TAVR & Antithrombotics

Antiplatelets Only Not Sufficient : Still room for NOAC

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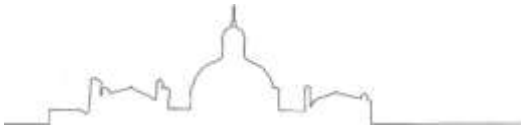

www.action-cœur.org

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Valve thrombosis

ETIOLOGY OF THROMBOEMBOLIC EVENTS AFTER TAVI

Antiplatelet Hypothesis

To obviate stent-mediated risk of platelet-related thrombosis/embolization

=> Use of DAPT

Antithrombin Hypothesis

To prevent thrombin-based thrombus formation during the first 3 months after implantation

=> Use of OAC

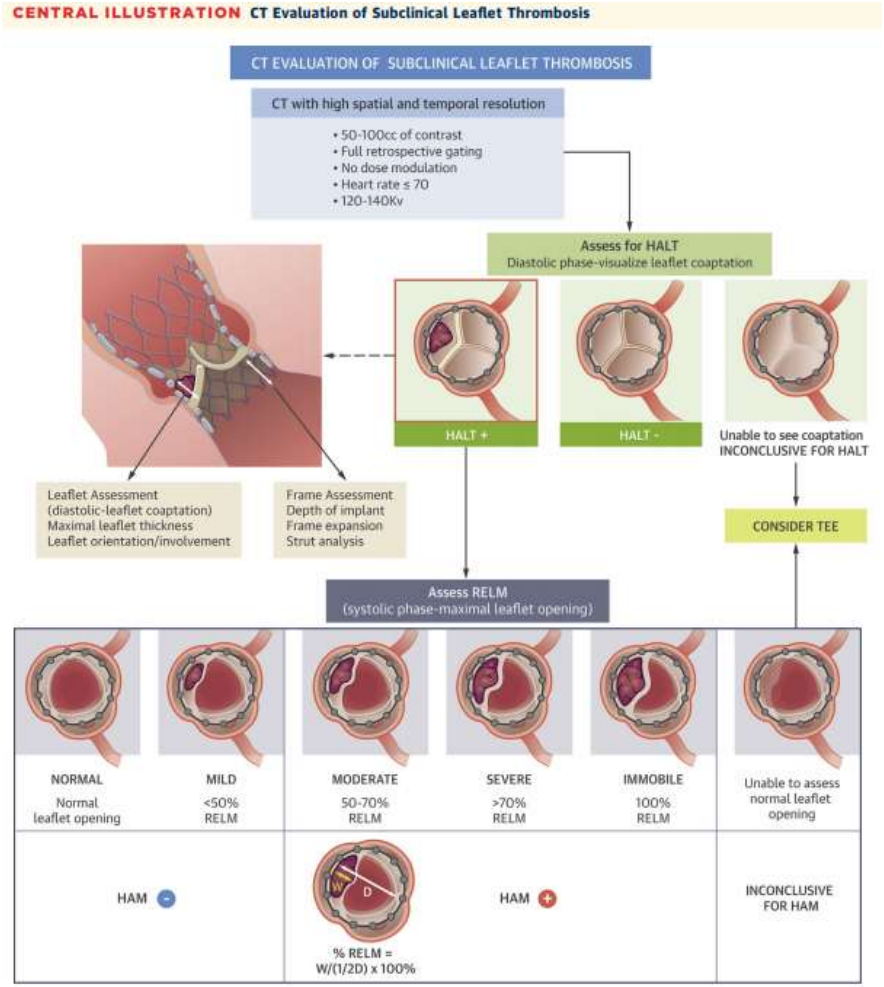
A clearer mechanistic understanding of the pathobiology of thromboembolic events during and after TAVI will provide a translatable foundation for optimal therapies

Adapted from Rodés-Cabau J, et al. J Am Coll Cardiol 2013;62:2349–2359.

Clinical and subclinical leaflet thrombosis

- **Implanted valve adds a prothrombotic environment, which may favour subclinical thrombosis**
- TAVI is associated with leaflet thickening affecting valve function - hypo-attenuated leaflet thickening (HALT)
- >50% motion reduction → hypo-attenuation affecting motion (HAM)
- May compromise implant durability, may increases risk of thromboembolism, stroke and TIAs
- **Subclinical leaflet thrombosis is an incidental finding →c**linically-significant valvular dysfunction or MACCE?

Adapted from Collet JP, et al. Am Heart J 2018;200:44–50.



Jilaihawi H, et al. JACC: Cardiovasc Imaging 2017;10:461–470.

