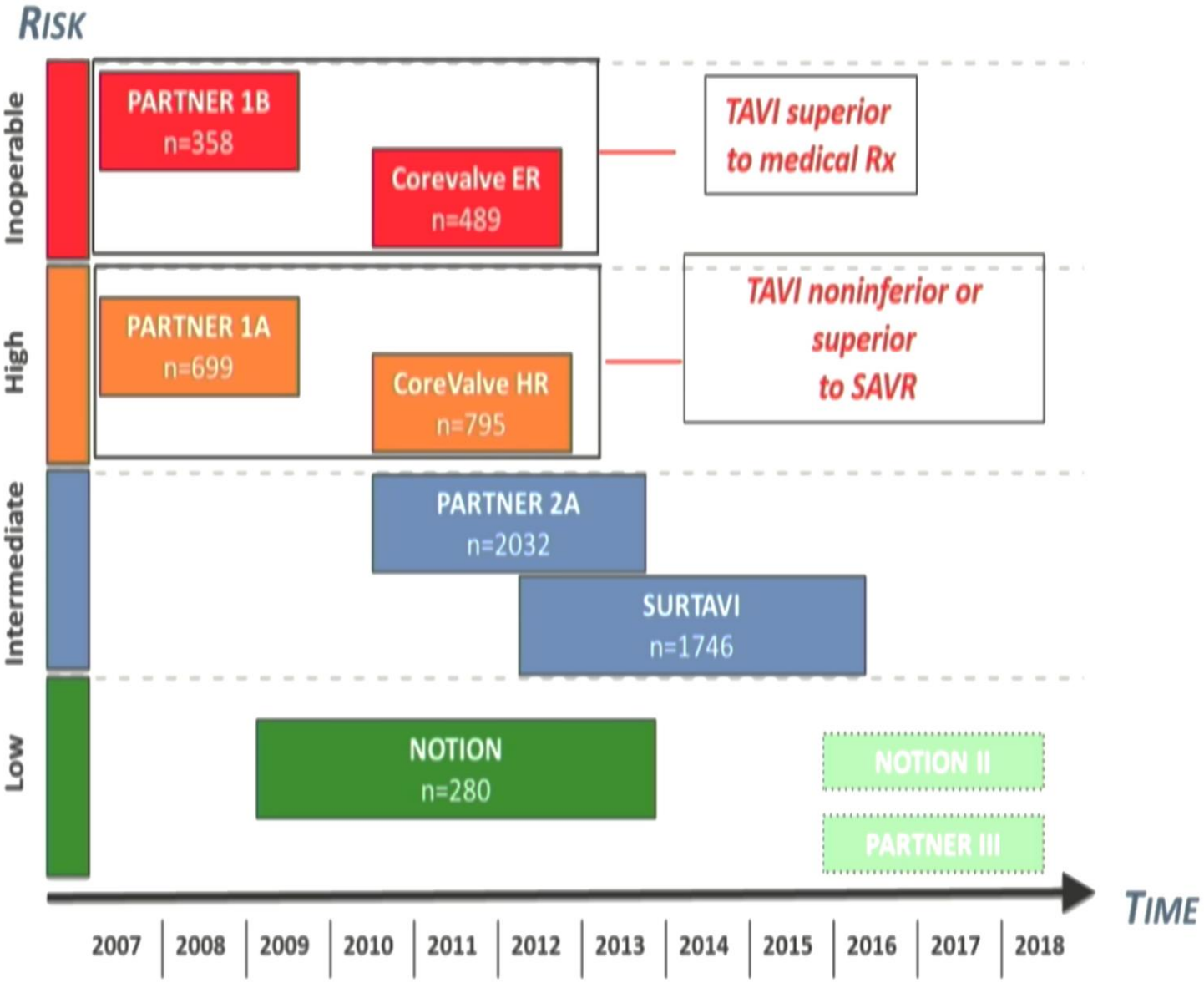

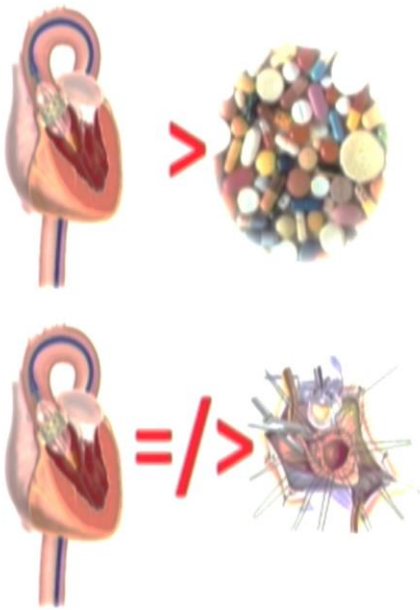

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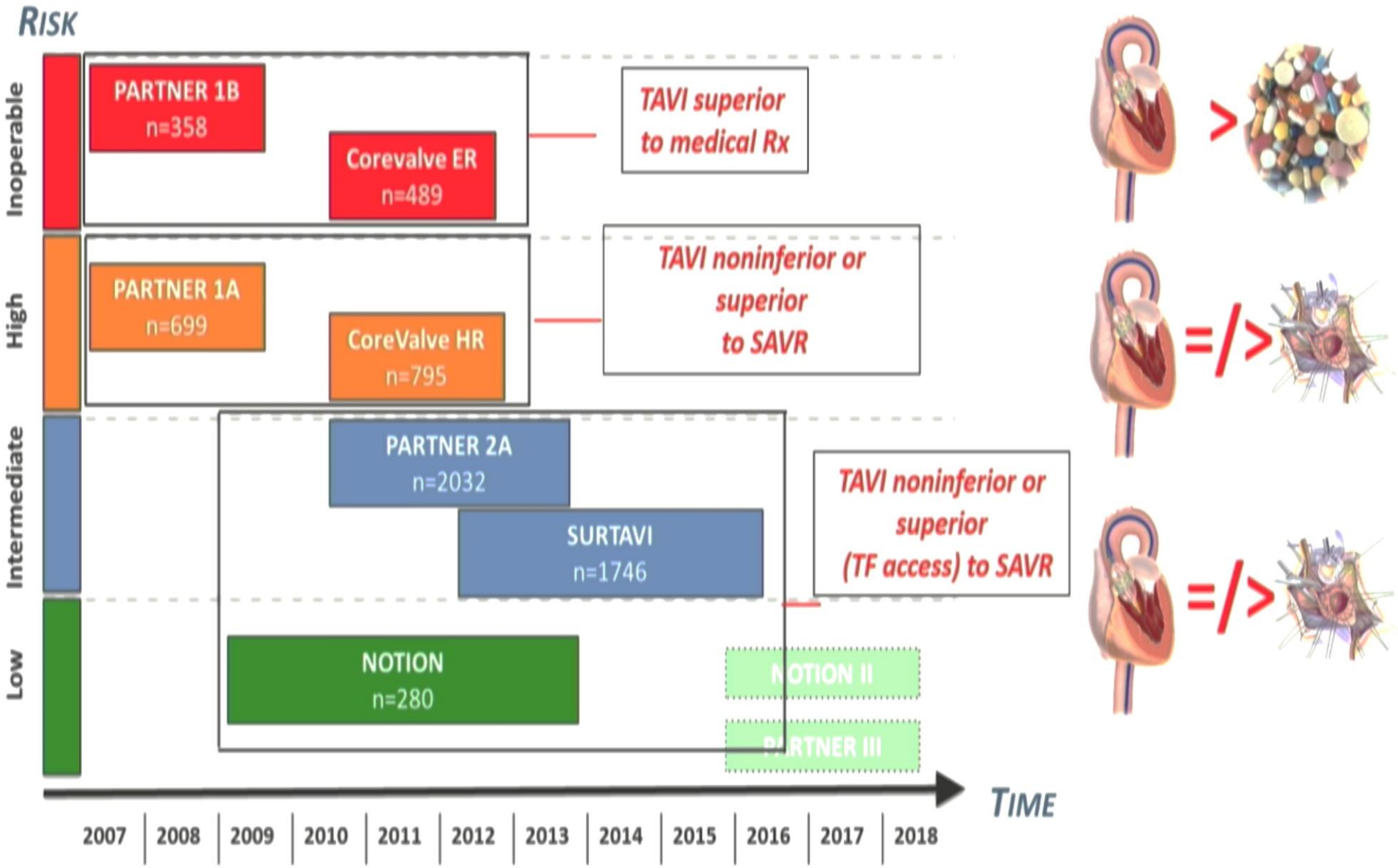
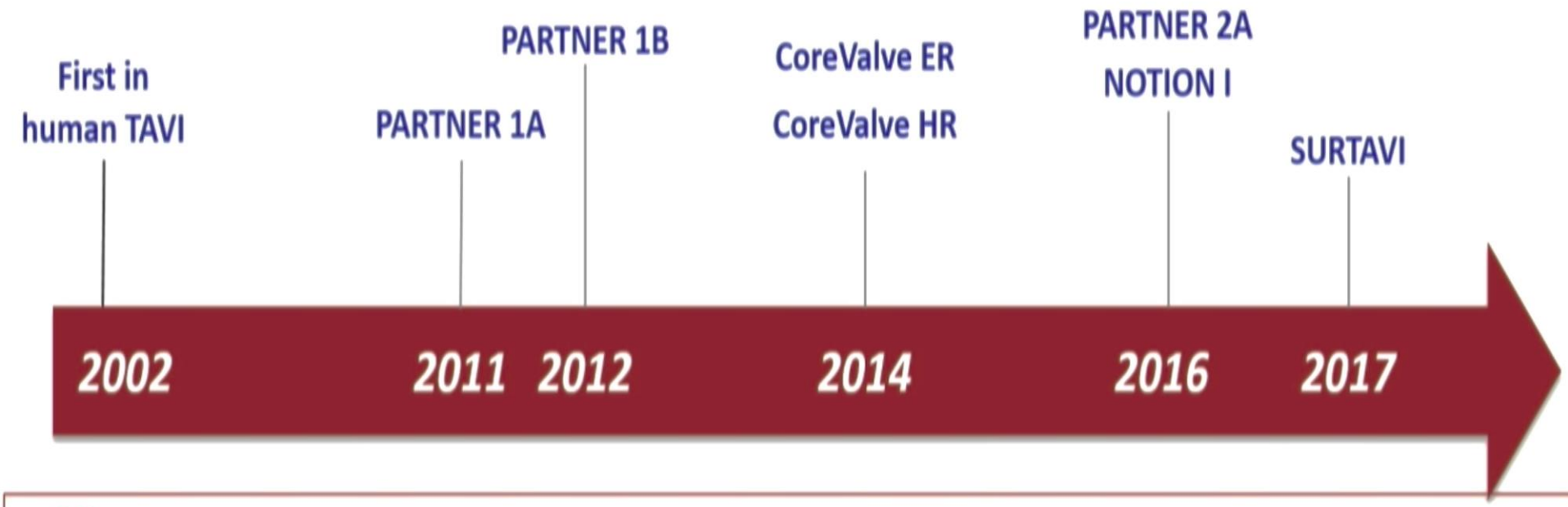


TAVI and Guidelines: European and US Timeline



ESC European Society of Cardiology

EACTS European Association For Cardio-Thoracic Surgery

Extreme risk	I	B
High-risk	IIa	B

Extreme risk	I	B
Increased risk	I	B

American Heart Association.

