TAVR Leaflet Thrombosis and Post-TAVR Pharmacological Therapy

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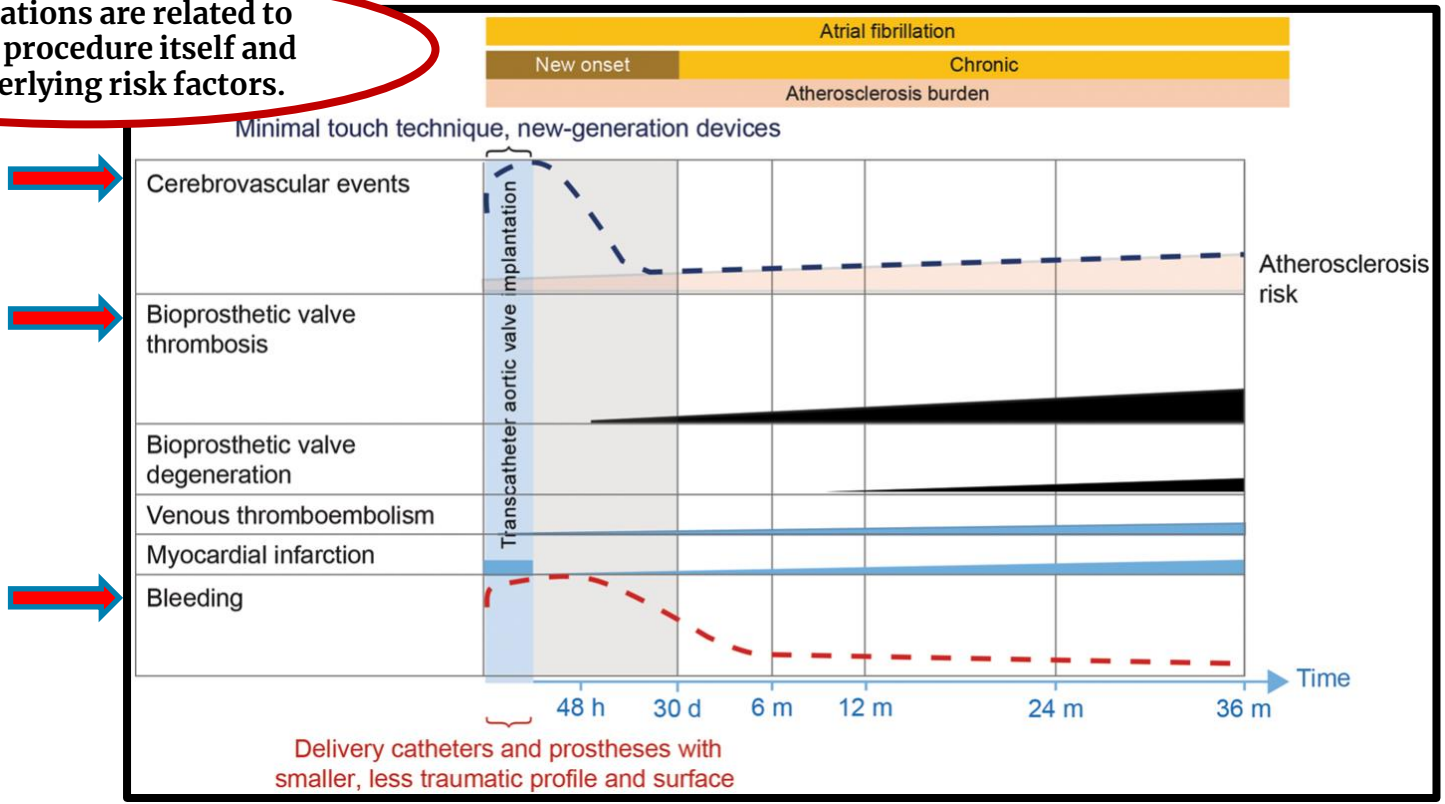
Disclosures

Research Grants to Institution from Bayer and Daiichi-Sankyo for PI of clinical trial and relevant consultation/lectures.

Bleeding vs. Ischemic Events After TAVR

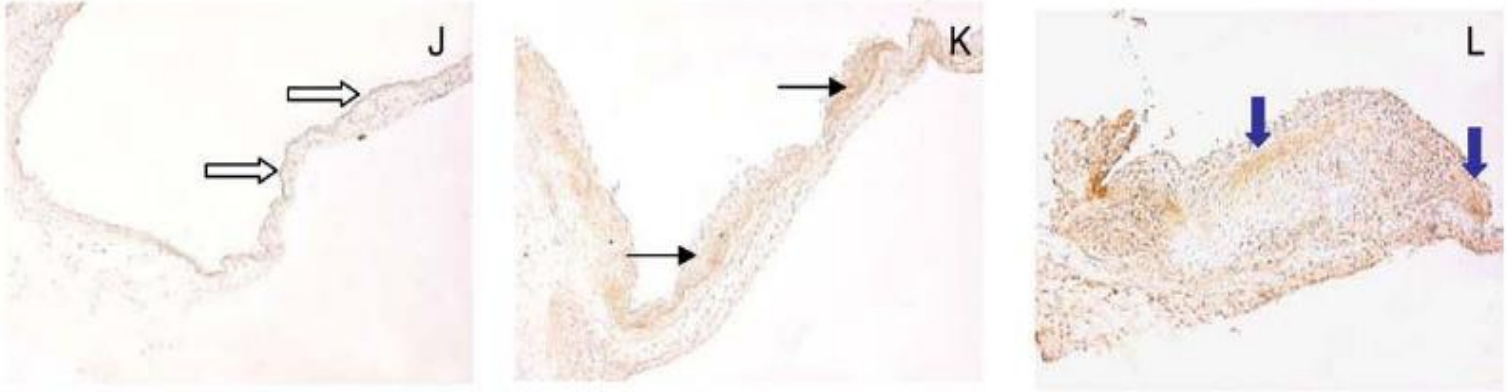
Complications are related to both the procedure itself and the underlying risk factors.