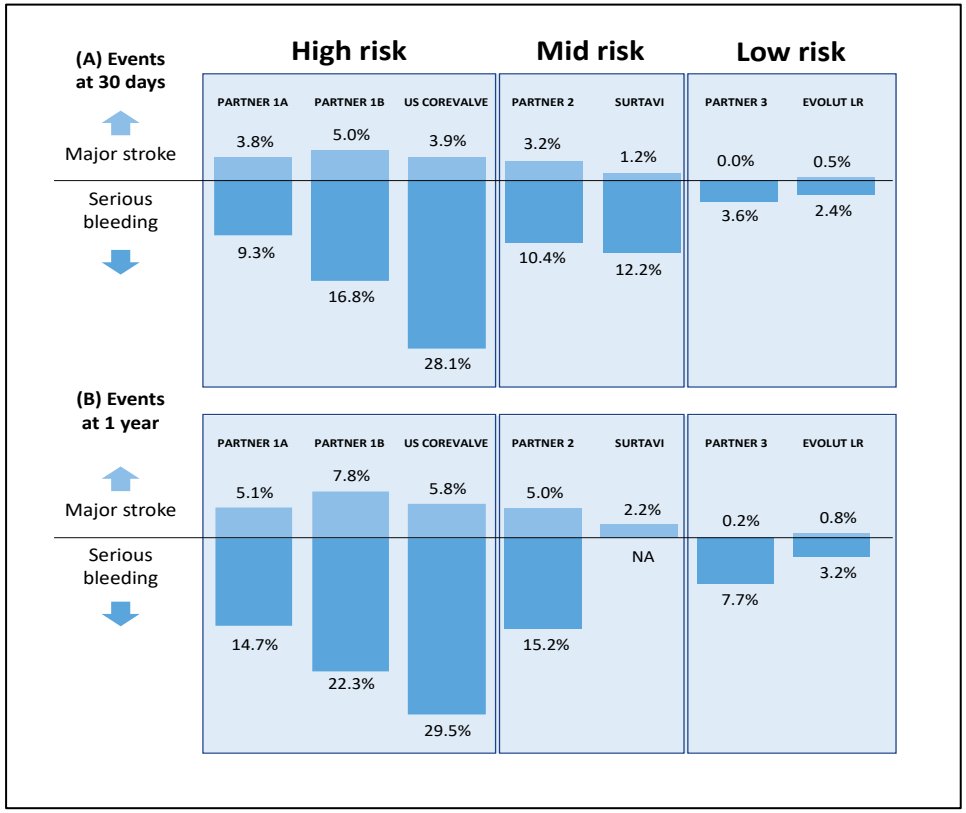
Independent correlates

N=2555	m=20 P-value	Adj. OR	95% CI upper	95% CI lower
BMI	0.002	1.05	1.02	1.09
Prior TAVI	0.025	2.96	1.15	7.64
Moderate/severe renal failure	0.034	1.46	1.03	2.08
Non-femoral access	0.049	0.53	0.28	1.02
Prosthesis ≤23 mm	<0.001	3.43	2.41	4.89
OAC at discharge	0.005	0.54	0.35	0.82

Adapted from Overtchouk P, et al. J Am Coll Cardiol 2019;73:13–21.

Thrombotic and bleeding events in the TAVI population

TRADE-OFF


(A) Events at 30 days
Major stroke
Serious bleeding
High risk
Mid risk
Low risk
PARTNER 1A
PARTNER 1B
US COREVALVE
PARTNER 2
SURTAVI
PARTNER 3
EVOLUT LR
3.8%
5.0%
3.9%
3.2%
1.2%
0.0%
0.5%
9.3%
16.8%
28.1%
10.4%
12.2%
3.6%
2.4%
(B) Events at 1 year
Major stroke
Serious bleeding
PARTNER 1A
PARTNER 1B
US COREVALVE
PARTNER 2
SURTAVI
PARTNER 3
EVOLUT LR
5.1%
7.8%
5.8%
5.0%
2.2%
0.2%
0.8%
14.7%
22.3%
29.5%
15.2%
NA
7.7%
3.2%

Determinants of Antithrombotic Therapy

- 1/3→ SCAD or stent PCI
- 1/3 → Secondary prevention for stroke
- 2/5 → Permanent AF or NOAF

- 30%→ Antiplatelet Therapy alone
- 50% → Oral Anticoagulation alone
- 25% → OAC + APT

SCAD, stable coronary artery disease.

Periprocedural management of TAVI

- TAVI is a minimally-invasive alternative for patients with aortic stenosis who need a valve replacement[1]
- 30% of patients undergoing TAVI have a history of atrial fibrillation (AF) and an additional 10% develop AF after TAVI[2]
- AF may have an independent impact on mortality in TAVI[3]
- Treating AF with anticoagulation is a balance between risk of bleeding and risk of thrombosis[4]

1. Collet JP, et al. Am Heart J 2018;200:44–50; 2. Franchin L, et al. Eur Heart J 2020;41 DOI: 10.1093/ehjci/ehaa946.2595; 3. Tarantini G, et al. Eur Heart J 2017;38:1285–1293; 4. Lip GYH. Stroke 2008;39:1406–1408.

Guidelines

Management of antithrombotics in patients with TAVI

2017 ESC/EACTS Guidelines for the management of valvular heart disease

	Class	Level
Anticoagulation		
DAPT should be considered for the first 3–6 months after TAVI, followed by lifelong SAPT in patients who do not need OAC for other reasons	IIa	C
SAPT may be considered after TAVI in the case of high bleeding risk	IIb	C
OAC may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis	IIb	C
NOACs should be considered as alternative to VKAs after the third month of implantation in patients who have AF associated with a SAVR or TAVI	IIa	C

Adapted from Baumgartner H, et al. Eur Heart J 2017;38:2739–2791.