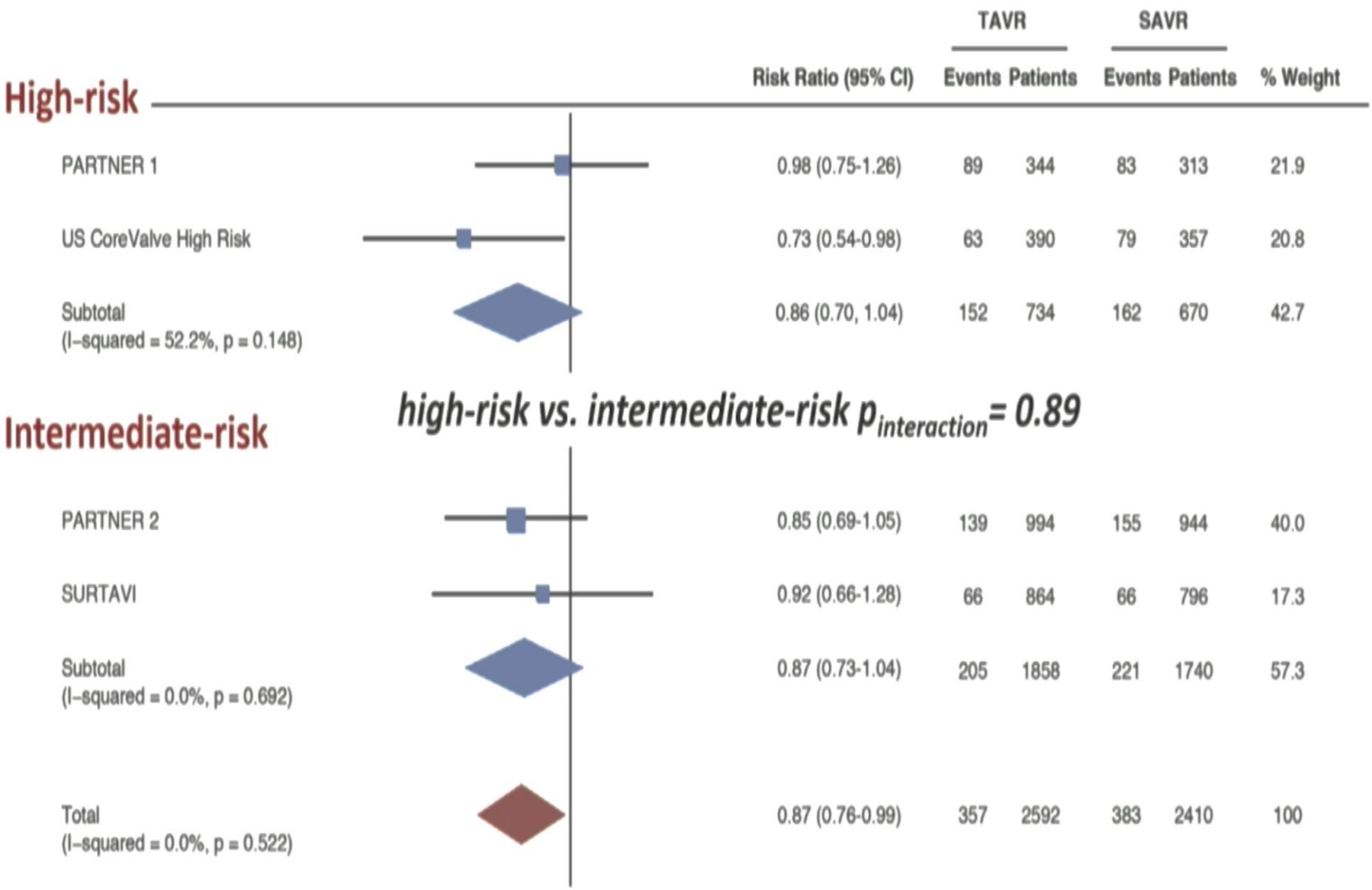
AMERICAN COLLEGE of CARDIOLOGY

Prohibitive risk	I	B
High-risk	IIa	B

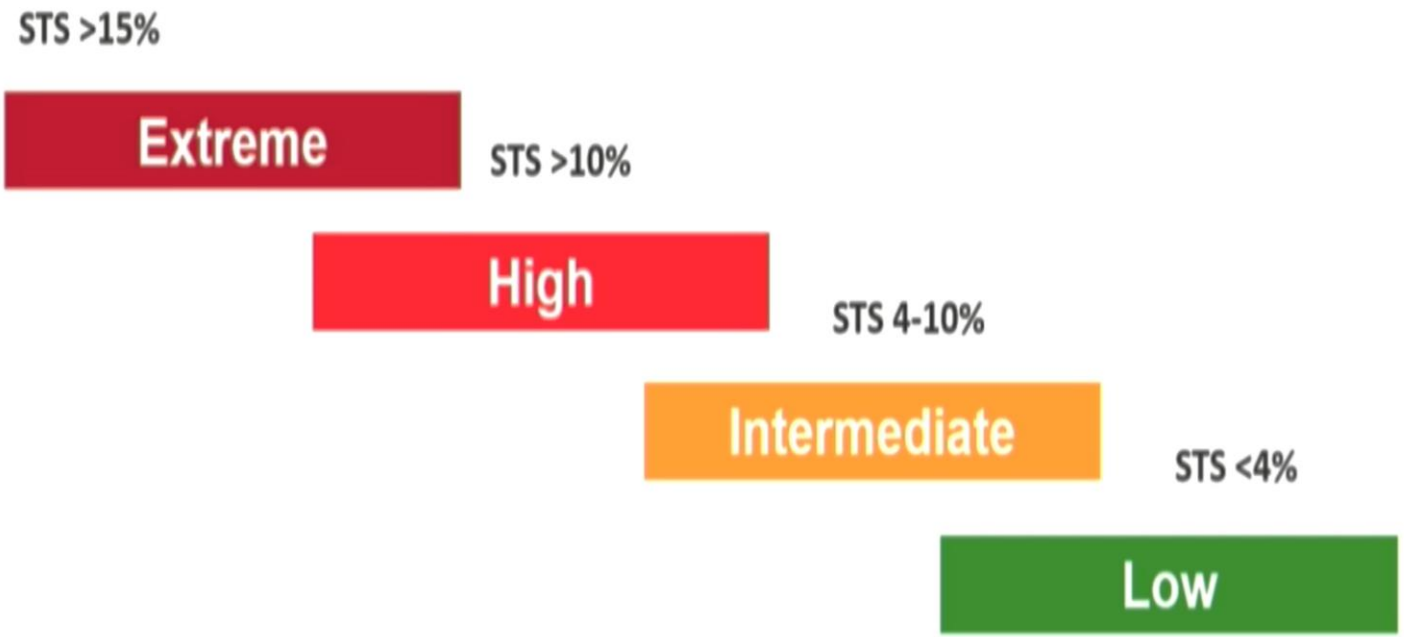
Prohibitive risk	I	A
High- risk	I	A
Intermediate risk	IIa	B-R

META-ANALYSIS OF RCTS

Pagnesi et al *JACC Cardiovasc Interv.* 2017 Sep 25;10(18):1899-1901



2017 ESC/EACTS Guidelines for the Management of AS: Update in Risk Categorization



"The favourable results of TAVI have been reproduced in multiple large-scale, nationwide registries supporting the generalizability of outcomes observed in randomized controlled trials. This favours the use of TAVI over surgery in elderly patients at increased surgical risk. However, the final decision between SAVR and TAVI (including the choice of access route) should be made by the Heart Team."

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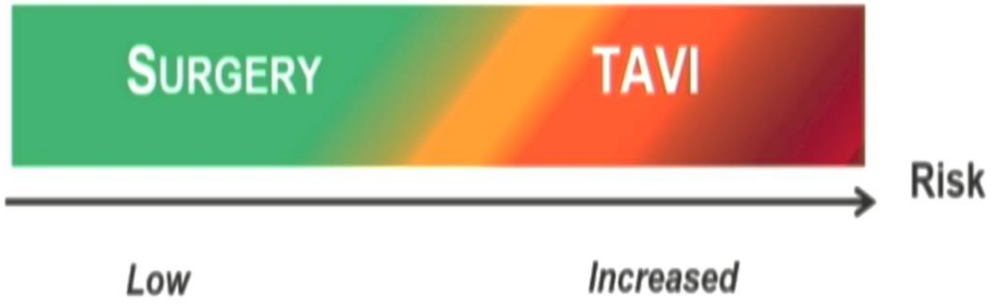

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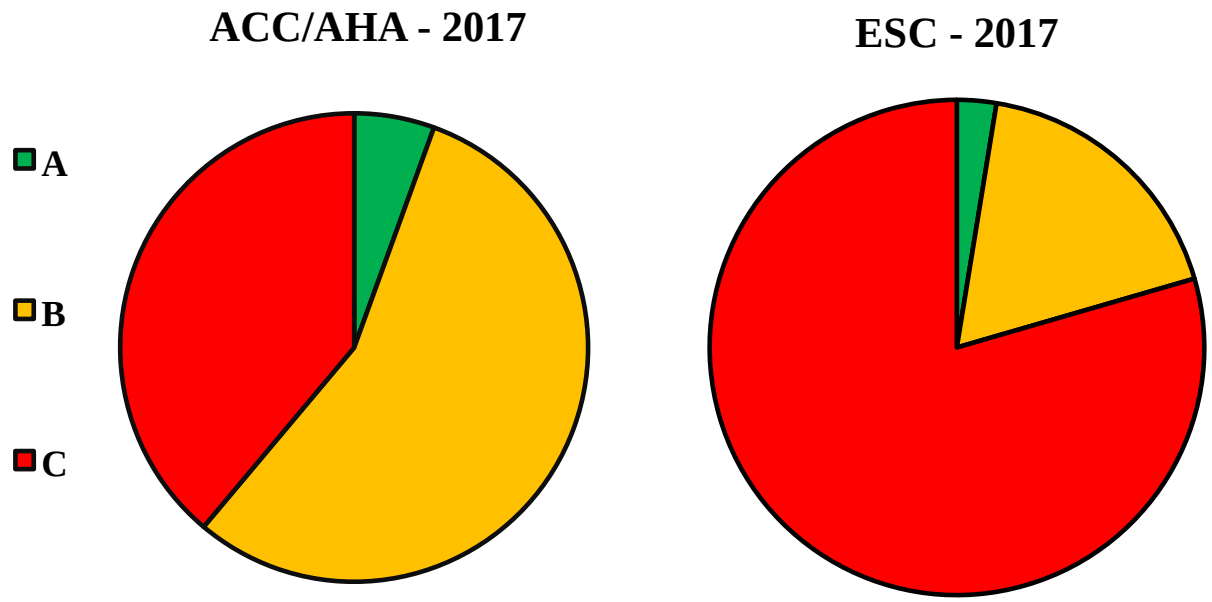
Level of Evidence Pertaining to Prosthetic Valve Management ACC/AHA-2017 and ESC-2017 guidelines



A=level of evidence ‘A’, B=level of evidence ‘B’, C=level of evidence ‘C’

Gaps in Evidence: Expanding Clinical Indications

Gaps in Evidence: Expanding Clinical Indications

Low Risk Patients

PARTNER 3
NCT02675114

Evolut R Low Risk Trial
NCT02701283

NOTION-2
NCT02825134

Asymptomatic Patients

EARLY TAVR TRIAL
NCT03042104

Moderate Aortic Stenosis and Congestive Heart Failure

TAVR UNLOAD TRIAL
NCT02661451

The PARTNER 3 Trial
Study Design

THE PARTNER 3 TRIAL

Symptomatic Severe Calcific Aortic Stenosis

Low Risk ASSESSMENT by Heart Team
(STS < 4%, TF only)

1:1 Randomization
(n=1,228)

TF - TAVR (SAPIEN 3)	Surgery (Bioprosthetic Valve)
CT Imaging Sub-Study (n=200)	CT Imaging Sub-Study (n=200)
Actigraphy/QoL Sub-Study	Actigraphy/QoL Sub-Study

PARTNER 3 Registries

- Alternative Access (n=100) (TA/TAo/Subclavian)
- Bicuspid Valves (n=50)
- SAVR orTAVR ViV (n=100/25)
- Mitral ViV or ViR (n=50/50)

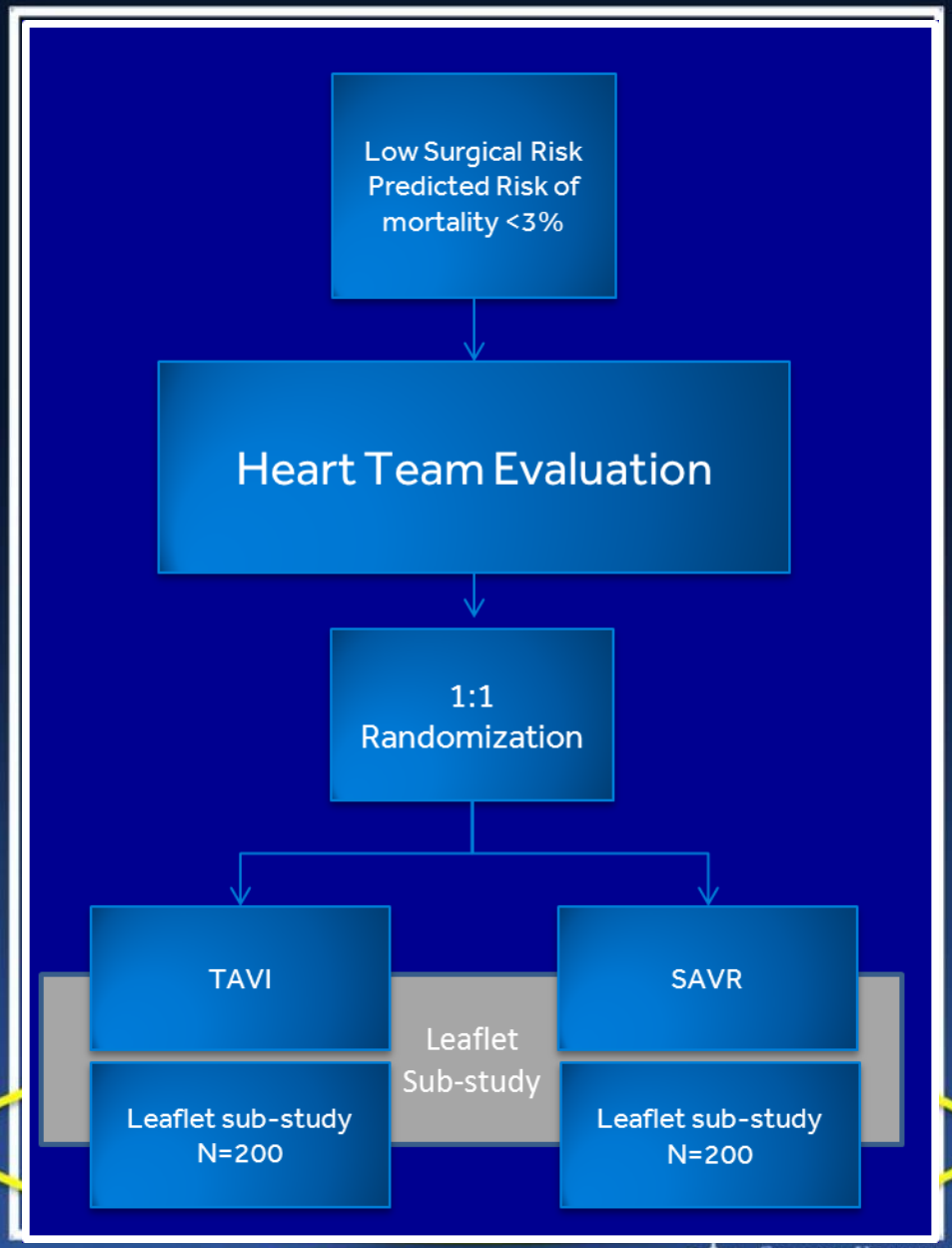
PRIMARY ENDPOINT:
Composite of all-cause mortality, all strokes, or re-hospitalization at 1 year post-procedure