P. Vranckx et al. European Heart Journal (2017) 38, 3341–3350

Expression of Tissue Factor in Aortic Valve Leaflets of Varying Status

Tissue factor



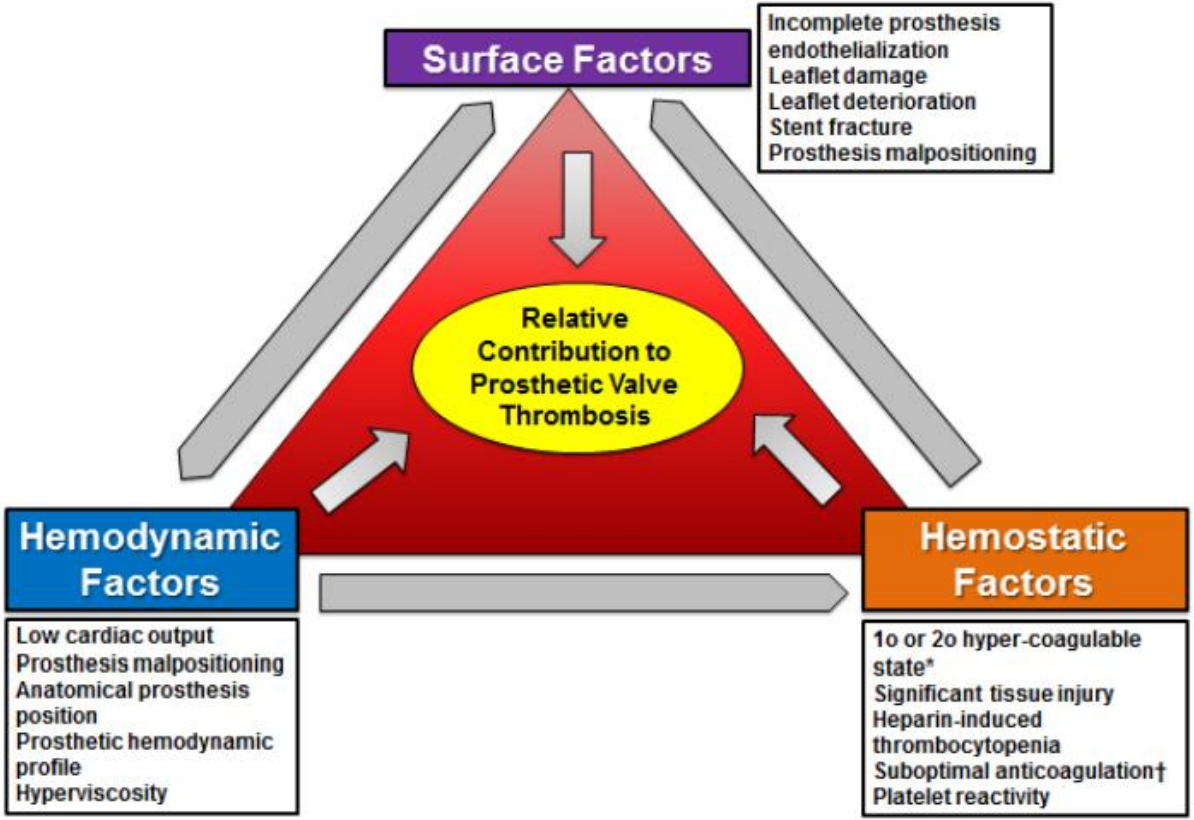
normal

sclerotic

stenotic

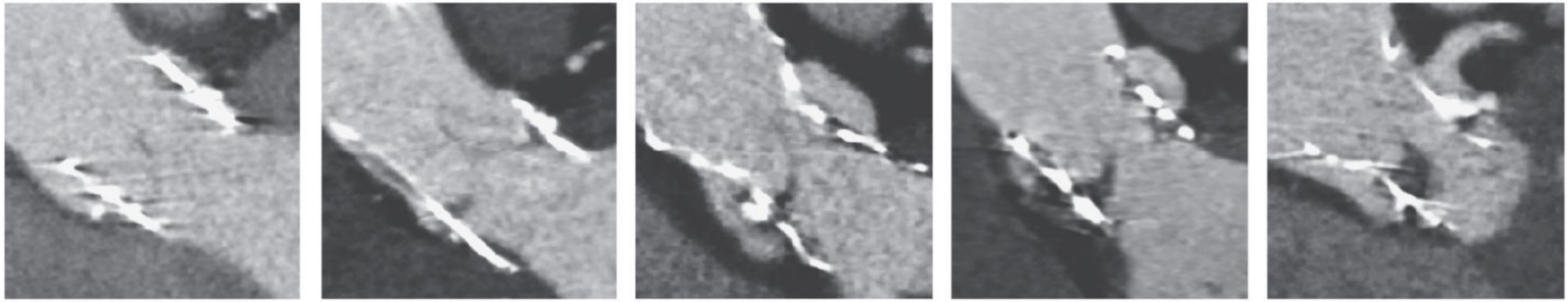
Maréchaux et al. *Cardiovasc Pathol* 2009; 18(2):67-76

Mechanisms of Prosthetic Valve Thrombosis



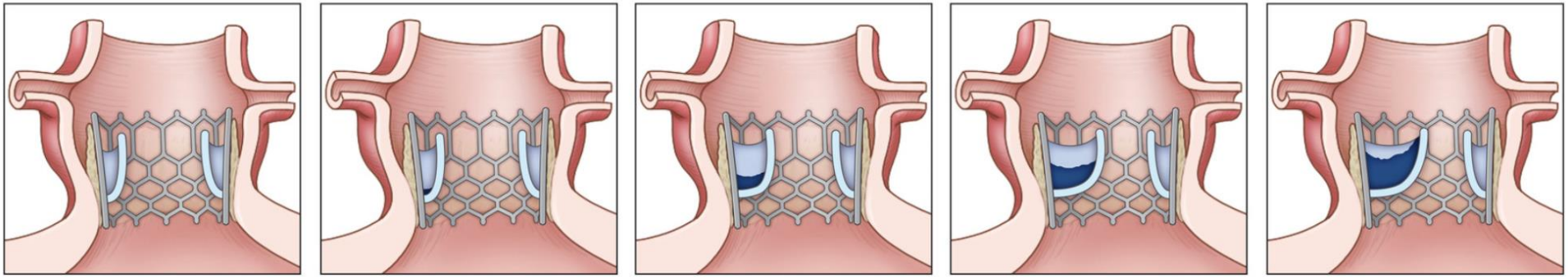
Dangas G, Weitz J, Giustino G, Makkar R, Mehran R. JACC 2016

Hypoattenuated Leaflet Thickening (HALT)



No thickening | <25% of Leaflet | 25–50% of Leaflet | 50–75% of Leaflet | >75% of Leaflet

Reduced Leaflet Motion (HAM)

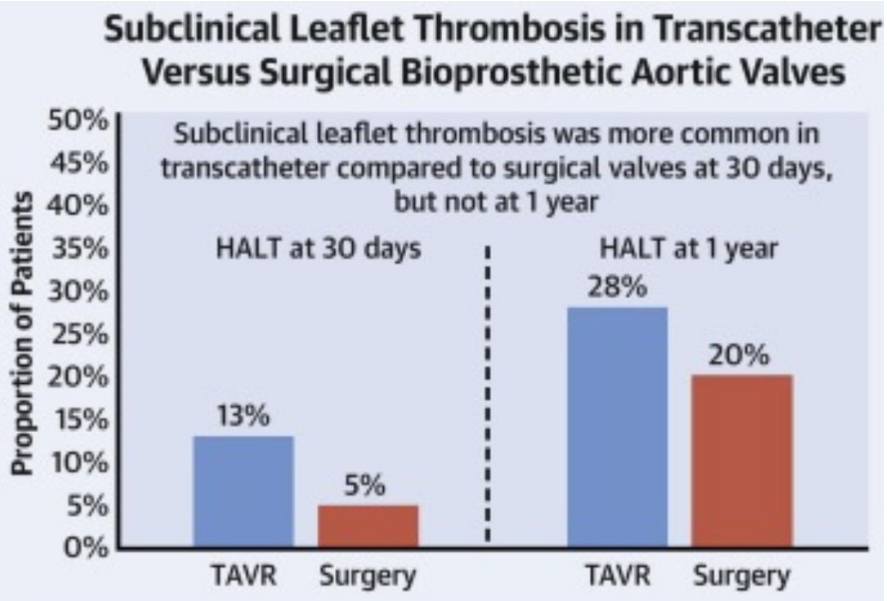


Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4

De Backer et al, N Engl J Med. 2020 Jan 9;382(2):130-139.