Management of antithrombotics in patients with TAVI

2020 ACC/AHA Guideline for the Management of Patients With

1	A	1. For patients with AF and native valve heart disease (except rheumatic mitral stenosis [MS]) or who received a bioprosthetic valve >3 months ago, a non-vitamin K oral anticoagulant (NOAC) is an effective alternative to VKA anticoagulation and should be administered on the basis of the patient's CHA_2DS_2-VASc score (17,18).
2a	B-NR	3. For patients with new-onset AF ≤3 months after surgical or transcatheter bioprosthetic valve replacement, anticoagulation with a VKA is reasonable (19-22).
2a	B-R	5. For patients with a bioprosthetic TAVI, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants (426-428).
2b	B-NR	10. For patients with a bioprosthetic TAVI who are at low risk of bleeding, dual-antiplatelet therapy with aspirin 75 to 100 mg and clopidogrel 75 mg may be reasonable for 3 to 6 months after valve implantation (426,427,443).
2b	B-NR	11. For patients with a bioprosthetic TAVI who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after valve implantation (437, 445-447).
3: Harm	B-R	12. For patients with bioprosthetic TAVI, treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75-100 mg) is contraindicated in the absence of other indications for oral anticoagulants (444).

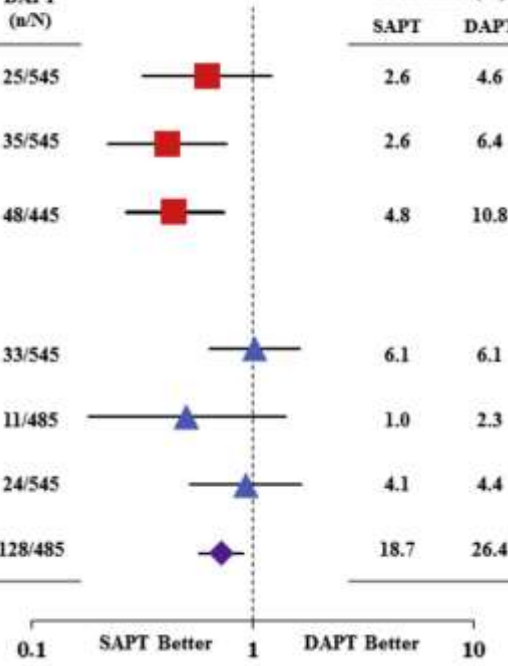
Adapted from Otto CM, et al. J Am Coll Cardiol 2021;77:e25–197.

No indication for oral anticoagulation

CLINICAL TRIALS

FIGURE 1 Safety and Efficacy of SAPT Versus DAPT

Included trials:	POPular TAVI cohort A (n=665 ; 61.2%)		ARTE (n=222 ; 20.4%)	SAT-TAVI (n=120 ; 11.1%)	Ussia et al. (n=79 ; 7.3%)				
SAFETY OUTCOMES	SAPT (n/N)	DAPT (n/N)	Event rates (%) SAPT	DAPT	Risk ratio	95%CI	I^2	P-value	
Life-threatening or disabling bleeding	14/541	25/545	2.6	4.6	0.56	0.30 – 1.07	0%	0.08	
Major bleeding	14/541	35/545	2.6	6.4	0.40	0.22 – 0.74	0%	0.003	
Life-threatening, disabling or major bleeding	21/442	48/445	4.8	10.8	0.44	0.27 – 0.72	0%	0.001	
EFFICACY OUTCOMES									
All-cause death	33/541	33/545	6.1	6.1	1.01	0.63 – 1.61	0%	0.97	
Myocardial infarction	5/481	11/485	1.0	2.3	0.48	0.18 – 1.32	0%	0.16	
Stroke	22/541	24/545	4.1	4.4	0.92	0.53 – 1.63	0%	0.79	
Composite of safety or efficacy outcomes	90/481	128/485	18.7	26.4	0.71	0.56 – 0.90	0%	0.004	



Guedeney P, et al. J Am Coll Cardiol Cardiovasc Interv 2021;14:234–236.

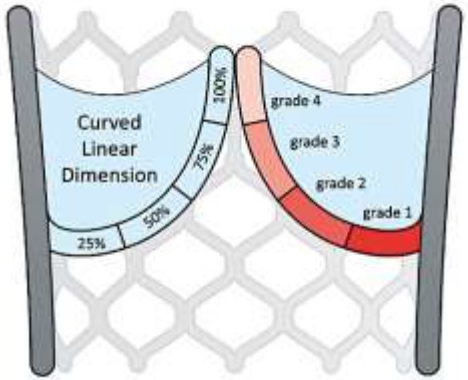
POPULAR TAVI – no OAC cohort

	Aspirin (N=331)	Aspirin + clopidogrel (N=334)	RISK RATIO (95% CI)
Death, n (%)			
Death from any cause	21 (6.3)	19 (5.7)	1.12 (0.61 to 2.04)
Death from cardiovascular causes	14 (4.2)	13 (3.9)	1.09 (0.52 to 2.28)
Stroke, n (%)			
Ischemic	17 (5.1)	18 (5.4)	0.95 (0.5 to 1.82)
Hemorrhagic	0	1 (0.3)	
Myocardial infarction, n (%)	4 (1.2)	6 (1.8)	0.67 (0.19 to 2.36)
Bleeding, n (%)			
Major, life-threatening, or disabling	17 (5.1)	36 (10.8)	0.48 (0.27 to 0.83)
Minor	33 (10.0)	53 (15.9)	0.63 (0.42 to 0.94)