Follow-up: 30 days, 6 mos, 1 year and annually through 10 years

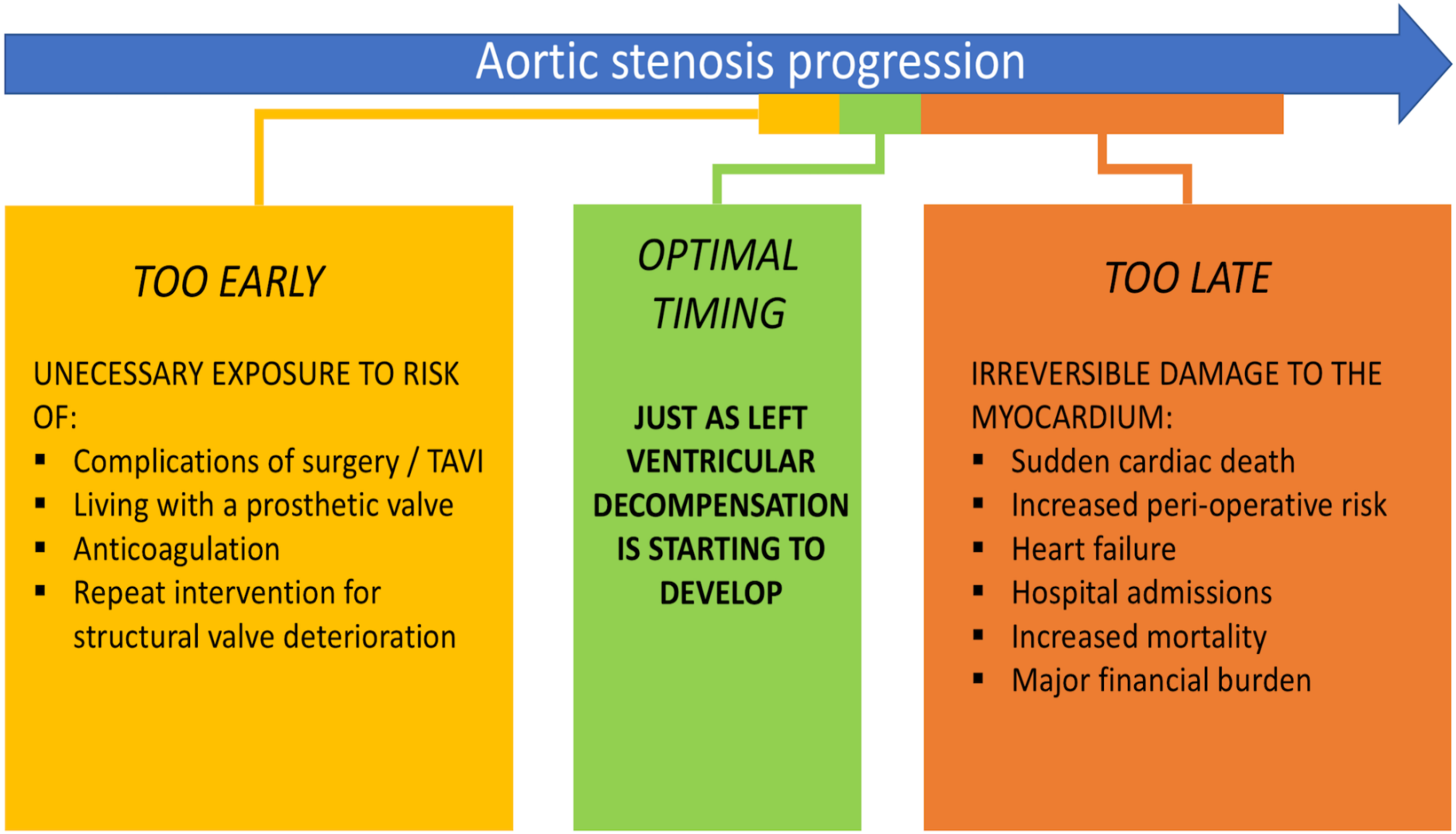
MEDTRONIC TAVR RCT IN LOW RISK PATIENTS

TRIAL DESIGN & LEAFLET SUB-STUDY

- **Patient Population: Low Risk Cohort**
  - Determined by Heart Team to be low surgical risk
- **Primary Endpoint:**
  - Safety: Death, all stroke, life-threatening bleeding, major vascular complications, or AKI at 30 days
  - Efficacy: Death or major stroke at 2 years
- **Sample Size: ~1200 Subjects**
- **Follow-up Evaluations:**
  - 30-days, 6-month , 18-month, and 1 thru 5 years
- **Number of Sites: Up to 80 sites**



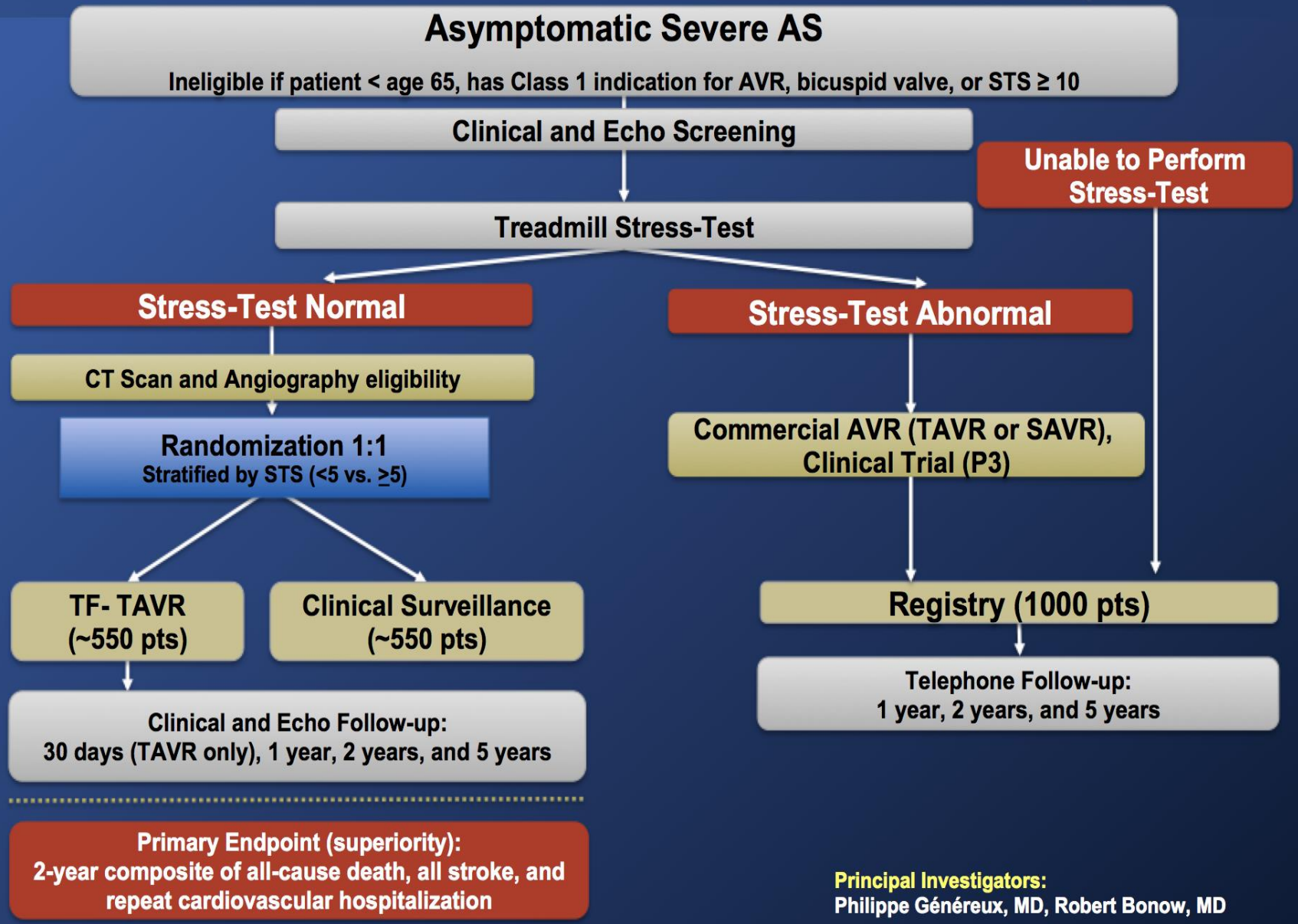
Asymptomatic AS: When Should We Offer AVR?



EARLY TAVR Trial

Flow Chart

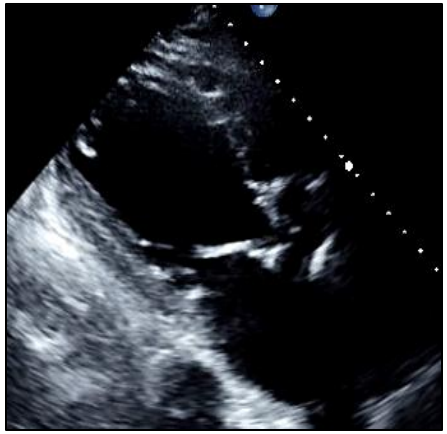
THE PARTNER 3 TRIAL



Principal Investigators:
Philippe Généreux, MD, Robert Bonow, MD

Moderate AS with Low LVEF and HF (Stage B2?)

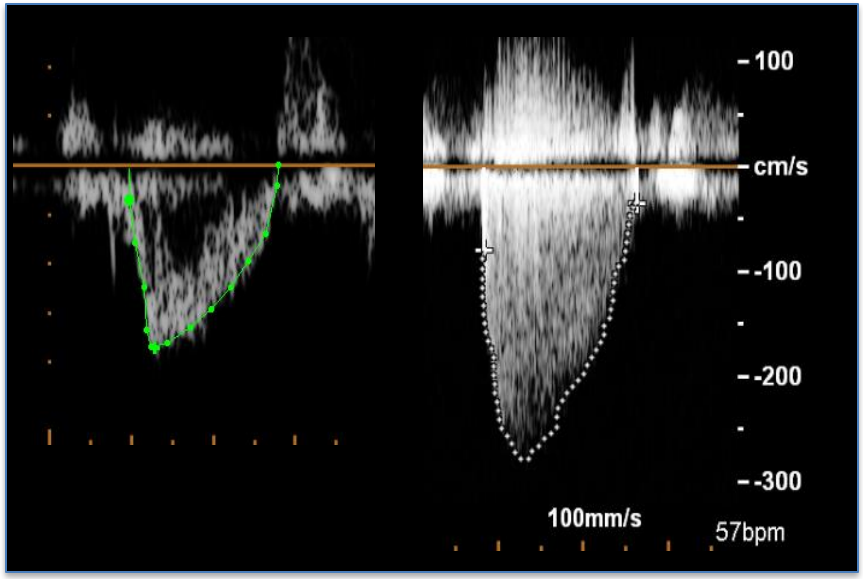
Rest

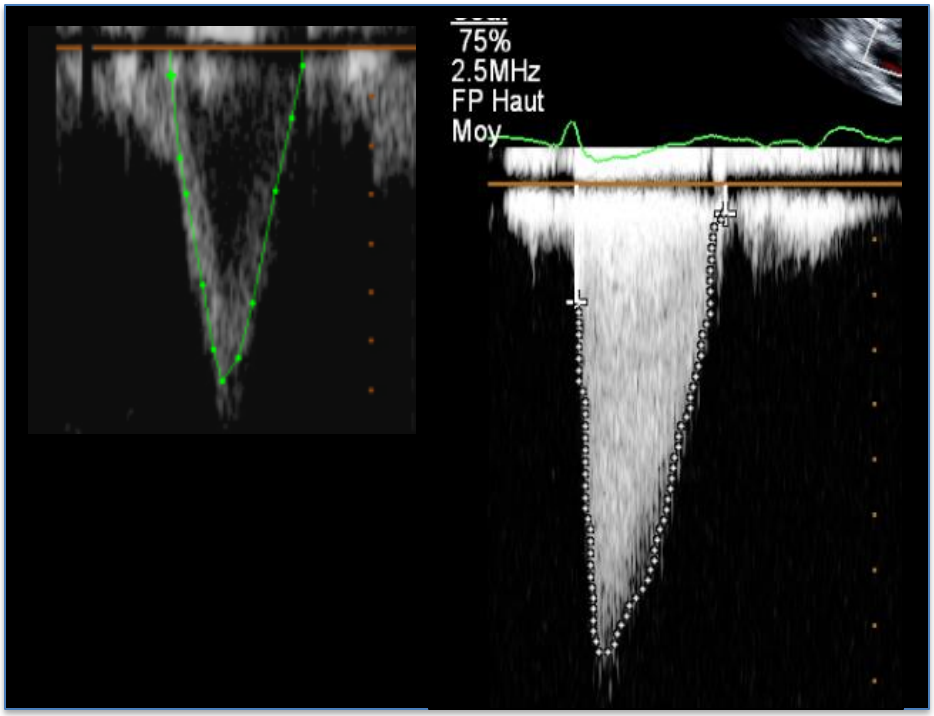


SV= 36 ml
Q_{mean}=139 ml/s
LVEF=20%
ΔP= 35 / 22 mmHg
AVA= 0.85 cm^2

DSE

SV= 55 ml
Q_{mean}=243 ml/s
LVEF=30%
ΔP= 63 / 32 mmHg
AVA= 1.1 cm^2





TAVR UNLOAD Trial

Study Design

(600 patients, 1:1 Randomized)