Subclinical Leaflet Thrombosis in PARTNER 3 Trial – Imaging Substudy

- 221 patients undergoing TAVR and 214 underdoing SAVR
- **Patients on OAC excluded** (minimizes this confounder and allows for better understanding of the natural history of HALT/RELM)

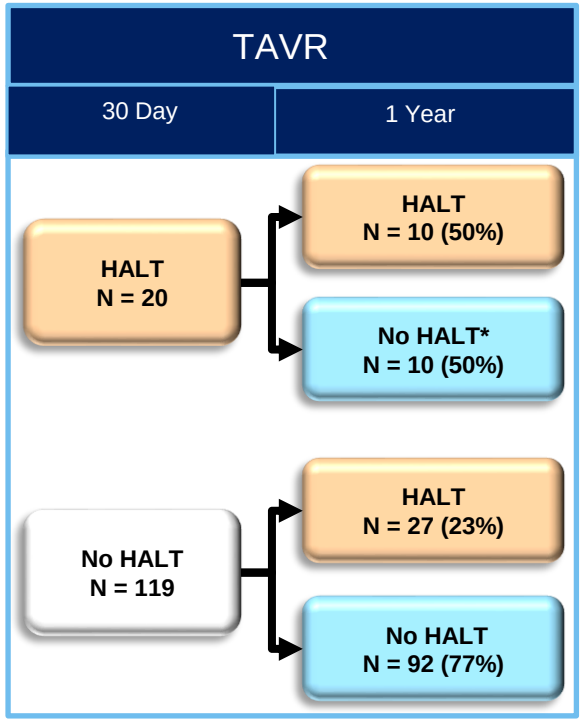


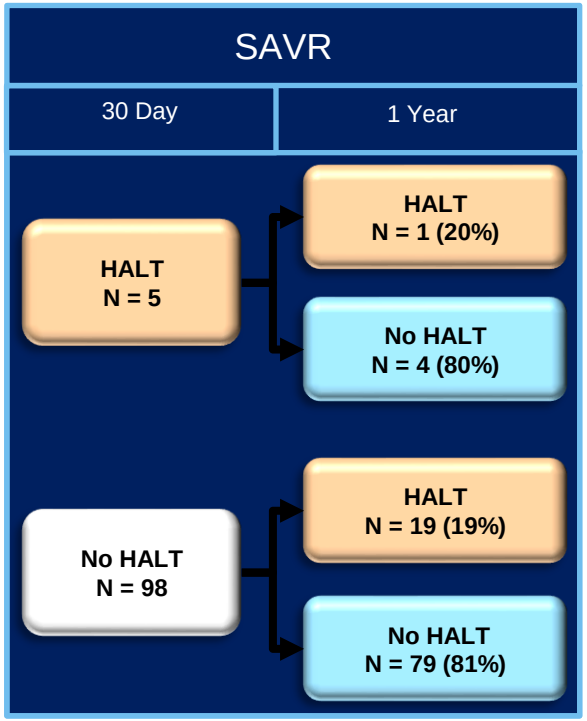
Impact of subclinical leaflet thrombosis on valve hemodynamics and clinical outcomes

- No difference in aortic valve mean gradients between patients with or without HALT at 30 days or 1 year
- Increased aortic valve gradients in patients with increasing severity of HALT; and in patients with persistent HALT at 30 days and 1 year
- Increased rates of clinical valve thrombosis and composite endpoint of stroke/transient ischemic attack/thromboembolic complications in patients with HALT

Makkar R. et al. JACC, 2020; 75(24):3003-15

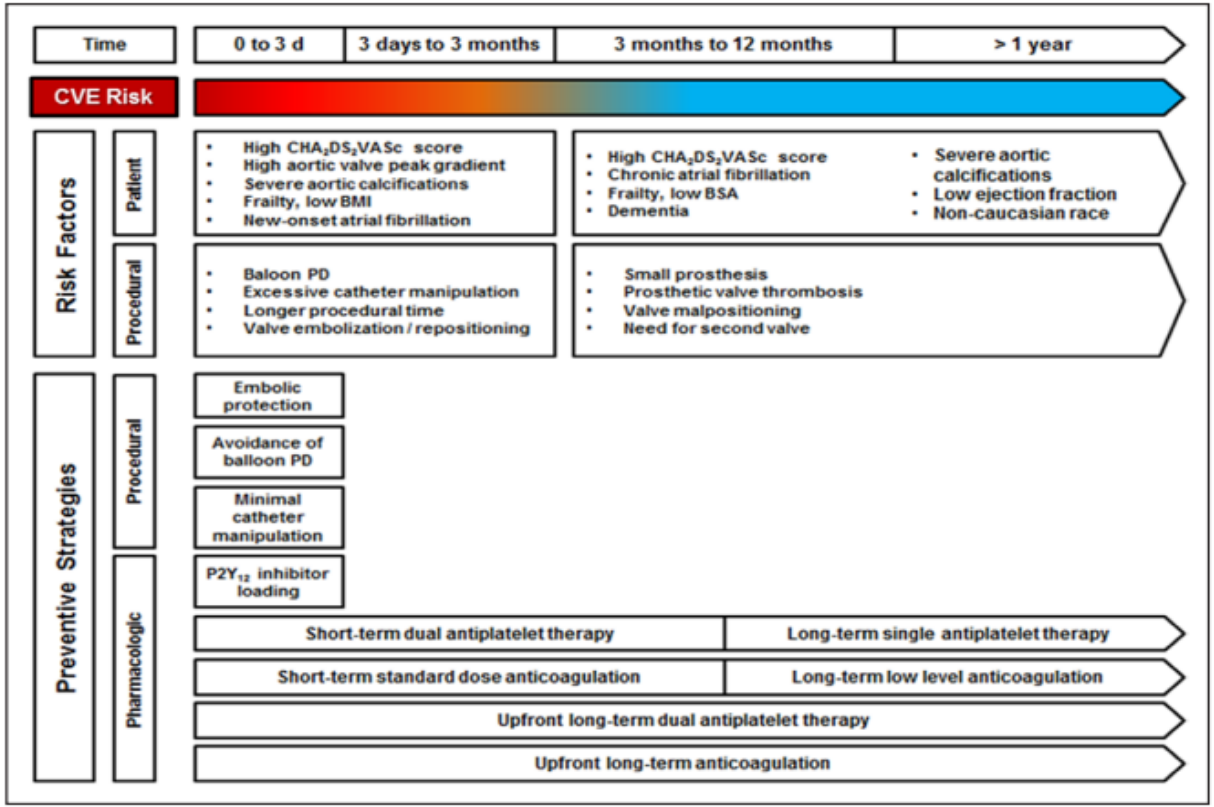
Subclinical Leaflet Thrombosis at 30 days and 1 year follow-up





Presented by Raj R. Makkar, MD on behalf of the PARTNER 3 Trial Investigators, TCT 2019

Art and Science of Cerebrovascular Event Prevention After TAVR



The evolving concepts of timing, risk factor contributions, and preventive strategies for cerebrovascular events (CVE) in patients undergoing TAVR

Dangas G and Giustino G *Circulation Cardiovascular Intervention* 2016; 9 e004307

Thirty-day outcomes of DAPT versus Aspirin after TAVR

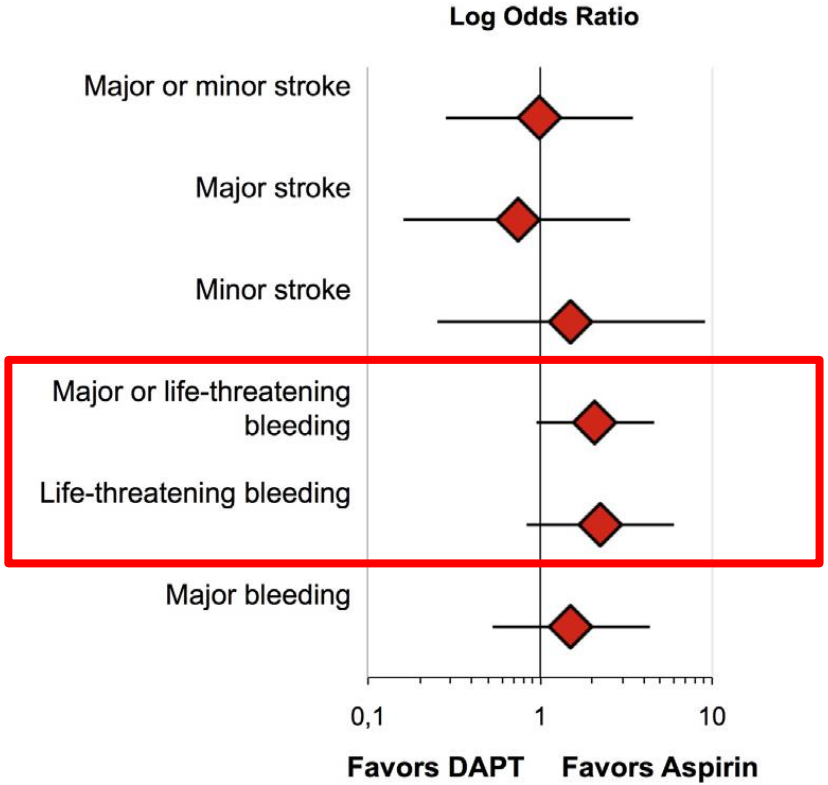
Meta-analysis of 421 patients from 3 RCTs