Brouwer J, et al. N Eng J Med 2020;383:1447–1457.

Valve Thrombosis – 4DCT analysis

- Reduced leaflet motion (RLM) was defined as:
  - **Grade 0**: normal/unrestricted
  - **Grade 1**: minimally restricted (<25%)
  - **Grade 2**: mildly restricted (25-50%)
  - **Grade 3**: moderately restricted (50-75%)
  - **Grade 4**: largely immobile (>75%)



Blanke P, et al. JACC Cardiovasc Imaging. 2019;12:1-24.

Adapted from Blanke P, et al. JACC Cardiovasc Imaging 2019;12:1–24.

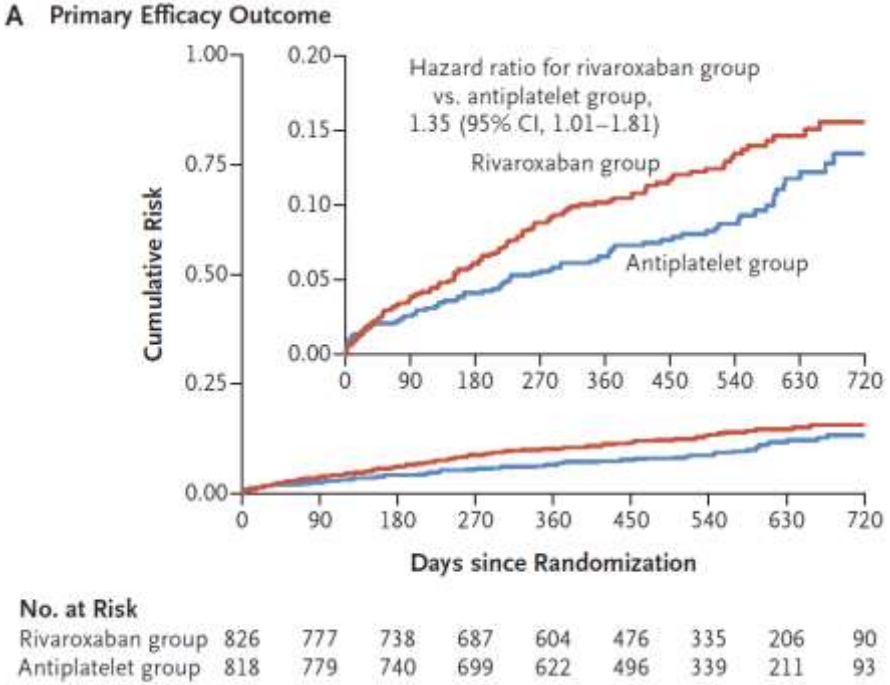
4DCT outcomes

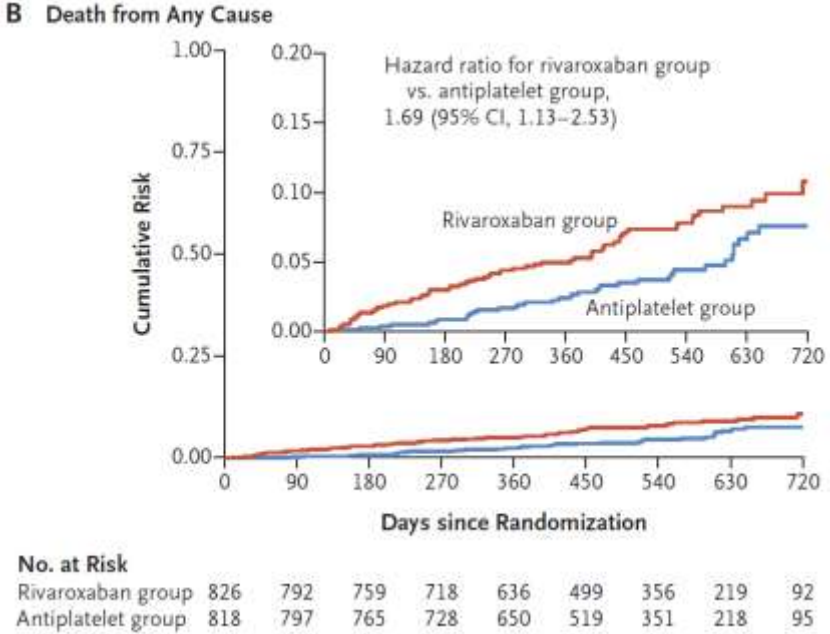
Reduced leaflet motion (RLM)			
Analysis at patient level	Rivaroxaban (N=97)	Antiplatelet (N=101)	Δ proportions (95%CI)
At least one leaflet with RLM grade ≥ 3	2.1%	10.9%	-8.8% (-16.5 to - 1.9%)
Analysis at leaflet level	Rivaroxaban (N=291)	Antiplatelet (N=303)	Δ proportions (95%CI)
Number of leaflets with RLM grade ≥ 3	1.0%	4.6%	-3.6% (-6.7 to -0.9%)

Primary endpoint

Backer OD, et al. N Eng J Med 2020;382:130–139.