TAVR UNLOAD Trial

International Multicenter Randomized

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

R

TAVR + OHFT

OHFT Alone

Follow-up:
1 month
6 months
1 year

Clinical endpoints
Symptoms
Echo
QoL

Primary Endpoint
Hierarchical occurrence of:
- All-cause death
- Disabling stroke
- Hospitalizations for HF, aortic valve disease
- Change in KCCQ

Reduced AFTERLOAD
Improved LV systolic and diastolic function

NewYork-Presbyterian
Columbia University Medical Center

Erasmus MC
Universitair Medisch Centrum Rotterdam

Institut universitaire de cardiologie et de pneumologie de Québec
Université Laval

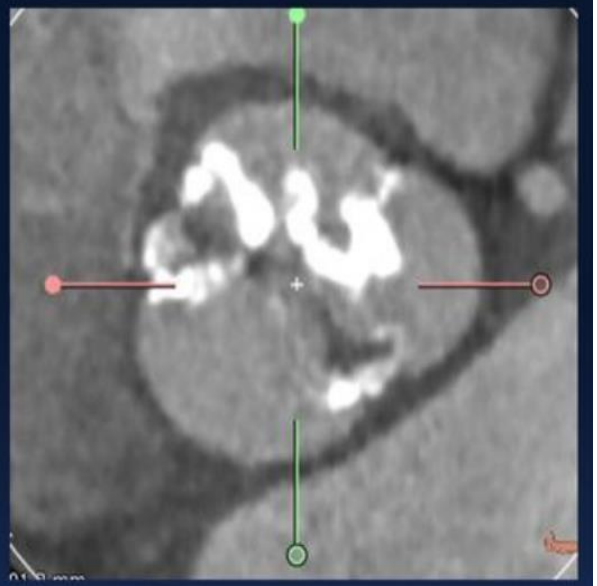
Gaps in Evidence: Off-Label Use

→ Bicuspid Anatomy

→ Failes Surgical Prosthesis

Why Bicuspids are Problematic for TAVR?

- Bulky Eccentric Calcification
  - Incomplete valve expansion
  - Paravalvar leak
  - Annulus rupture
  - Higher PPM Rate
- Abnormal/lower coronary orifices
- Ascending Aortopathy- 25%
  - Needs Treatment
  - Risk of rupture/dissection
- Ovality of annulus
  - Risk of paravalvar leak
  - Long-term durability of the TAVI valve?



- For these reasons bicuspid valves had been excluded from all randomized trials
- Relative contraindication for TAVI according to guidelines

TAVI in Bicuspid Anatomy

BIVOLUT-X

Bicuspid aortic Valves with eVOLUT platform international eXperience

PI's: Didier Tchétché, Toulouse /Nicolas van Mieghem, Rotterdam

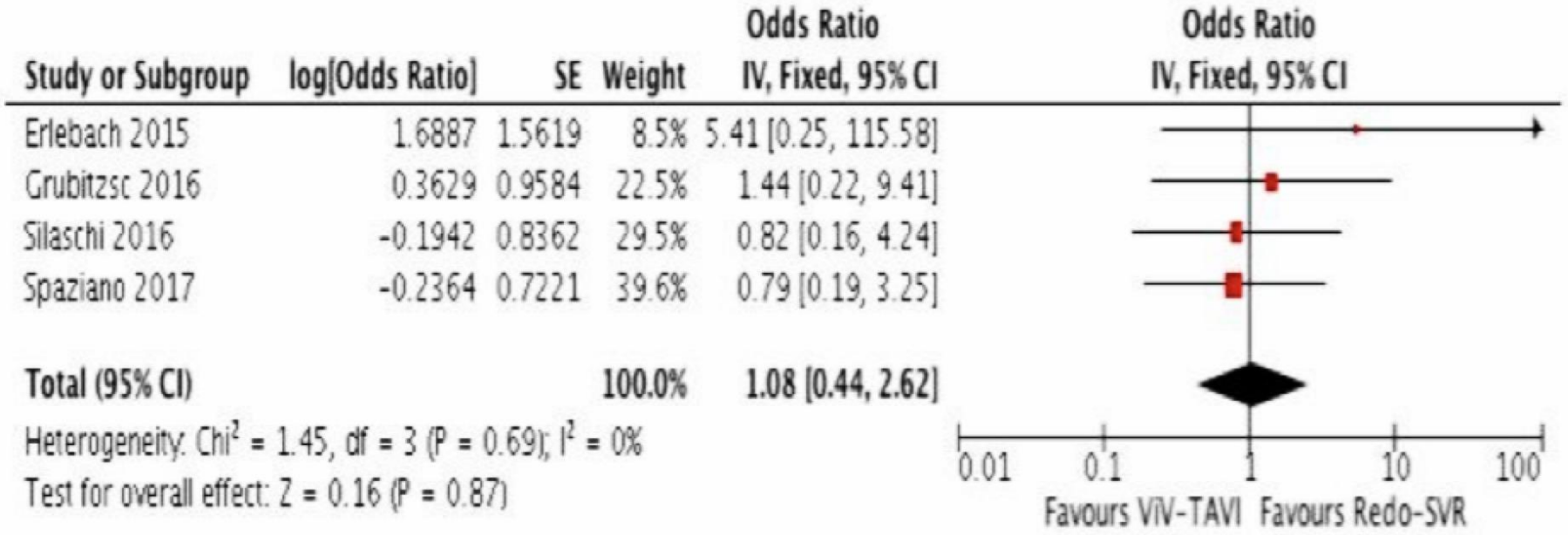
Design: Prospective registry

Endpoint: Valve performance and VARC-2 outcomes at 30 days and 1 year

Centres: Up to 20 European Centers

Update: 10/150 patients recruited

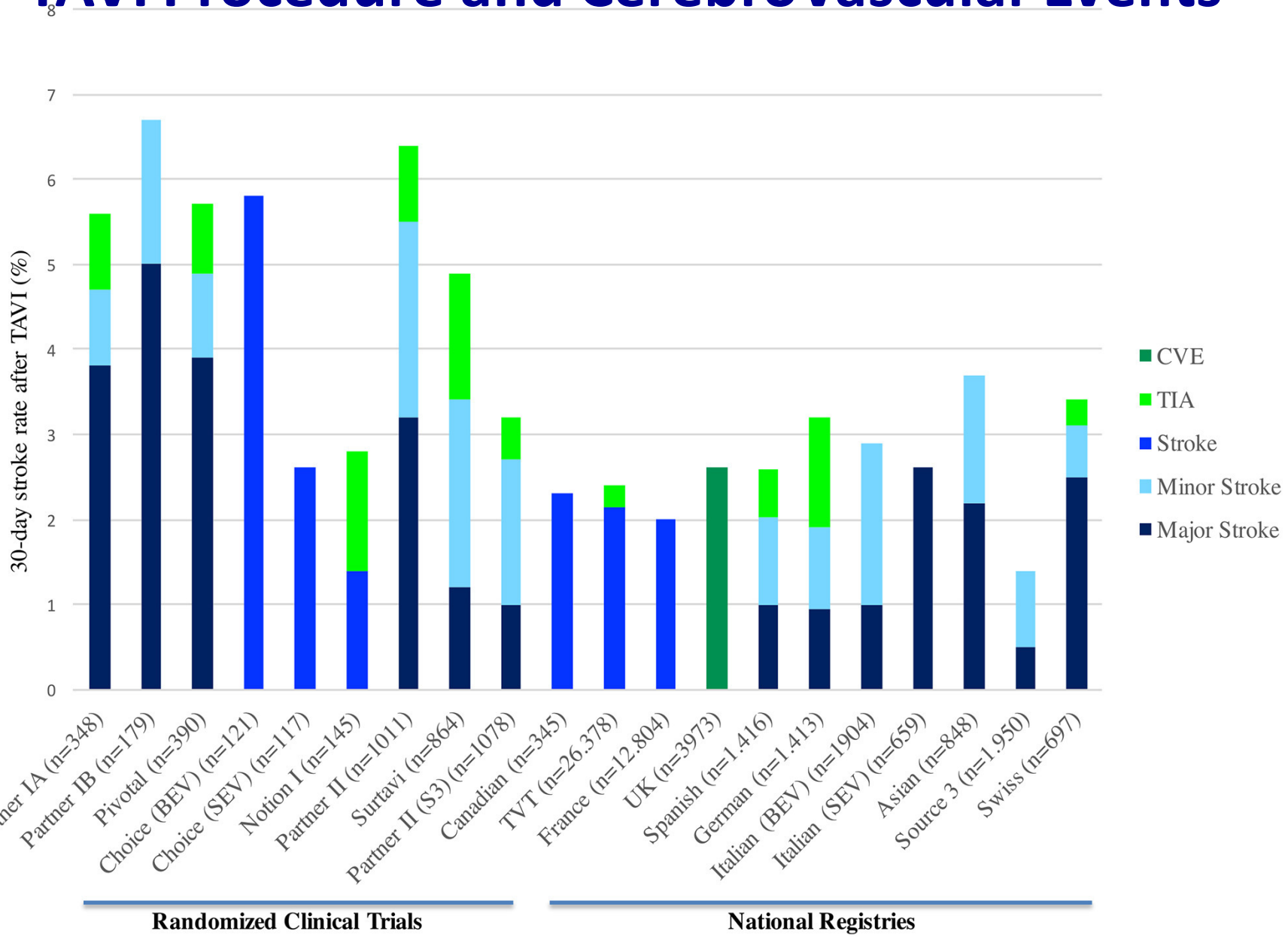
Metanalysis of Transcatheter Valve-in-Valve Implantation Versus Redo Aortic Valve Surgery for Bioprosthetic Aortic Valve Dysfunction



- **This meta-analysis of non-randomized studies with modest number of patients suggested that ViV-TAVI had similar 30-day survival compared with redo-SAVR for aortic BPV dysfunction**

TAVI Procedure: – Will cerebral embolic protection become the standard for TAVR in the future?