Three trials on DAPT versus aspirin after TAVR in non-OAC patients are actually available:

- ARTE follows 2 previous
- Stabile E et al 2014
- Ussia GP et al 2011

The pooled results of the 3 trials now cumulatively suggest:

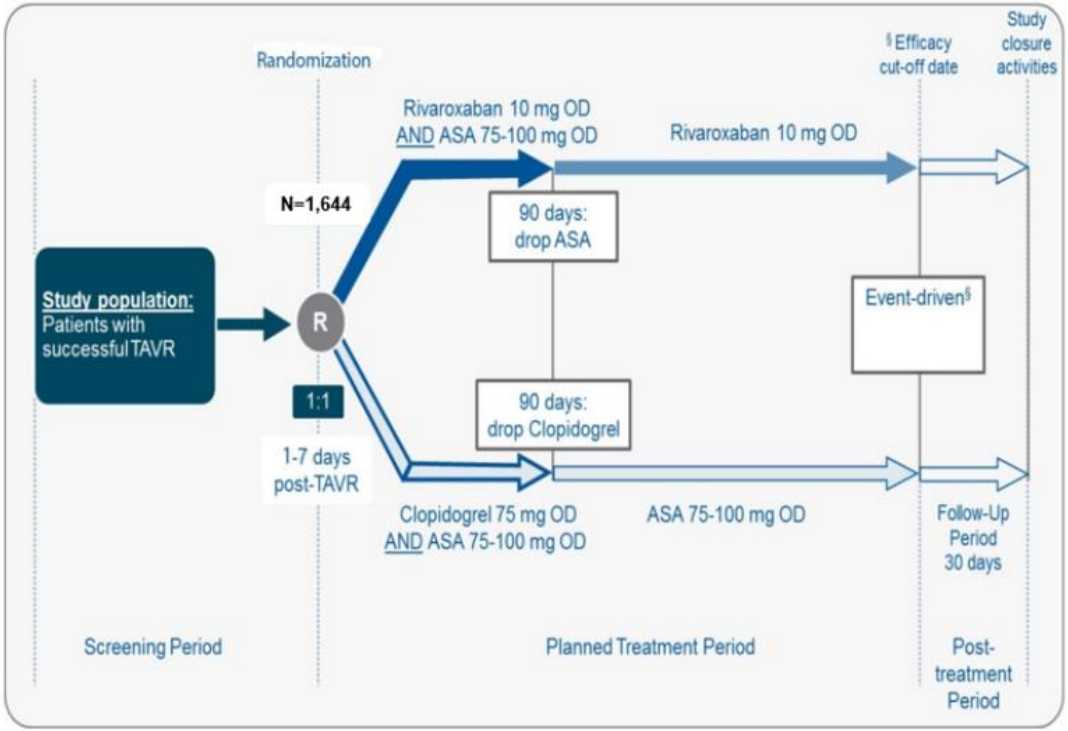
- no benefit of DAPT in reducing 30-day stroke
- trend toward an increase in major or life-threatening bleeding over



Capodanno D. JACC Cardiovasc Interv. 2017 May 11. pii: S1936-8798(17)30898-1

The GALILEO Trial in Patients w/o OAC indication

Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After TAVR to Optimize Clinical Outcomes

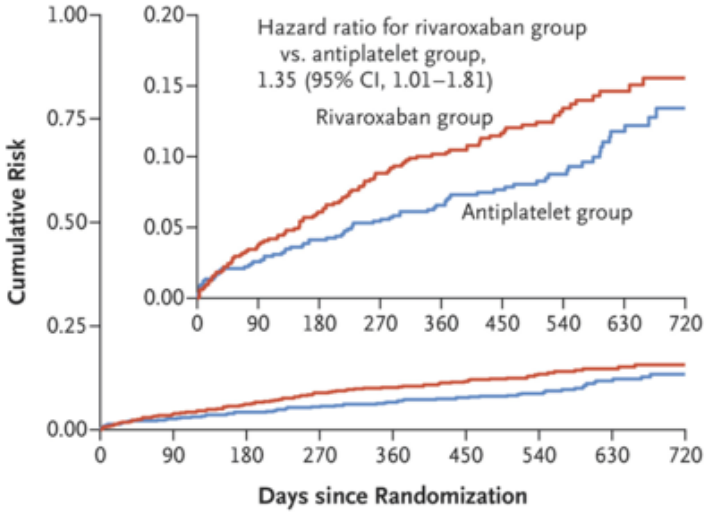


Windecker S et al, Am Heart J. 2017 Feb;184:81-87.

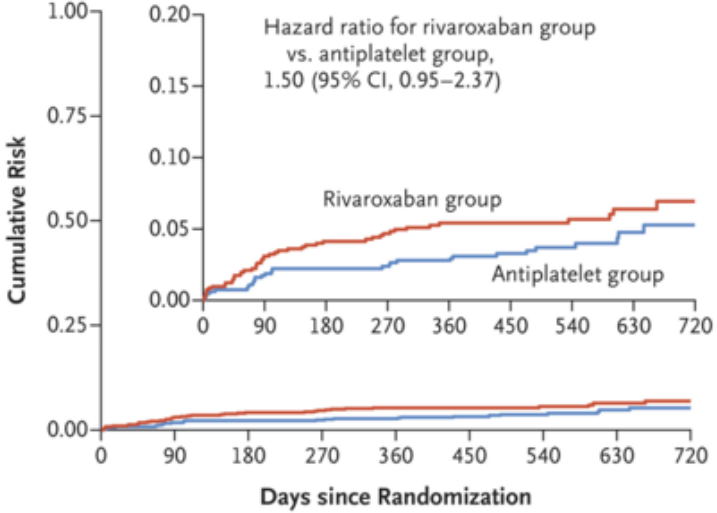
The GALILEO Trial

RESULTS

Primary Efficacy Outcome
(Composite of death, stroke, MI, valve thrombosis, pulmonary embolism, DVT, or systemic embolism)