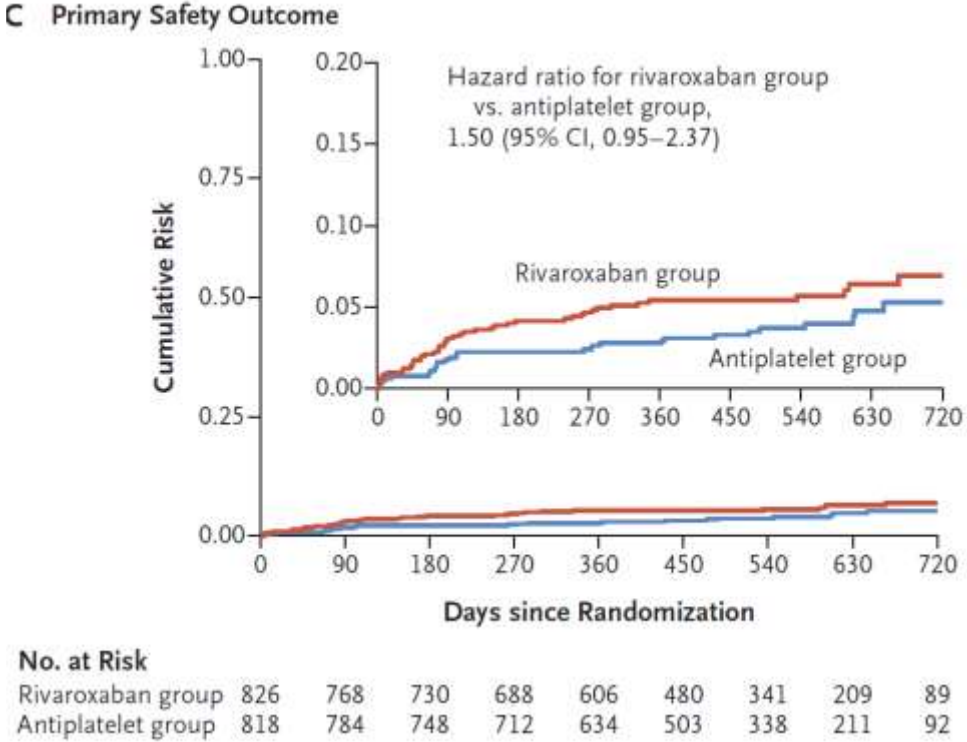
The GALILEO Study





Dangas GD, et al. N Eng J Med 2020;382:120–129.

The GALILEO Study

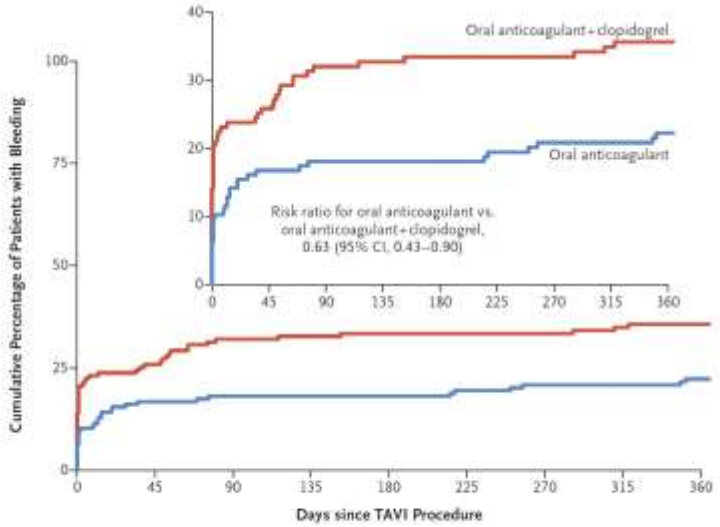


Dangas GD, et al. N Eng J Med 2020;382:120–129.