TAVI Procedure and CerebroVascular Events



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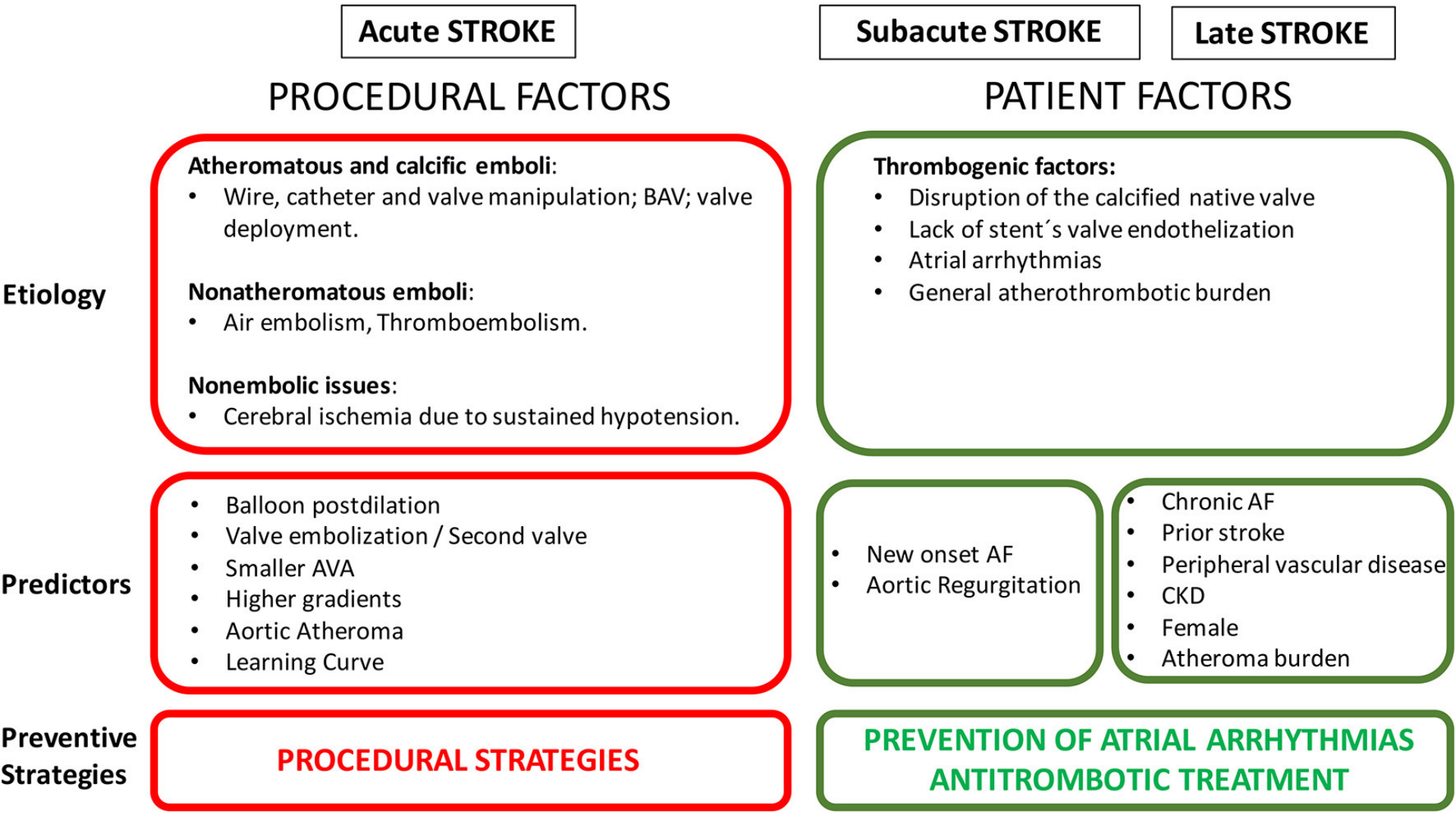

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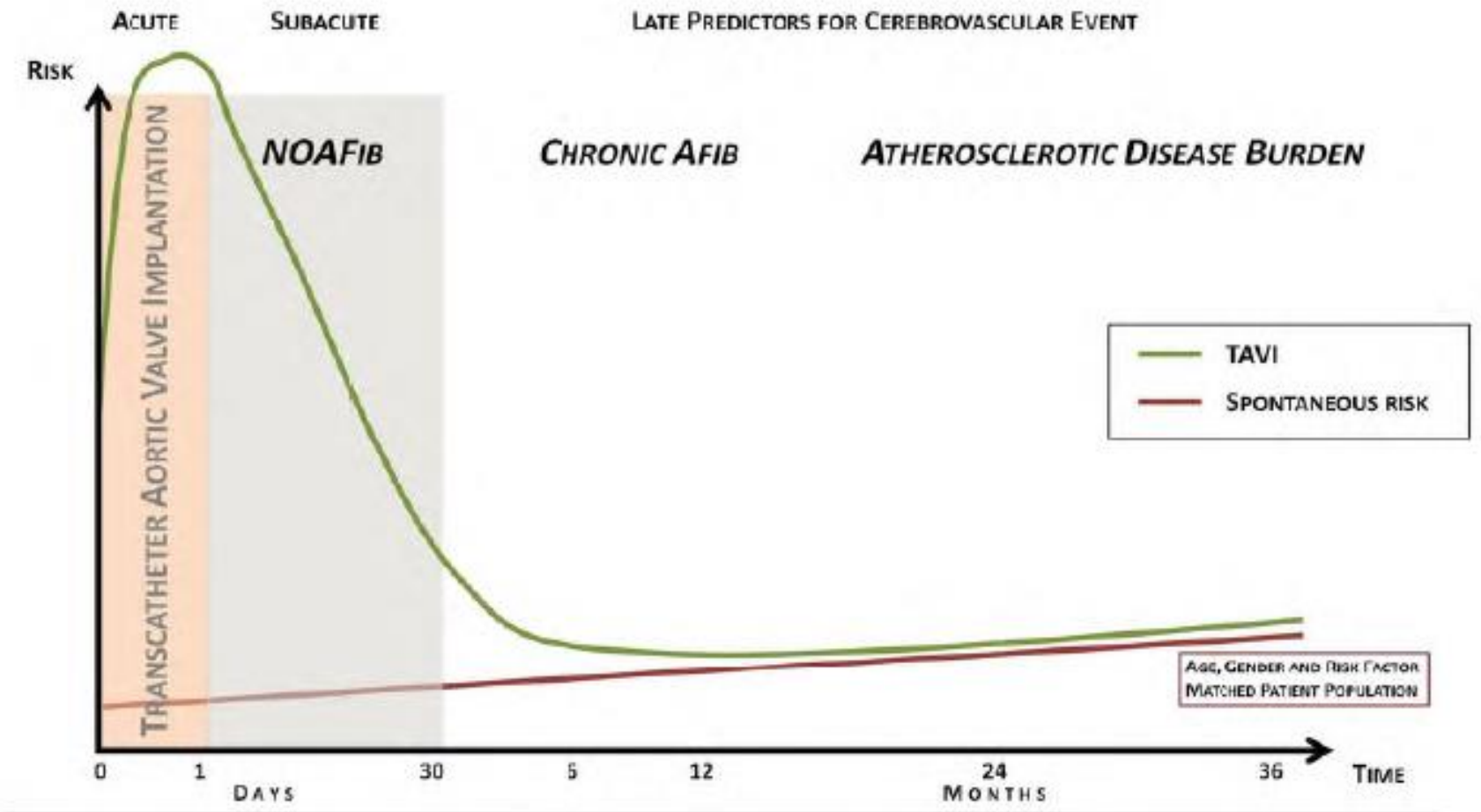
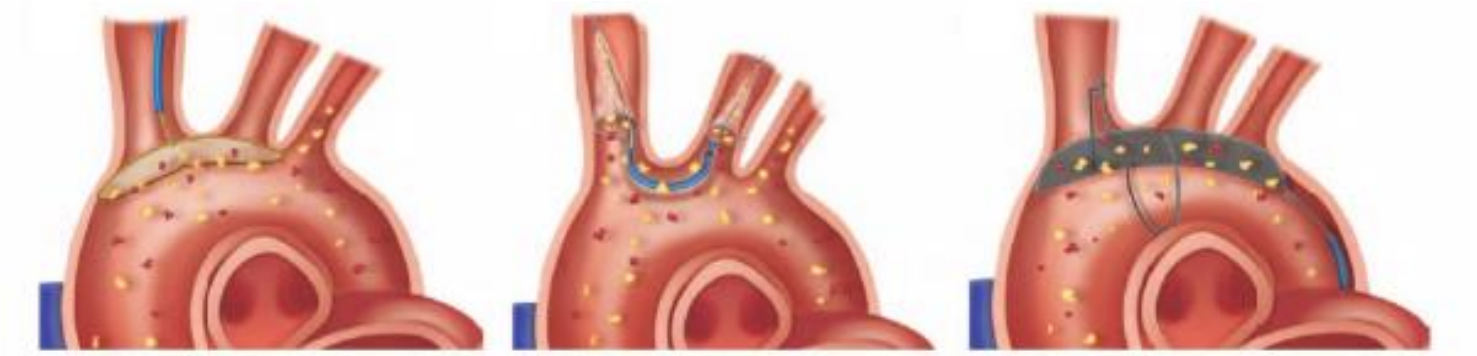


Stortecky, Windecker. *Circulation* 2012;126:2921-4

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

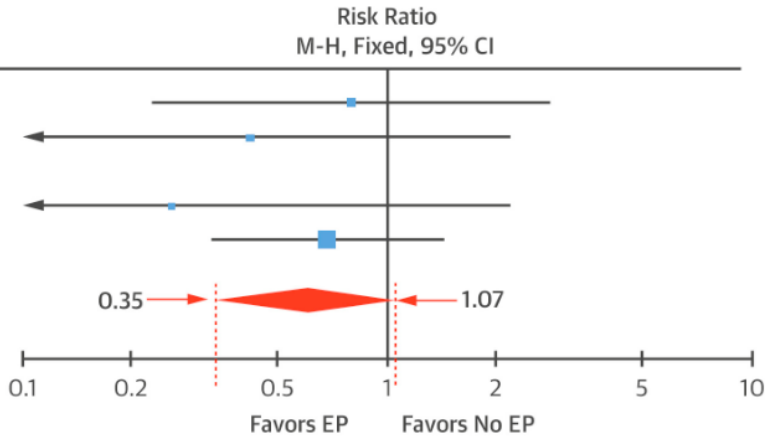
Cerebral Embolic Protection During TAVR

A Clinical Event Meta-Analysis

Study or Subgroup	Embolic Protection Events	Embolic Protection Total	No Embolic Protection Events	No Embolic Protection Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CLEAN-TAVI	4	50	5	50	17.7%	0.80 [0.23, 2.81]
DEFLECT-III	2	46	4	39	15.4%	0.42 [0.08, 2.19]
EMBOL-X	0	14	0	16		Not estimable
MISTRAL-C	1	32	4	33	14.0%	0.26 [0.03, 2.18]
SENTINEL	16	234	11	111	52.9%	0.69 [0.33, 1.44]
Total (95% CI)		**376**		**249**	**100.0%**	**0.61 [0.35, 1.07]**
Total events	23		24			

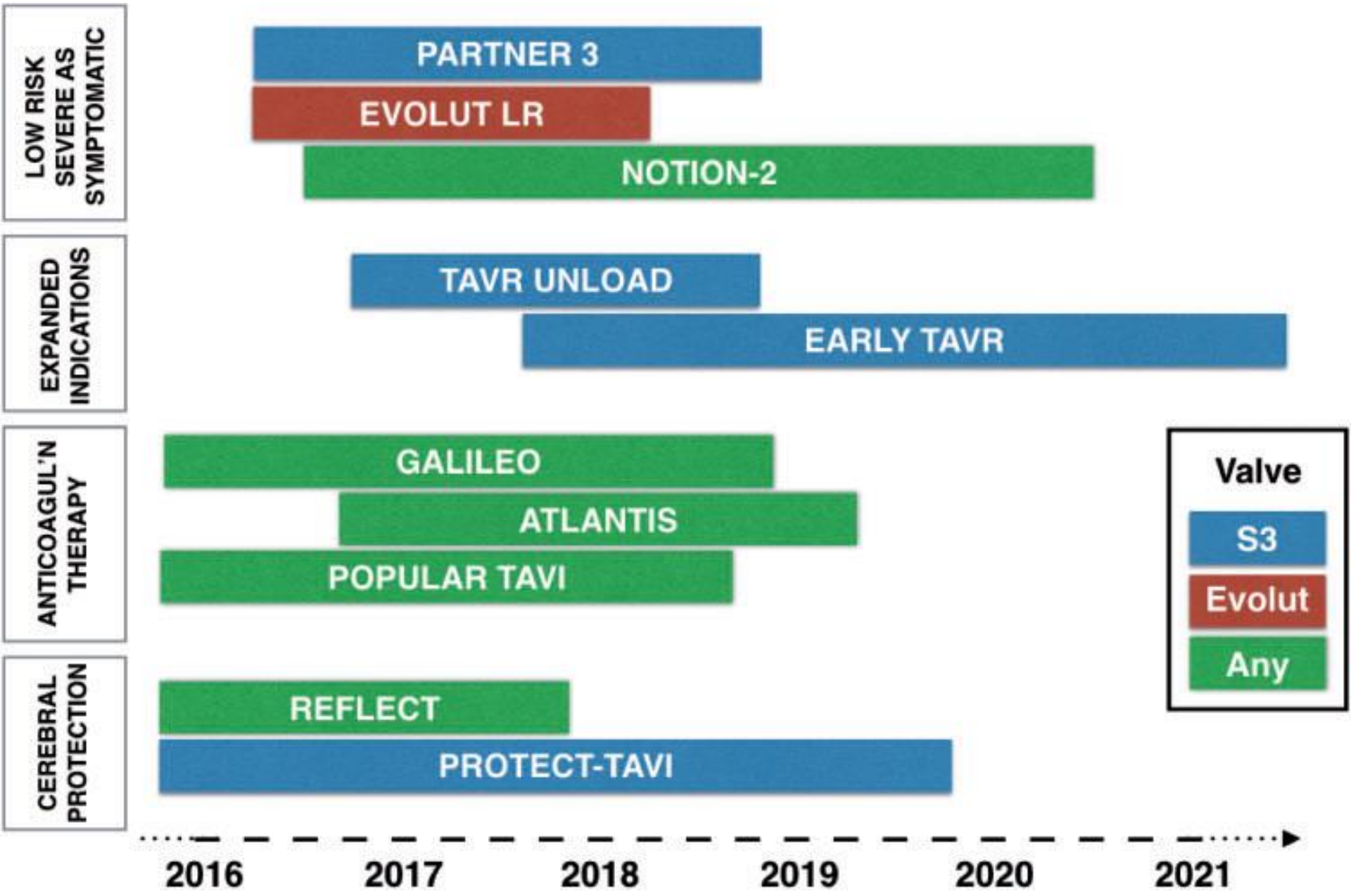
Heterogeneity: $Chi^2 = 1.10$, df = 3 (P = 0.78); $I^2 = 0\%$