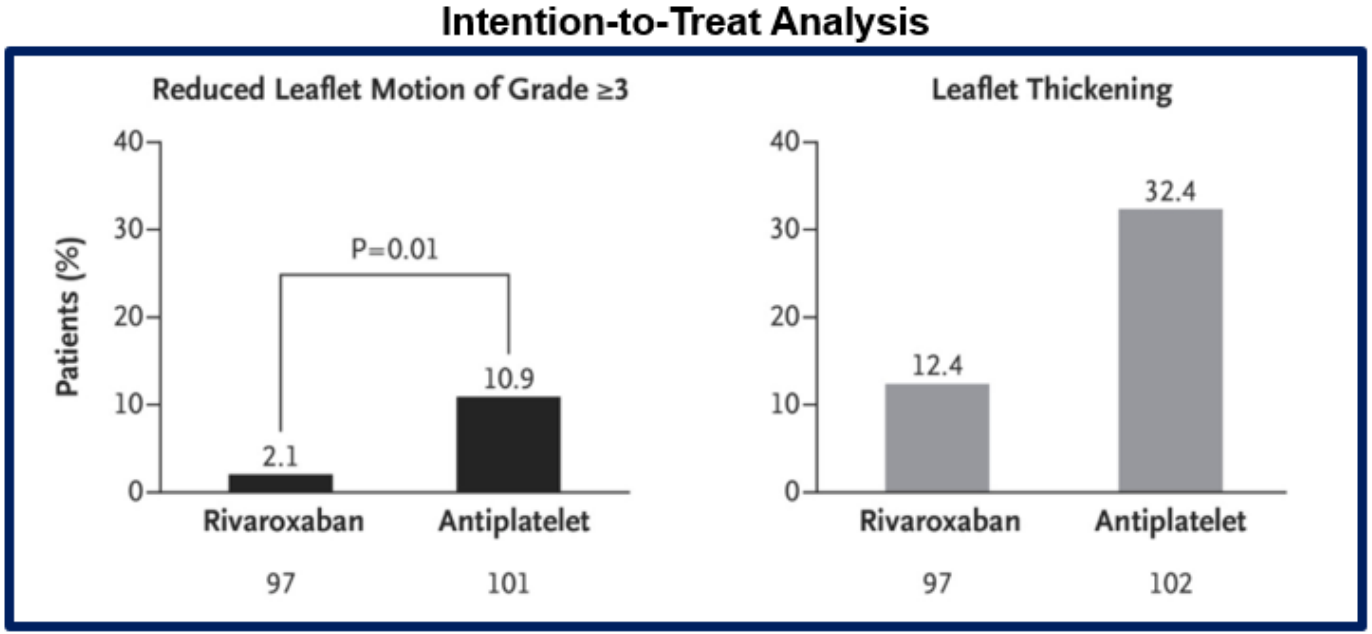
Primary Safety Outcome
(Composite of VARC life-threatening, disabling, or major bleeding)



Dangas G *et al*, *N Engl J Med. 2020 Jan 9;382(2):120-129.*

Reduced Leaflet Motion after TAVR

A Sub study of the GALILEO Trial - **GALILEO 4D**

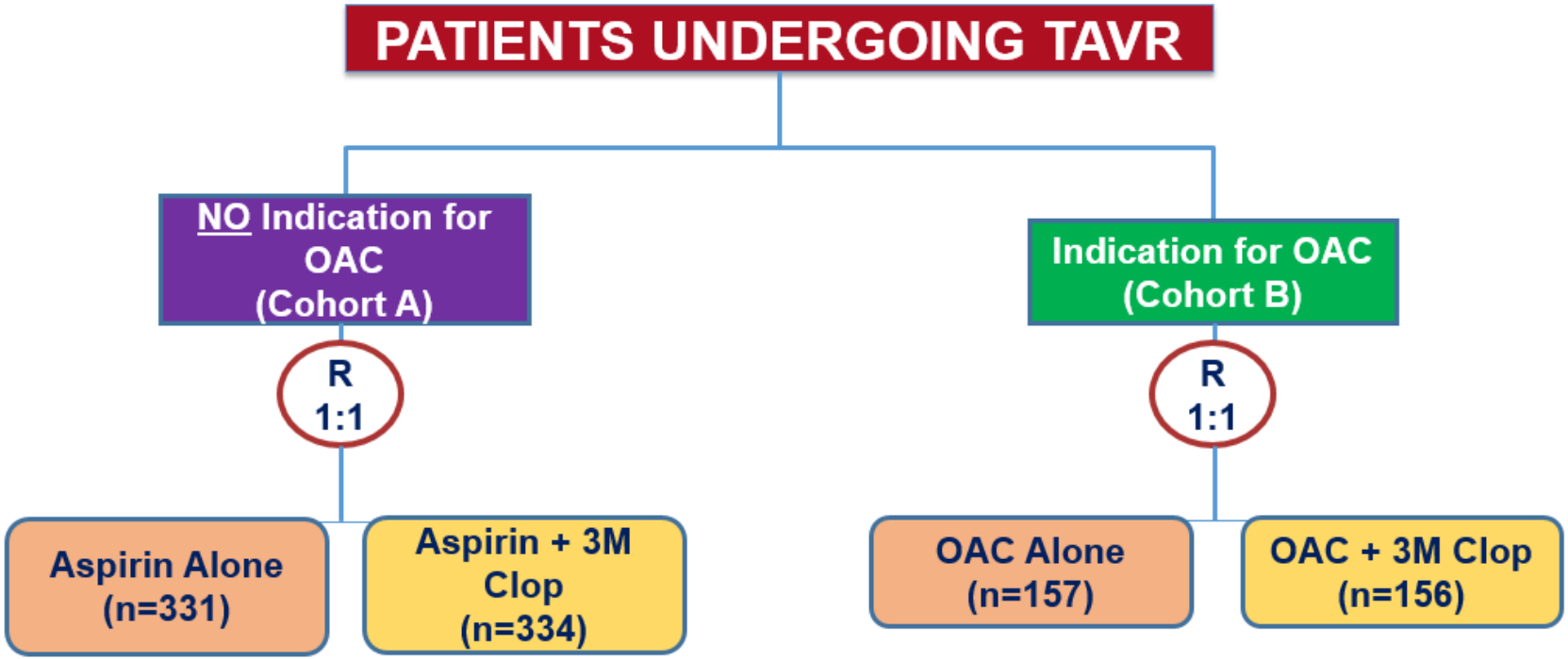


A rivaroxaban-based antithrombotic strategy was more effective than an antiplatelet-based strategy in preventing subclinical leaflet-motion abnormalities.

De Backer *et al*, *N Engl J Med. 2020 Jan 9;382(2):130-139.*

POPULAR TAVI:

Antithrombotic Therapy for Patients Undergoing TAVR

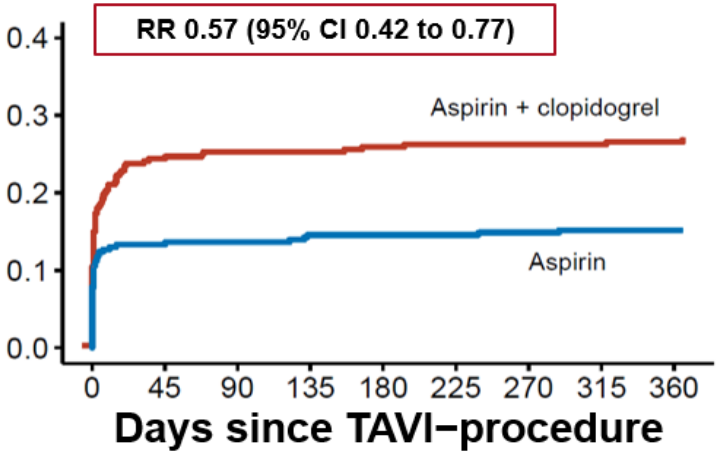


POPULAR TAVI – no OAC:

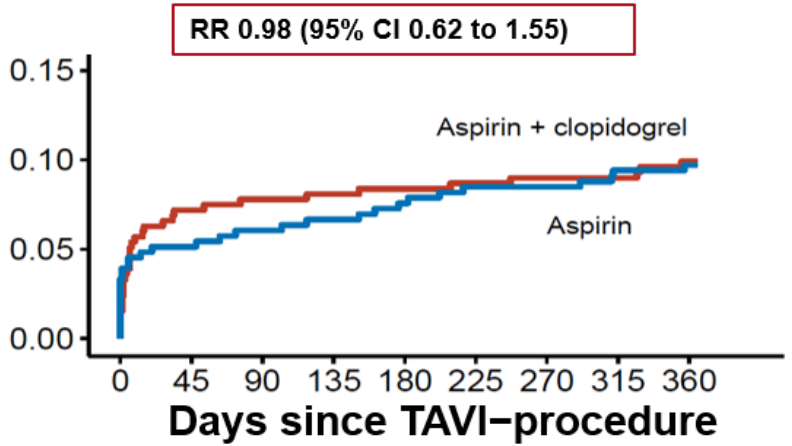
All Medications started preTAVI

Patients WITHOUT an Indication for Long-term Anticoagulation

Primary Outcomes of All Bleeding



Death from CV Causes, Ischemic Stroke, or MI

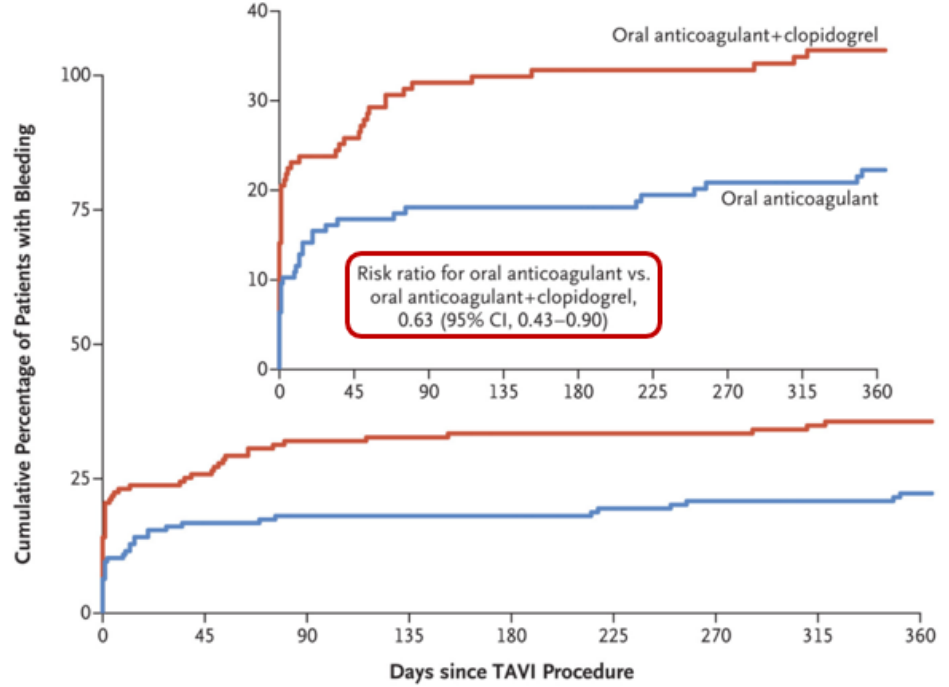


Brouwer J et al, N Engl J Med. 2020 Aug 30.

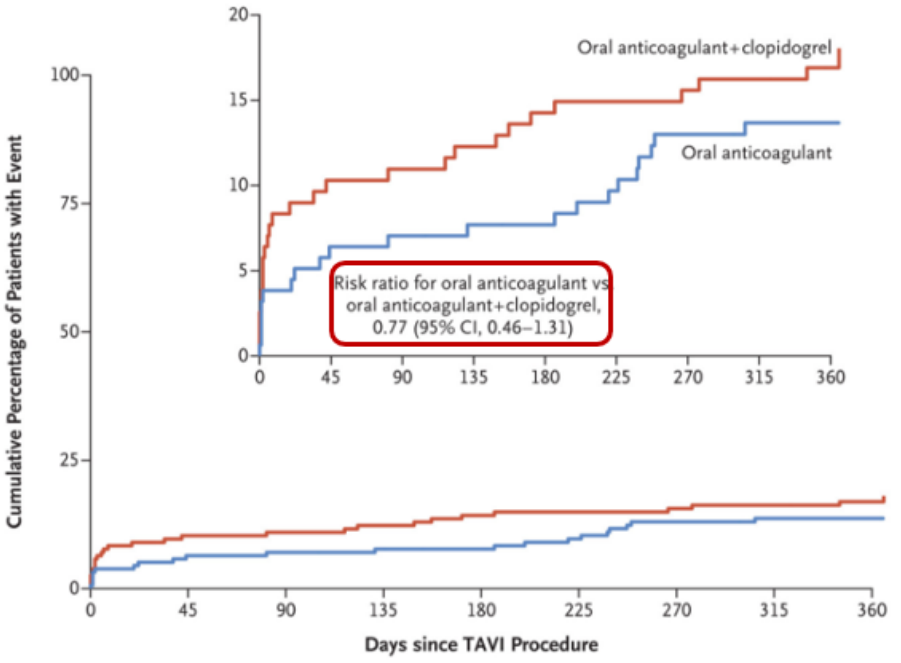
POPULAR TAVI – OAC:

Patients <u>WITH</u> an Indication for Long-term Anticoagulation (meds started preTAVI)

Primary Outcomes of All Bleeding



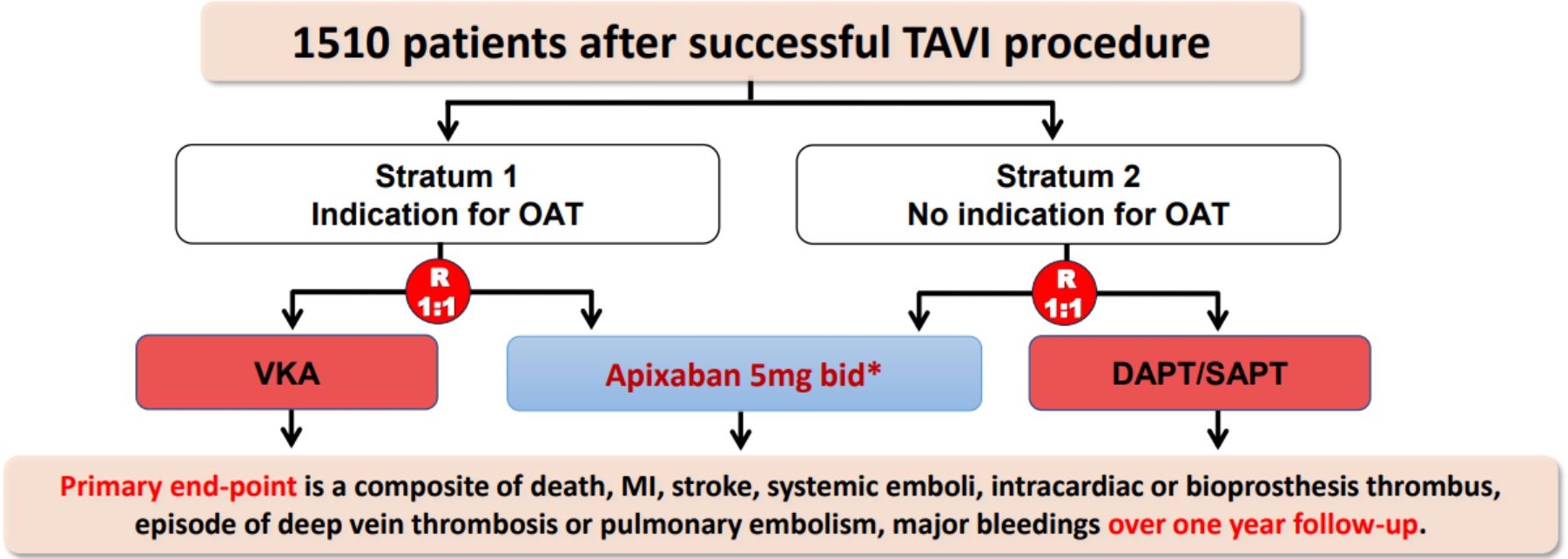
Death from CV Causes, Ischemic Stroke, or MI