Indication for oral anticoagulation

POPULAR TAVI (NCT02247128)

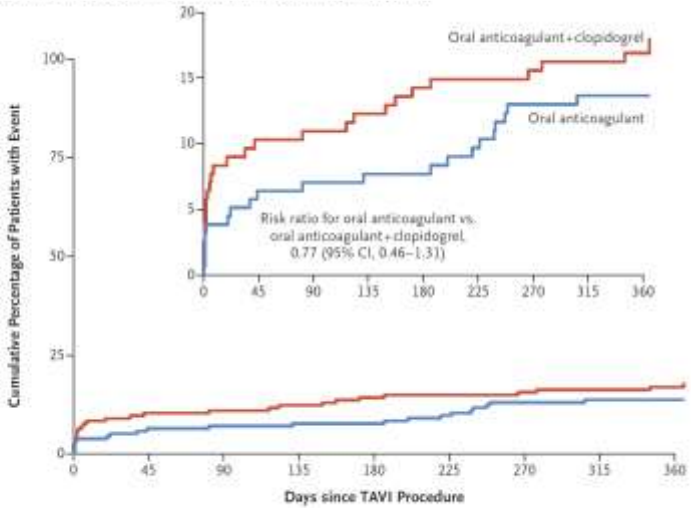
Primary outcome: All bleeding



No. at Risk

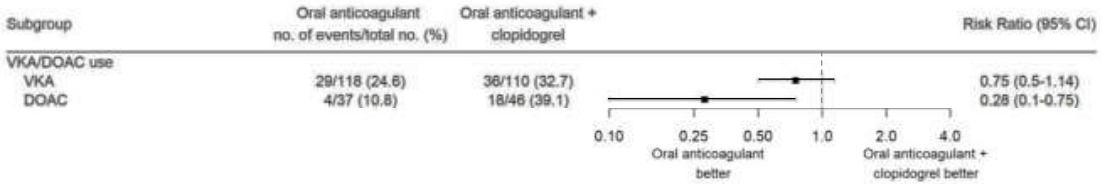
Oral anticoagulant + clopidogrel	156	108	98	96	92	91	91	88	87
Oral anticoagulant	157	126	123	123	123	117	114	112	110

Ischemic events



No. at Risk

Oral anticoagulant + clopidogrel	156	136	135	133	130	129	128	127	124
Oral anticoagulant	157	146	145	143	141	136	131	129	129



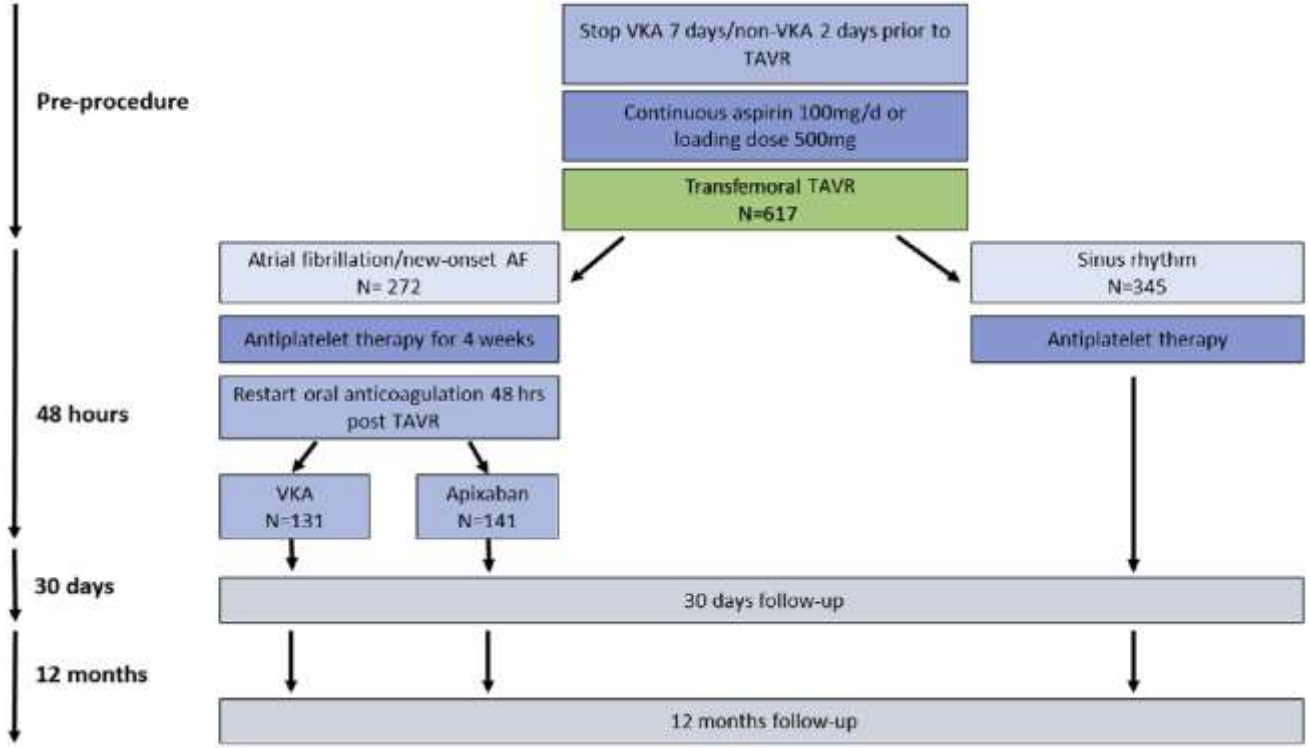
Nijenhuis VJ, et al. N Eng J Med 2020;382:1696–1707.