Test for overall effect: Z = 1.73 (P = 0.08)



- **"In conclusion, the totality of the data suggests that use of EP during TAVR appears to be associated with a non-significant trend towards reduction in death or stroke."**

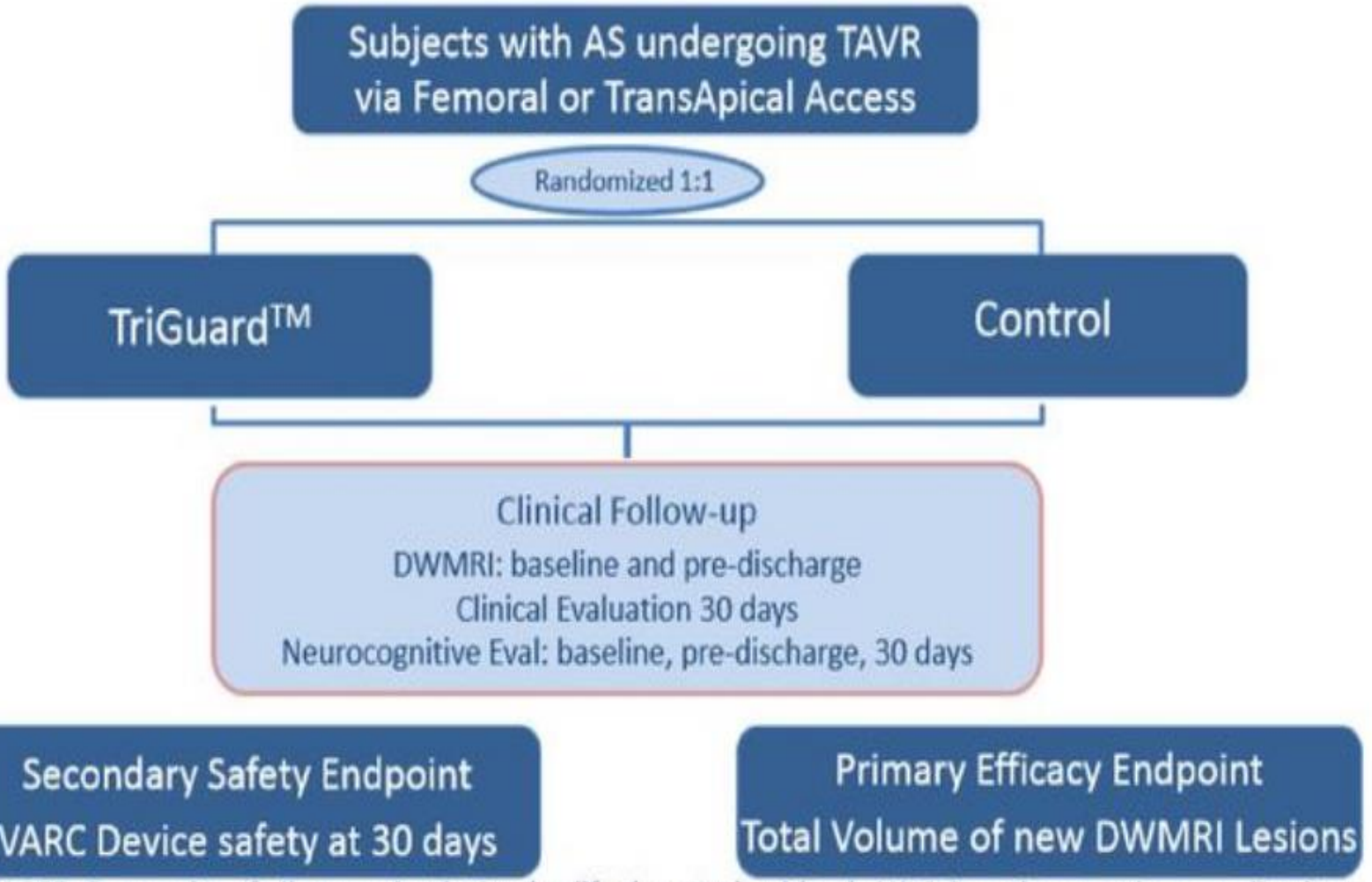
JACC 2017;31:463–70


LOW RISK SEVERE AS SYMPTOMATIC
PARTNER 3
EVOLUT LR
NOTION-2
EXPANDED INDICATIONS
TAVR UNLOAD
EARLY TAVR
ANTICOAGUL'N THERAPY
GALILEO
ATLANTIS
POPULAR TAVI
CEREBRAL PROTECTION
REFLECT
PROTECT-TAVI
Valve
S3
Evolut
Any
2016
2017
2018
2019
2020
2021

REFLECT US IDE Trial

A prospective multicenter randomized trial of TriGuard™ neuro protection vs no protection in patients undergoing TAVR at clinical centers in EU and US

PI: Jeff Moses and Andreas Baumbach



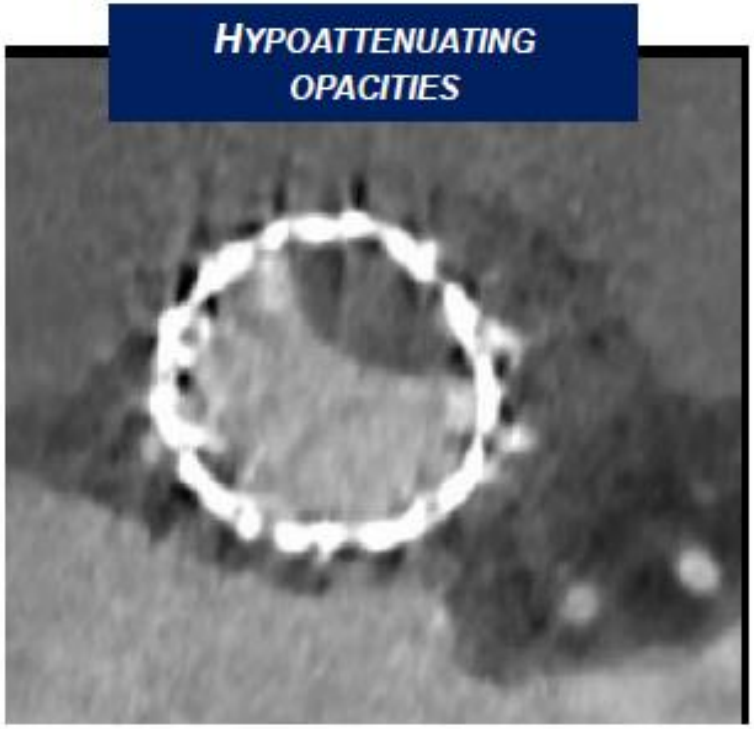
MACCE: Composite of all cause death, Stroke, life threatening bleed, AKI 2-3, major vascular complications

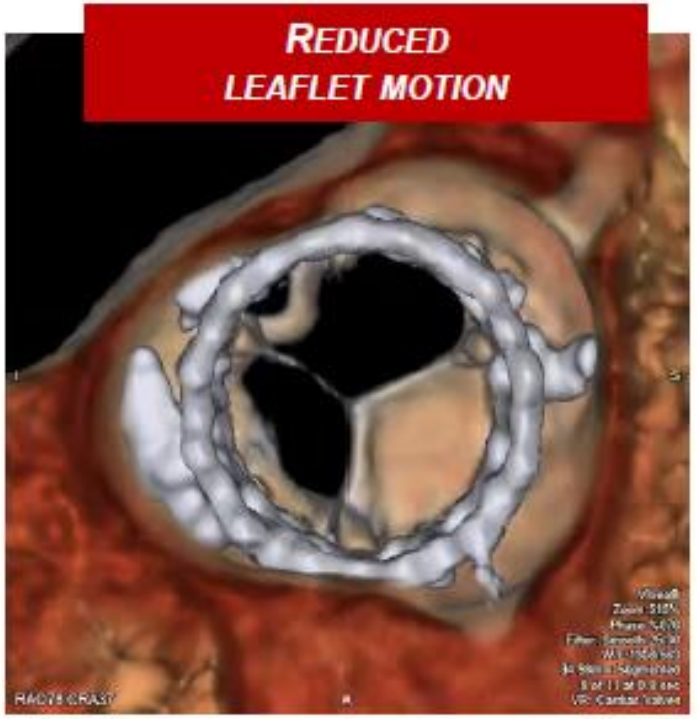
TAVR Adjunct Pharmacology
Customized Patient-Based Therapy