Nijenhuis et al., N Engl J Med 2020; 382:1696-1707

ATLANTIS Trial

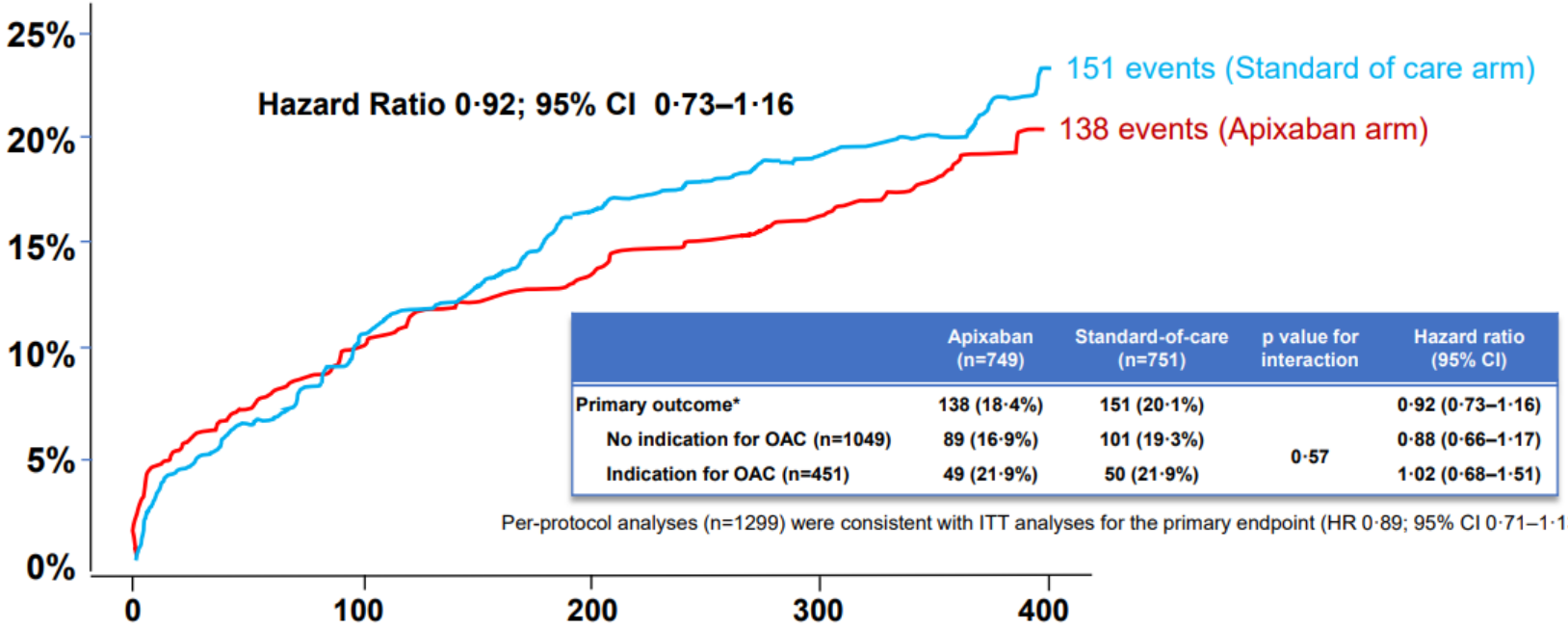
Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after TransAortic Valve Implantation for Aortic Stenosis



Presented by Collet JP at ACC 2021

ATLANTIS Trial – Primary Endpoint (Intention-to-treat)

Time to death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings



	Apixaban (n=749)	Standard-of-care (n=751)	p value for interaction	Hazard ratio (95% CI)
Primary outcome*	138 (18·4%)	151 (20·1%)		0·92 (0·73–1·16)
No indication for OAC (n=1049)	89 (16·9%)	101 (19·3%)	0·57	0·88 (0·66–1·17)
Indication for OAC (n=451)	49 (21·9%)	50 (21·9%)		1·02 (0·68–1·51)

Per-protocol analyses (n=1299) were consistent with ITT analyses for the primary endpoint (HR 0·89; 95% CI 0·71–1·13).

Presented by Collet JP at ACC 2021

ATLANTIS Trial - Outcomes in stratum 1 (post-hoc)

Indication for oral anticoagulation

	Apixaban (n=223)	Standard of Care (n=228)	Hazard ratio (95% CI)
Primary outcome*	**49 (21·9%)**	**50 (21·9%)**	**1.02 (0.68-1.51)**
Secondary efficacy outcomes			
Death, MI, any stroke/TIA	29 (13·0%)	27 (11·8%)	1.13 (0.67-1.91)
Death, any stroke/TIA or systemic embolism	28 (12·6%)	27 (11·8%)	1.09 (0.64-1.85)
Death	23 (10·3%)	23 (10·1%)	1.04 (0.58-1.86)
Safety outcomes			
Primary safety endpoint†	23 (10·3%)	26 (11·4%)	0.92 (0.52-1.60)
Minor bleeding (BARC 2 or 3a)	21 (9·5%)	27 (10·4%)	0.79 (0.44-1.39)
Any bleeding	59 (26·4%)	58 (25·4%)	1.05 (0.73-1.51)
Any Valve Thrombosis**	**2 (0·9%)**	**3 (1·3%)**	**0.67 (0.11-4.04)**

***death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings; †Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, b and 3c), as defined by Valve Academic Research Consortium-2 (VARC-2);**

**** Any evidence for valve thrombosis including HALT ¾.**

Presented by Collet JP at ACC 2021

ATLANTIS Trial - Outcomes in stratum 2 (post-hoc)

No indication for oral anticoagulation

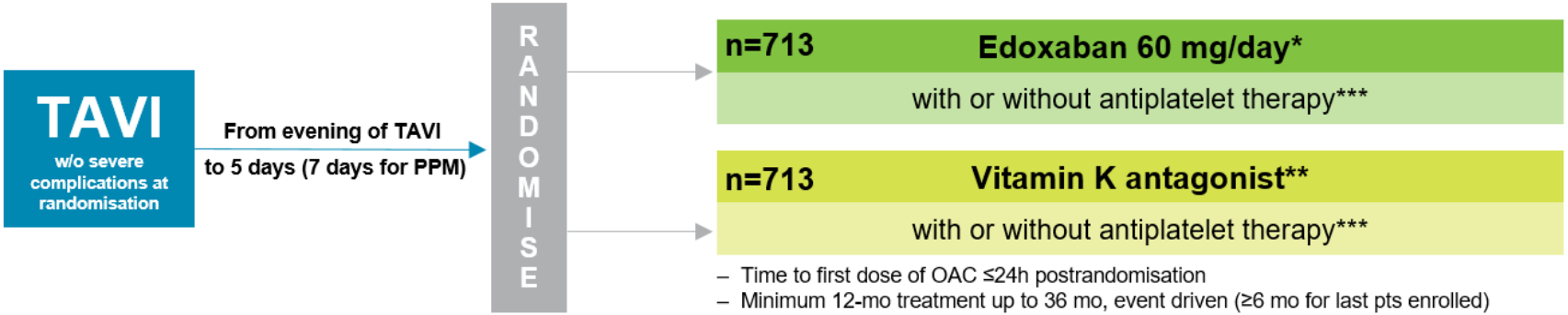
	Apixaban (n=526)	Standard of Care (n=523)	Hazard ratio (95% CI)
Primary outcome*	**89 (16·9%)**	**101 (19·3%)**	**0.88 (0.66-1.17)**
Secondary efficacy outcomes			
Death, MI, any stroke/TIA	50 (9·5%)	35 (6·7%)	1.48 (0.96-2.30)
Death, any stroke/TIA or systemic embolism	**50 (9·5%)**	**33 (6·3%)**	**1.56 (1.01-2.43)**
Death	**31 (5·9%)**	**18 (3·4%)**	**1.86 (1.04-3.34)**
• **Cardiovascular death**	**17 (3.2%)**	**13 (2·5%)**	**1·42 (0·69-2·94)**
• **Non cardiovascular death**	**14 (2·66%)**	**5 (0·96%)**	**2·99 (1·07-8·35)**
Safety outcomes			
Primary safety endpoint†	41 (7·8%)	38 (7·3%)	1.09 (0.69-1.69)
Minor bleeding (BARC 2 or 3a)	49 (9·3%)	51 (9·7%)	0.96 (0.65-1.42)
Any bleeding	115 (21·%)	112 (21·8%)	1.04 (0.80-1.35)
Any Valve Thrombosis**	**6 (1·1%)**	**32 (6·1%)**	**0.19 (0.08-0.47)**

*death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings; †Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, b and 3c), as defined by Valve Academic Research Consortium-2 (VARC-2);
** Any evidence for valve thrombosis including HALT ¾.