Secondary outcome

	OAC (N=157)	OAC + CLOPIDOGREL (N=156)	RISK RATIO (95% CI)
Death, n (%)			
Death from any cause	21 (13.4)	24 (15.4)	0.87 (0.51 to 1.50)
Death from cardiovascular causes	13 (8.3)	20 (12.8)	0.65 (0.33 to 1.25)
Stroke, n (%)			
Ischemic	8 (5.1)	9 (5.8)	0.88 (0.35 to 2.23)
Hemorrhagic	1 (0.6)	0	
Myocardial infarction, n (%)	1 (0.6)	1 (0.6)	0.99 (0.06 to 15.75)
Bleeding, n (%)			
Major, life-threatening, or disabling	14 (8.9)	26 (16.7)	0.54 (0.29 to 0.99)
Minor	20 (12.7)	28 (17.9)	0.71 (0.42 to 1.21)

Adapted from Nijenhuis VJ, et al. N Eng J Med 2020;382:1696–1707.

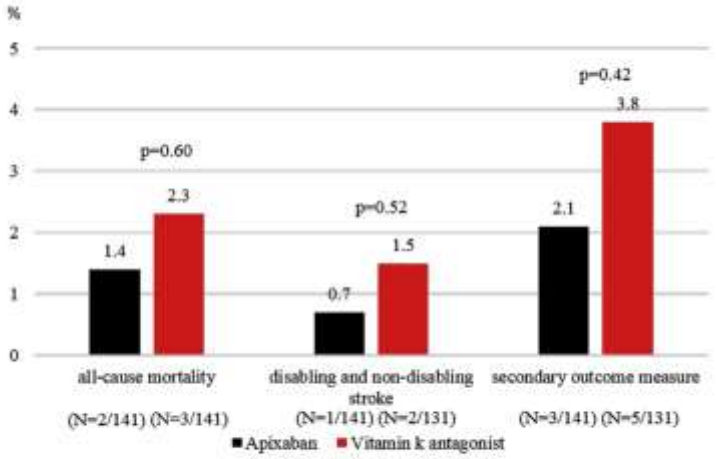
Apixaban in AF after TAVR



J Am Coll Cardiol Intv 2017;10:66–74

Apixaban in AF after TAVR

FIGURE 3 Short-Term Follow-Up Until 30 Days Post-Procedure



Apixaban was associated with lower rates of all-cause mortality and all stroke compared with a vitamin K antagonist in patients with atrial fibrillation.

TABLE 6 Patients With Atrial Fibrillation: 12-Month Follow-Up

	Apixaban (n = 81)	Vitamin K Antagonist (n = 50)	p Value
MACE	27.2 (22)	18.0 (9)	0.34
All-cause mortality	23.4 (19)	12.0 (6)	0.18
Disabling and nondisabling stroke	1.2 (1)	2.0 (1)	0.73
Rehospitalization	15.7 (14)	16.0 (8)	0.87
Secondary outcome measure*	24.7 (20)	14 (7)	0.23

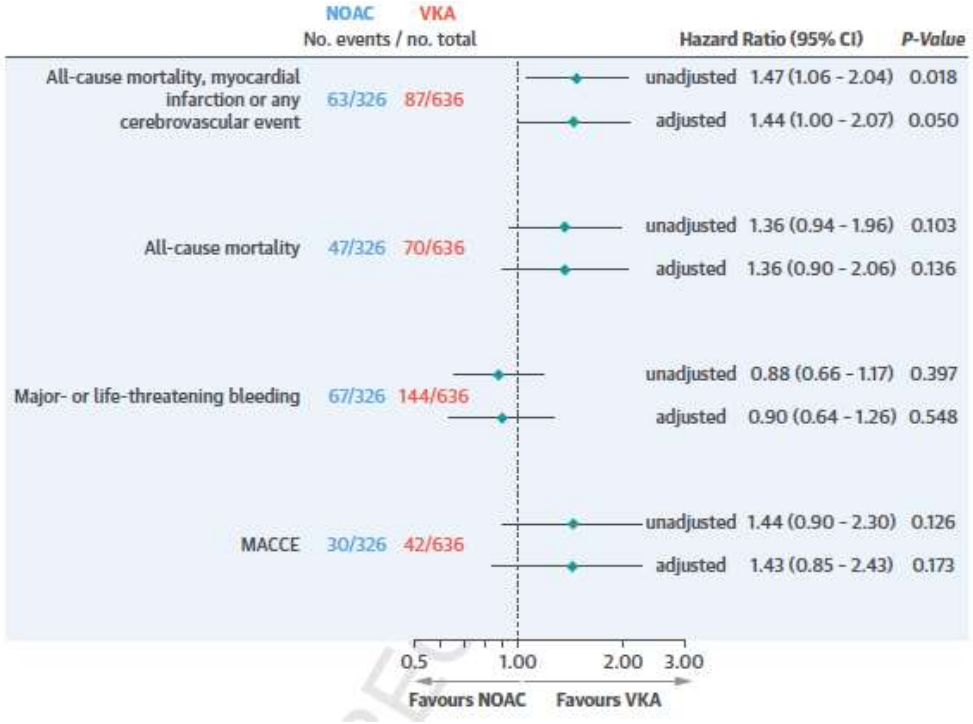
Values are % (n). *All-cause mortality and all stroke.
MACE = major adverse cardiac event(s).