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)*

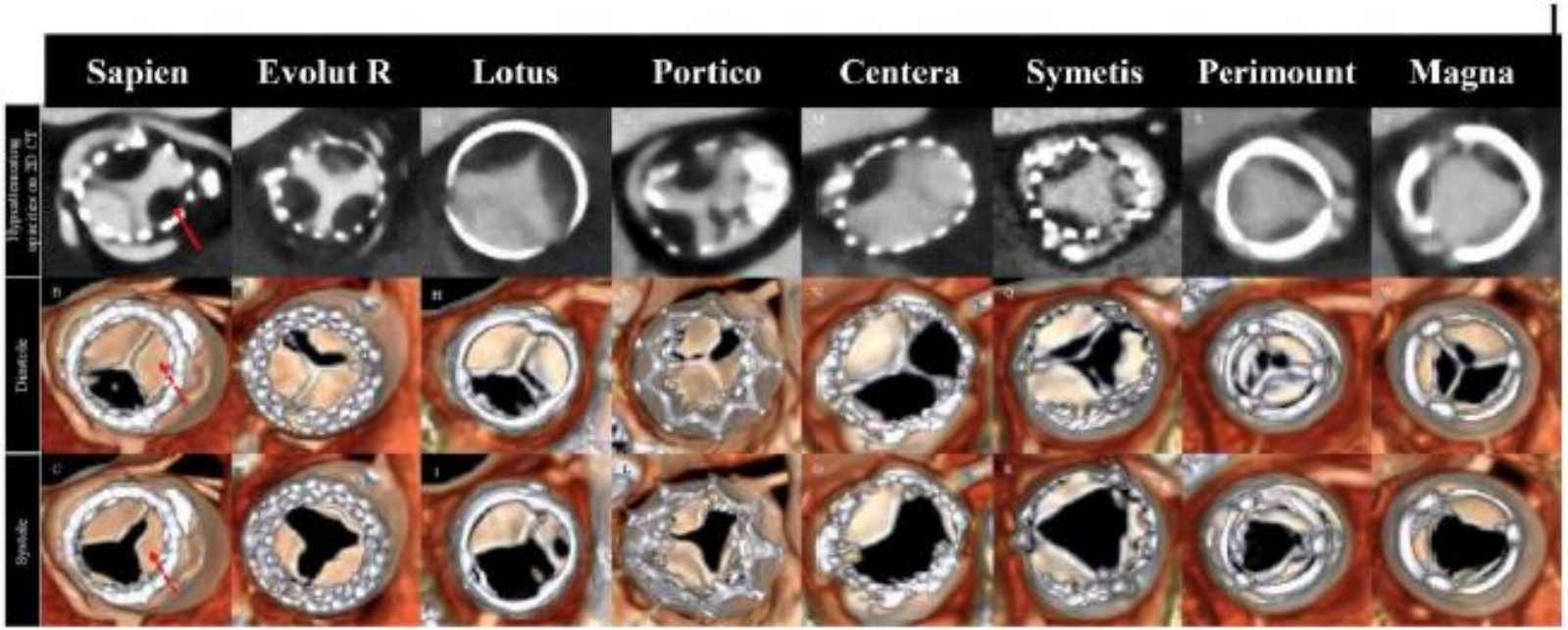




SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

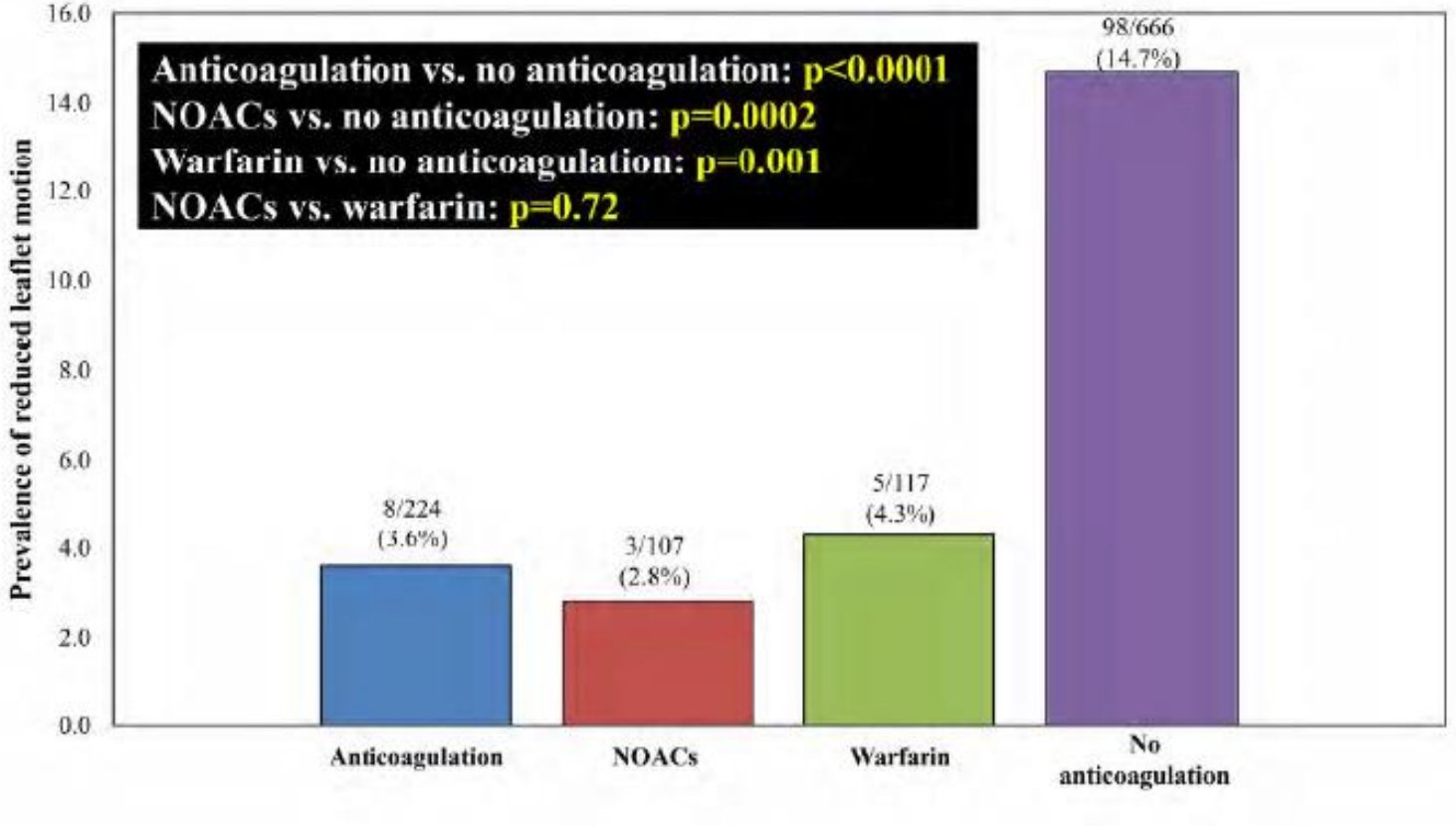
Chakravarty et al. Lancet 2017

- *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)*



SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

Chakravarty et al. Lancet 2017



SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

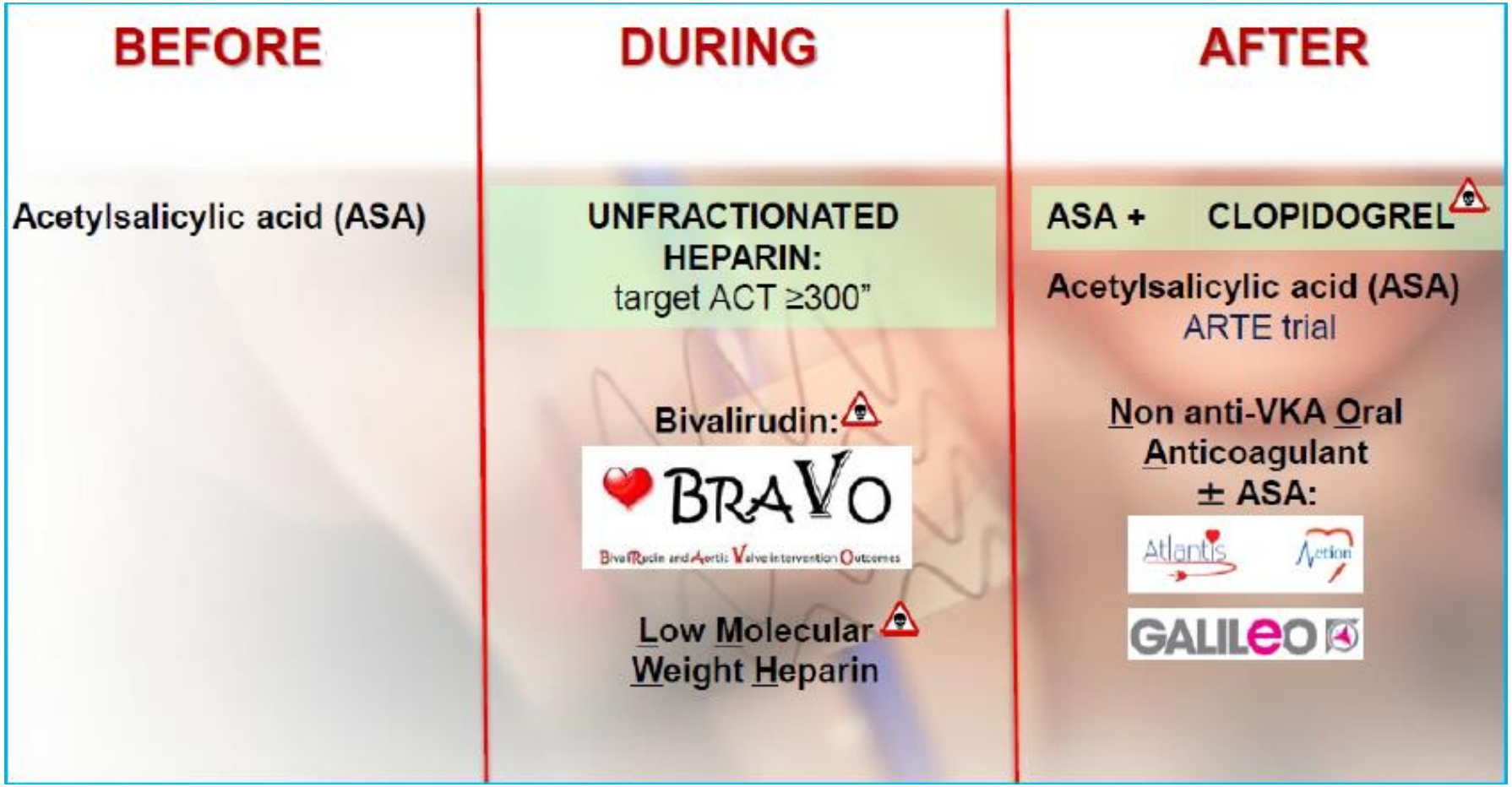
Chakravarty et al. *Lancet* 2017

	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

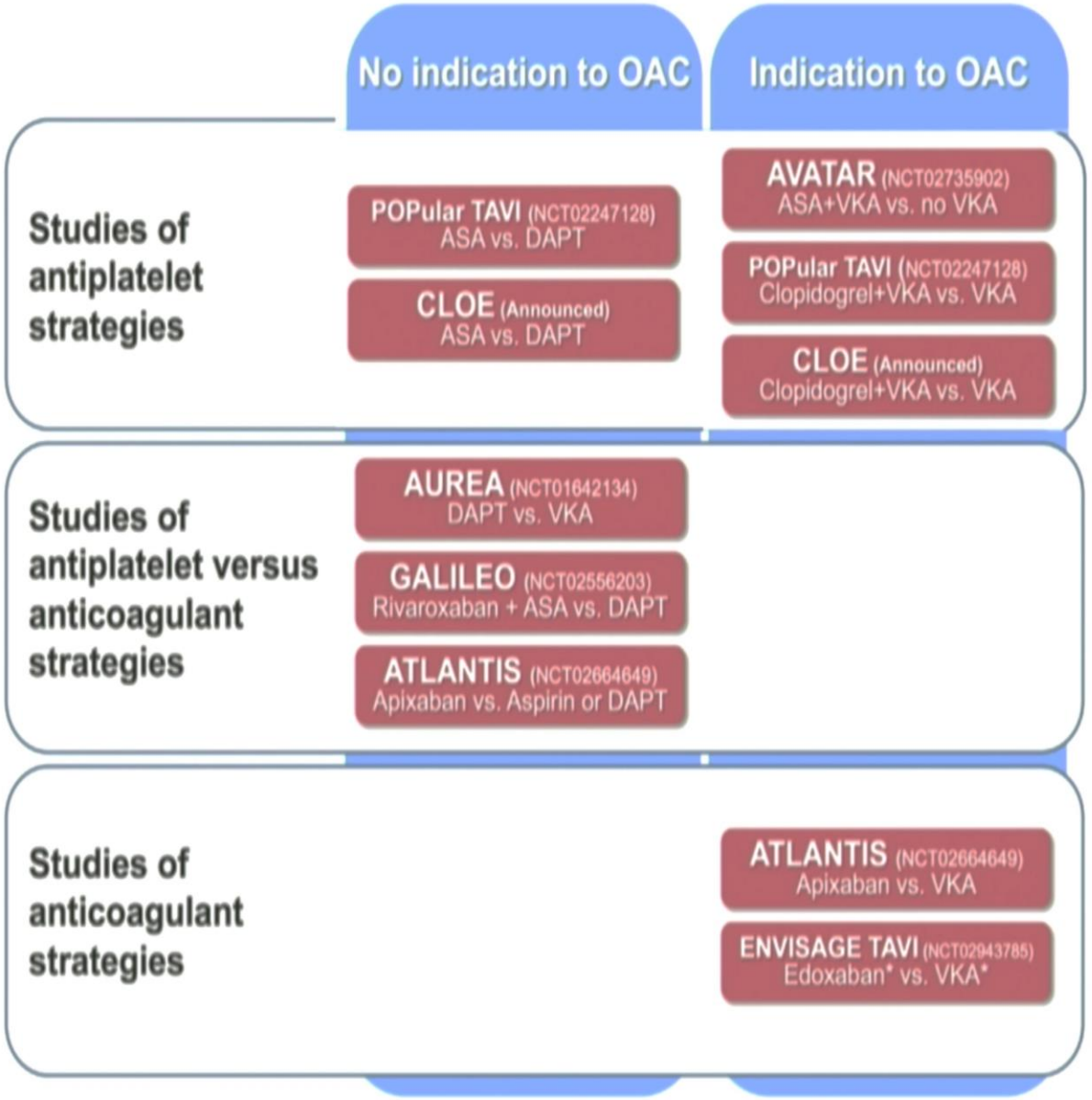
* All strokes include hemorrhagic and ischemic strokes

TAVR Adjunct Pharmacology
Customized Patient-Based Therapy



AntiThrombotic Therapy

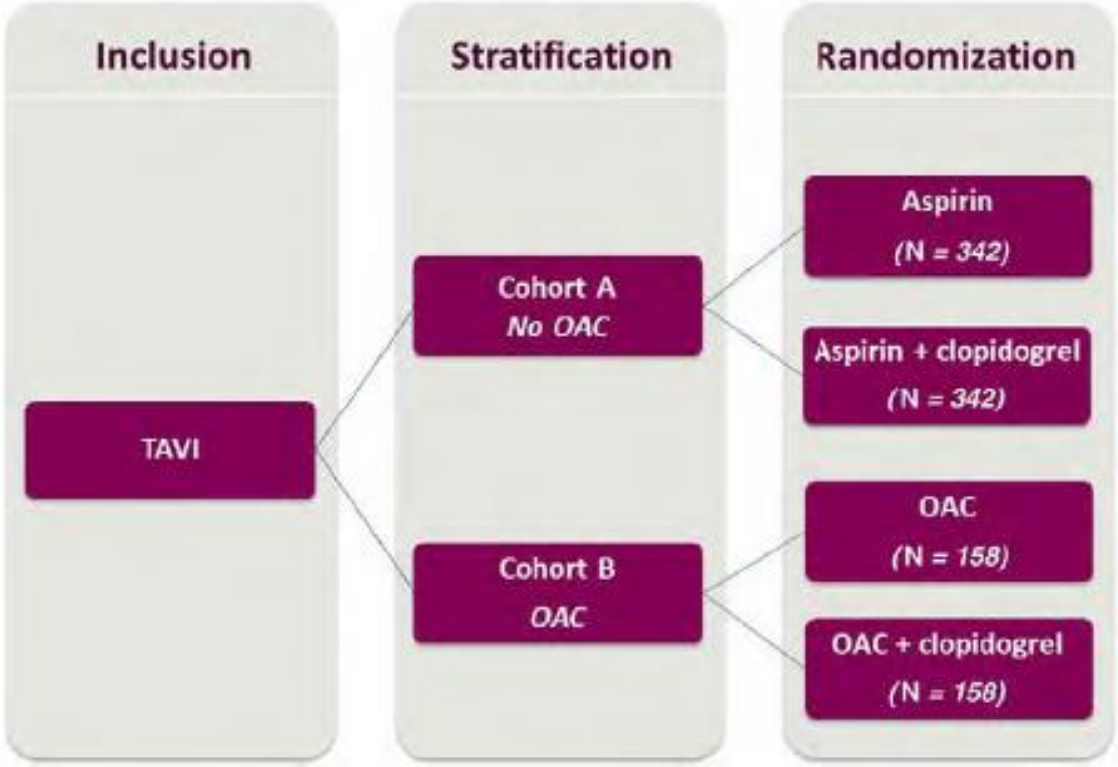
Adapted from Capodanno et *JACC Cardiovasc Interv*. 2017 Jul 10;10(13):1366-1369