Presented by Collet JP at ACC 2021

Edoxaban Versus VKA After TAVI in Patients with Atrial Fibrillation - The ENVISAGE-TAVI AF Trial

Prospective, randomised, open-label, blinded evaluation, edoxaban-based regimen vs VKA-based regimen in AF patients



Edoxaban dose reduction to 30 mg in AF patients, if:
- CrCl 15–≤50 ml/min
- BW ≤60 kg†
- P-gp inhibitors per local label†

†No dose reduction criteria in the US for AF

** VKA patients target INR 2–3

In Japan: pts ≥70 yrs 1.6–2.6

*** Stratification variable: specified use of APT

APT was allowed per the treating physician's discretion including
- DAPT up to 3 months, or
- SAPT indefinitely

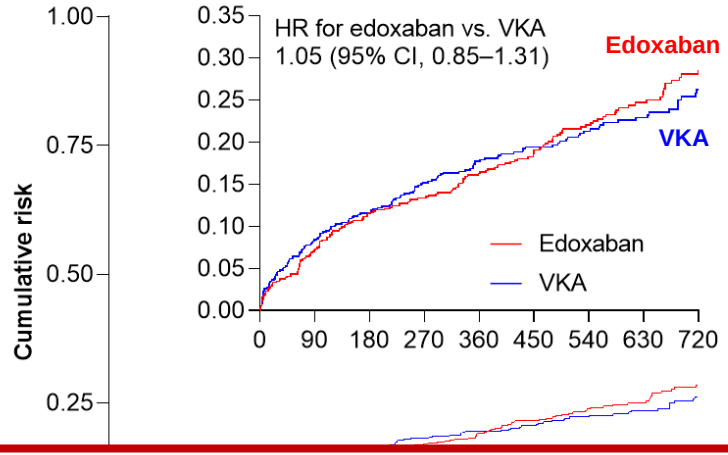
AF, atrial fibrillation; AP, antiplatelet; APT, antiplatelet therapy; ASA, aspirin; BW, body weight; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalised ratio; mo, month; OAC, oral anticoagulant; PCI, percutaneous intervention; PPM, permanent pacemaker; P-gp, P-glycoprotein; pt, patient; SAPT, single antiplatelet therapy; TAVI, transcatheter aortic valve implantation; VKA, vitamin K antagonist, yr, year.

Van Mieghem N., Dangas G et al., AHJ, 2018.

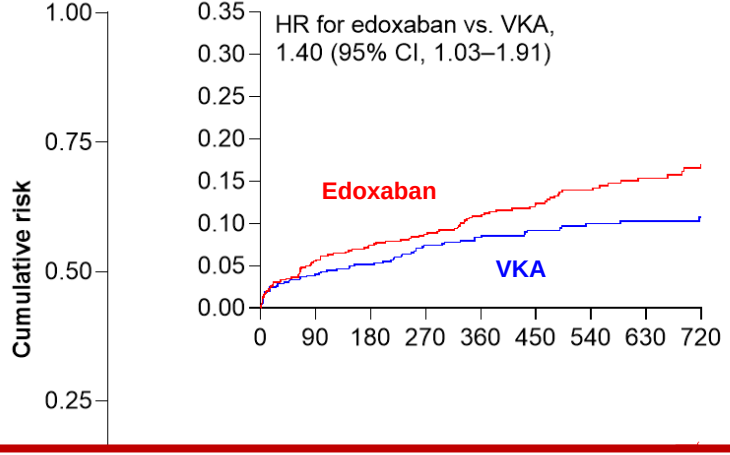
Edoxaban Versus VKA After TAVI in Patients with Atrial Fibrillation The ENVISAGE-TAVI AF Trial

NACE

(All-cause death, MI, ischemic stroke, systemic thromboembolism, valve thrombosis, and major bleeding)



Major bleeding by ISTH Definition

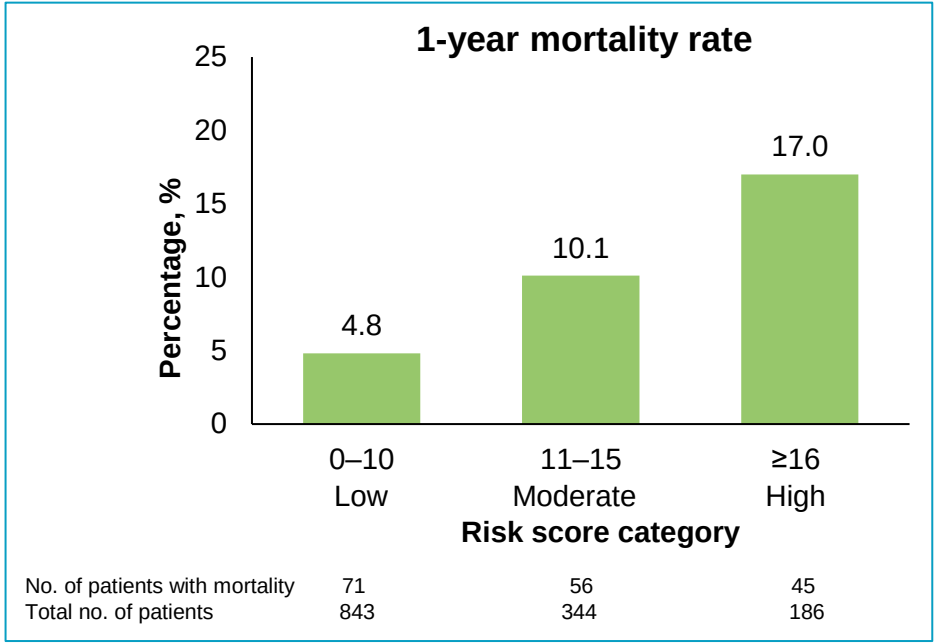


Edoxaban was non-inferior to VKA for the primary composite outcome of adverse clinical events.

Presented by Dr Dangas at ESC 2021.
Van Mieghem N and Dangas G et al, NEJM 2021 *(In Press)*

Risk Score – ENVISAGE TAVI AF

Model component	Weight
Age, years	
<80 years	0
80–89 years	4
≥90	9
CrCl, ml/min	
<30	8
30–45	2
>45	0
Type of AF	
Nonparoxysmal	4
Paroxysmal	0
NYHA, class III or IV	3
Excessive alcohol use	13
Peripheral artery disease history	5
Prior major bleeding or predisposition to bleeding	5



Analyses were Yes vs No unless otherwise indicated.
AF, atrial fibrillation; CrCl, creatinine clearance; No., number; NYHA, New York Heart Association.

Presented by Dr Dangas at ESC 2022.

Conclusions

- Limited evidence available regarding the choice of the optimal antithrombotic strategy after TAVR.

- Based on recent data from a series of clinical trials,
  - Even low dose OAC is effective against the CTA-driven diagnosis of TAVI leaflet thrombosis
  - When another OAC indication exists, monotherapy is the most reasonable option
  - No role for routine OAC (full or intermediate dose) when no clear indication exists
  - The up to now widespread clopidogrel loading pre-TAVI is no longer required
  - Prolonged combination antithrombotic strategies should be **avoided** if there is no indication for both antiplatelet and anticoagulant drugs.

- A **tailored approach** is mandatory, especially in light of the high burden of comorbidities of patients undergoing TAVR and NO obvious clinical correlation of the bothersome CTA-driven valve leaflet thrombosis
  - ? Valve durability impact of leaflet thrombosis and of the various antithrombotic regimens

More studies are required to develop a rational and customized strategic approach to balance the bleeding risks of new drug therapies and their antithrombotic value in preventing important valve-related thrombotic events.