Study limitations

- not a randomized controlled trial,
- First comparison between VKA and apixaban
- all the drawbacks of a registry,
- Larger randomized controlled trials are

J Am Coll Cardiol Intv 2017;10:66–74

Observational registry study of NOAC use in TAVI conducted in four European centers



Of the 326 patients discharged with NOAC therapy:

- 175 (53.7%) received rivaroxaban
- 128 (39.2%) received apixaban
- 23 (7.1%) were on dabigatran therapy

Study limitations

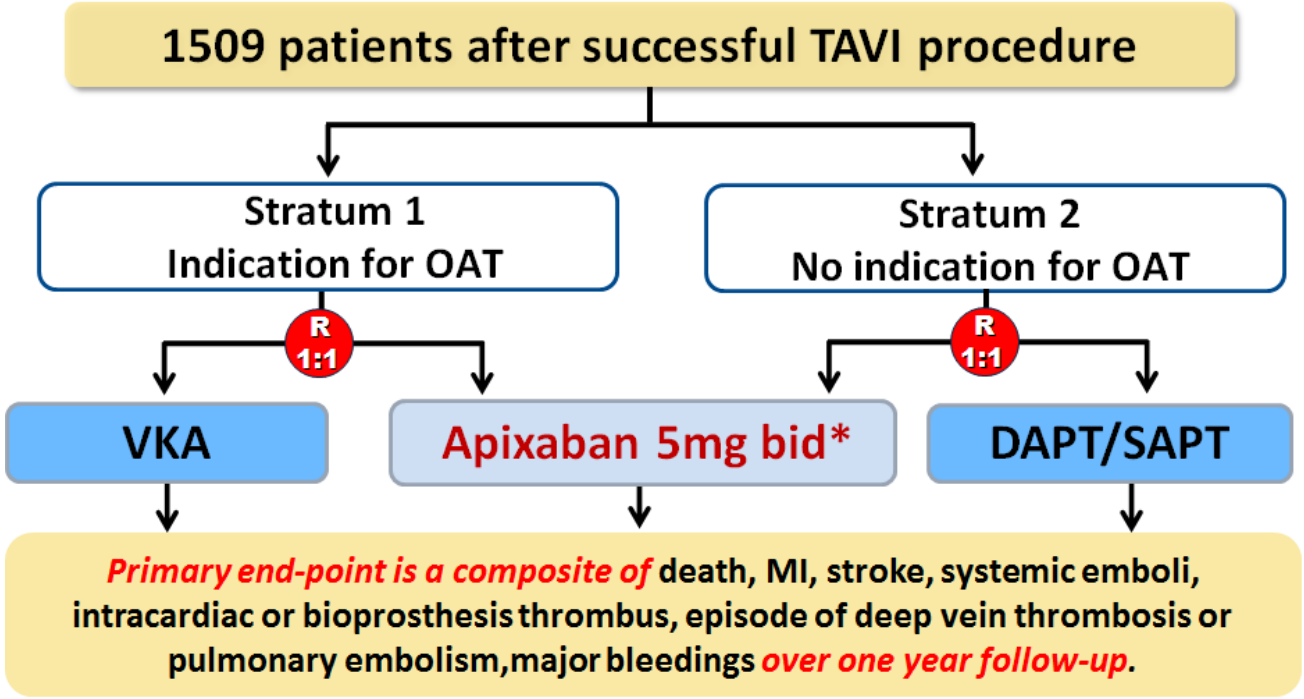
- Hypothesis-generating study in a non-randomized-controlled setting
- Lack of a centralized event adjudication
- Drug usage compliance and dosage was not assessed
- The timing of initiation and type of OAC treatment was done according to local regulations
- Lack of systematic computer tomography at follow-up (limiting ability to investigate rate of subclinical BVT)
- Lack of information about mitral valve disease

The higher ischemic event rate observed with NOACs needs to be evaluated in large randomized trials

Jochheim D, et al. JACC Cardiovasc Interv 2019;12:1566–1576.

ATLANTIS

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



*2.5mg bid if creatinine clearance 15–29 mL/min or if two of the following criteria: age ≥80 years, weight ≤60kg or creatinine ≥1.5mg/dL (133µMol/L).

The 2.5mg bid dose was also given to patients without these criteria but who require concomitant antiplatelet therapy due to recent stenting/ACS or if long-term SAPT is being maintained after randomization due to physician's choice.

CONCLUSIONS

- The valve adds a prothrombotic environment
- Bleeding is the predominant event
- AF and NOAF are strong determinants of CVE
- SAPT → default therapy if no need for OAC
- NAOC > SAPT for the prevention of subclinical valve thrombosis
- No need for antiplatelet therapy on top of OAC
- Whether NOAC should be the standard of care remains to be evaluated

Thank you