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



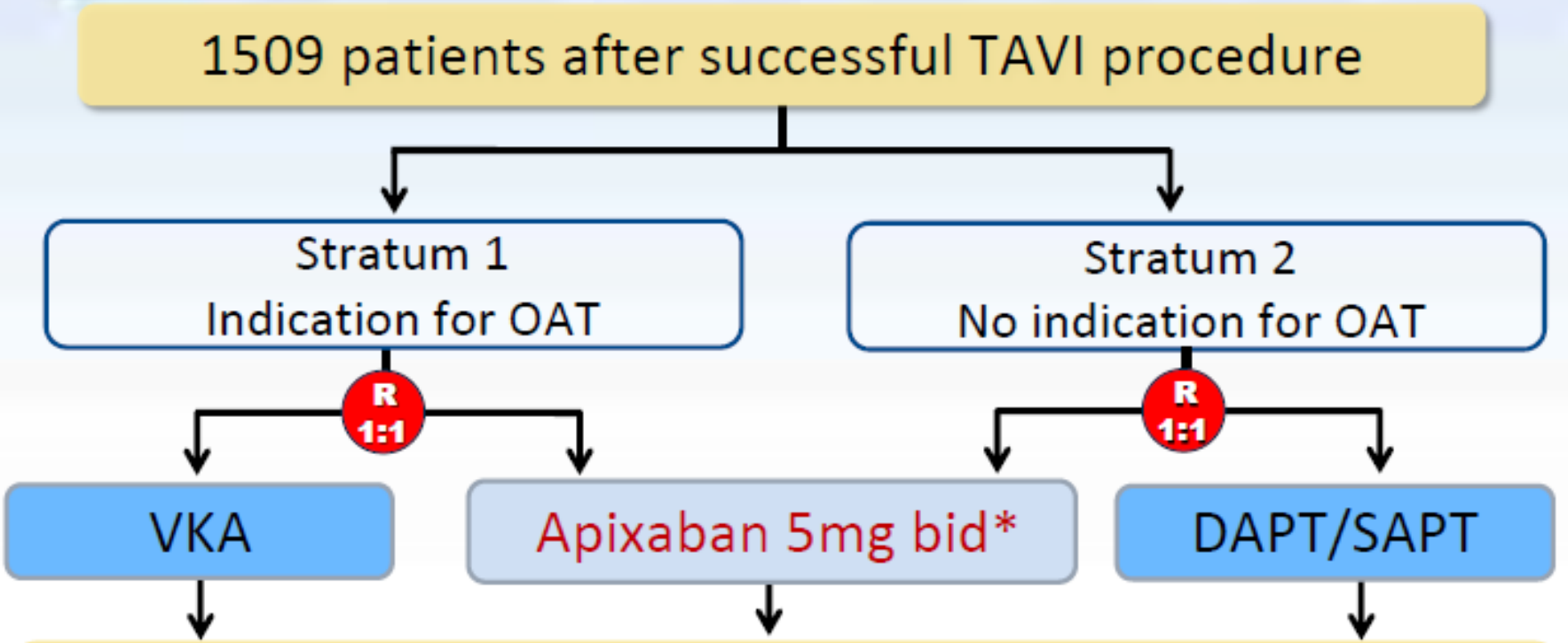
POPular TAVI

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*.

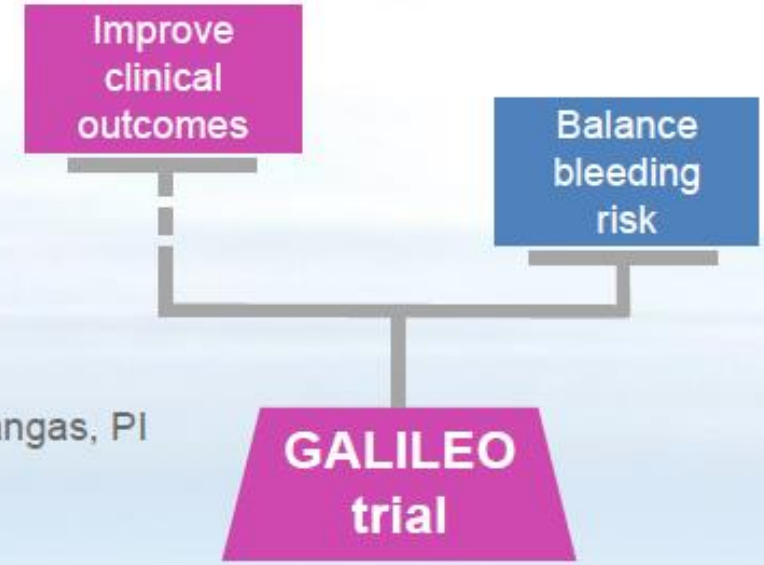
*2.5mg bid if creatinine clearance 15-29mL/min or if two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1,5mg/dL (133µMol).

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.

Discharge: The “minimalist” TAVR procedure strategy has become imbedded as a preferred treatment approach in the majority of patients

3M TAVR Study Design

To evaluate the efficacy, feasibility, and safety of next day discharge home in patients undergoing balloon-expandable transfemoral TAVR utilizing the Vancouver 3M Clinical Pathway

Patients undergoing elective Transfemoral TAVR

↓

Considered at *increased surgical risk* by the Heart Team

↓

Vancouver 3M Clinical Pathway (n = 411)
Meet all anatomical, functional, and peri-procedural exclusion criteria

↓

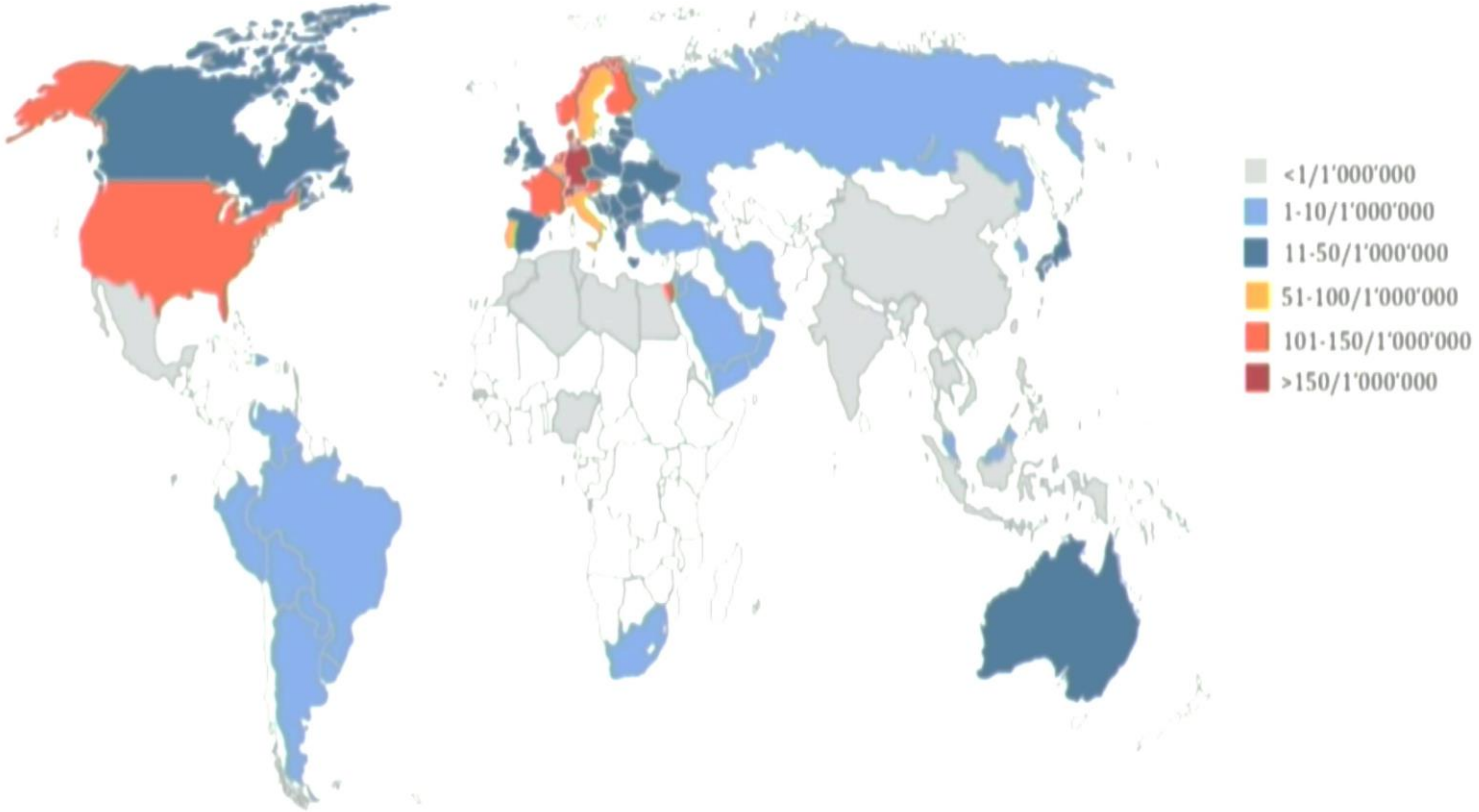
Primary Outcomes: 1) All cause mortality or stroke at 30 days
2) The proportion of patients discharged the next day

↓

Secondary Outcomes: 1) Readmission within 30 days
2) Greater than mild PAR at 30 days
3) New permanent pacemaker at 30 days
4) Major vascular complications, bleed, or repeat valve procedure at 30 days
5) Conversion to GA/Intubation
6) KCCQ and SF 12 at 2 weeks, 30 days, and 1 year
7) All cause mortality and stroke at 1 year

Gaps in Implementation: Geographical Dispersion and Socioeconomic Inequalities - TAVI

Pilgrim T et al. *Eur Heart J 2018*



Estimates for Q1–Q4 2017 (Western Europe) or Q4 2016–Q3 2017 (all other regions) including moving annual total (MAT) data.
Data are subject to end of year adjustment.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Clinical Study :

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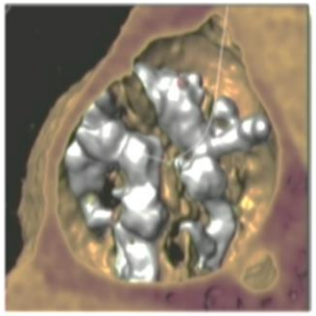
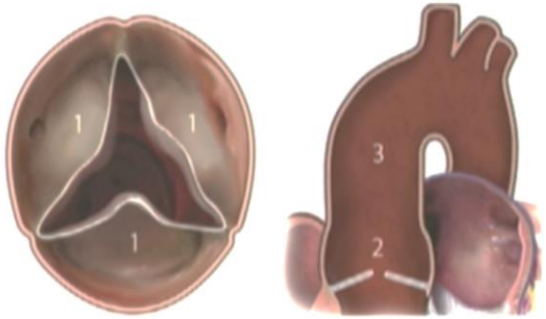
- [ ] Completed
- [ ] Withdrawn
- [ ] Unknown status†

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
11	☐	Recruiting	NVT ALLEGRA **TAVI** System TF in Failing Surgical Aortic Bioprosthesis	• **Transcatheter Aortic Valve Implantation**	• Device: **Transcatheter Aortic Valve Implantation (TAVI)**	• Universitäts-Herzzentrum Freiburg-Bad Krozingen Bad Krozingen, Germany • Segeberger Kliniken, Herzzentrum Bad Segeberg, Germany • Immanuel Klinik Bernau Herzzentrum Brandenburg Bernau bei Berlin, Germany • (and 5 more...)
12	☐	Recruiting	Safety and Efficacy Comparison Of Two **TAVI** Systems in a Prospective Randomized Evaluation II	• Aortic Valve Stenosis	• Device: Symetis ACURATE neo™ transfemoral **TAVI** system • Device: Medtronic CoreValve Evolut R **TAVI** System	• Heart Center, Rigshospitalet, University of Copenhagen Copenhagen, Denmark • Oulun University Hospital Oulu, Finland

Gaps in Evidence





- Expanding Clinical Indications
  - Low risk
  - Asymptomatic pts.
  - Moderate AS with CHF
  - Off-Label Use
    - Bicuspid Anatomy
    - Pure Native Aortic Regurgitation
    - Failes Surgical Prosthesis
- TAVI Procedure
  - Cerebral Protection
  - Valve Thrombosis → Anticoagulation
- Others
  - Valve Durability
  - Geographic inequalities
  - Comparision between valves

Thanks