TAVR Antithrombotics
Less is More

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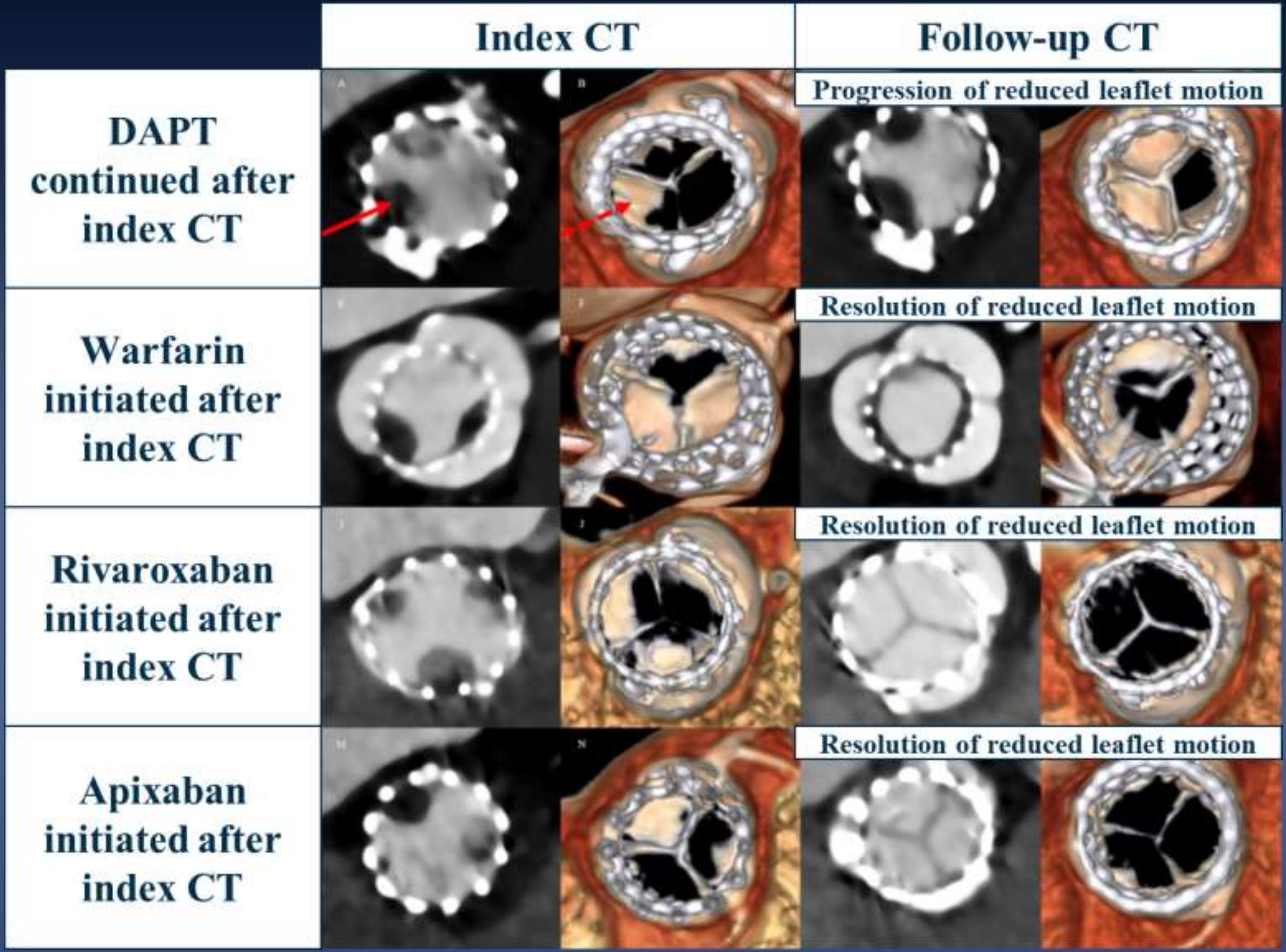
Disclosures

Research Grant to Institution:
Abbott, Bayer, Daiichi-Sankyo, Boston Scientific

Consultant/Advisory Board:
Janssen, Boston Scientific, Philips

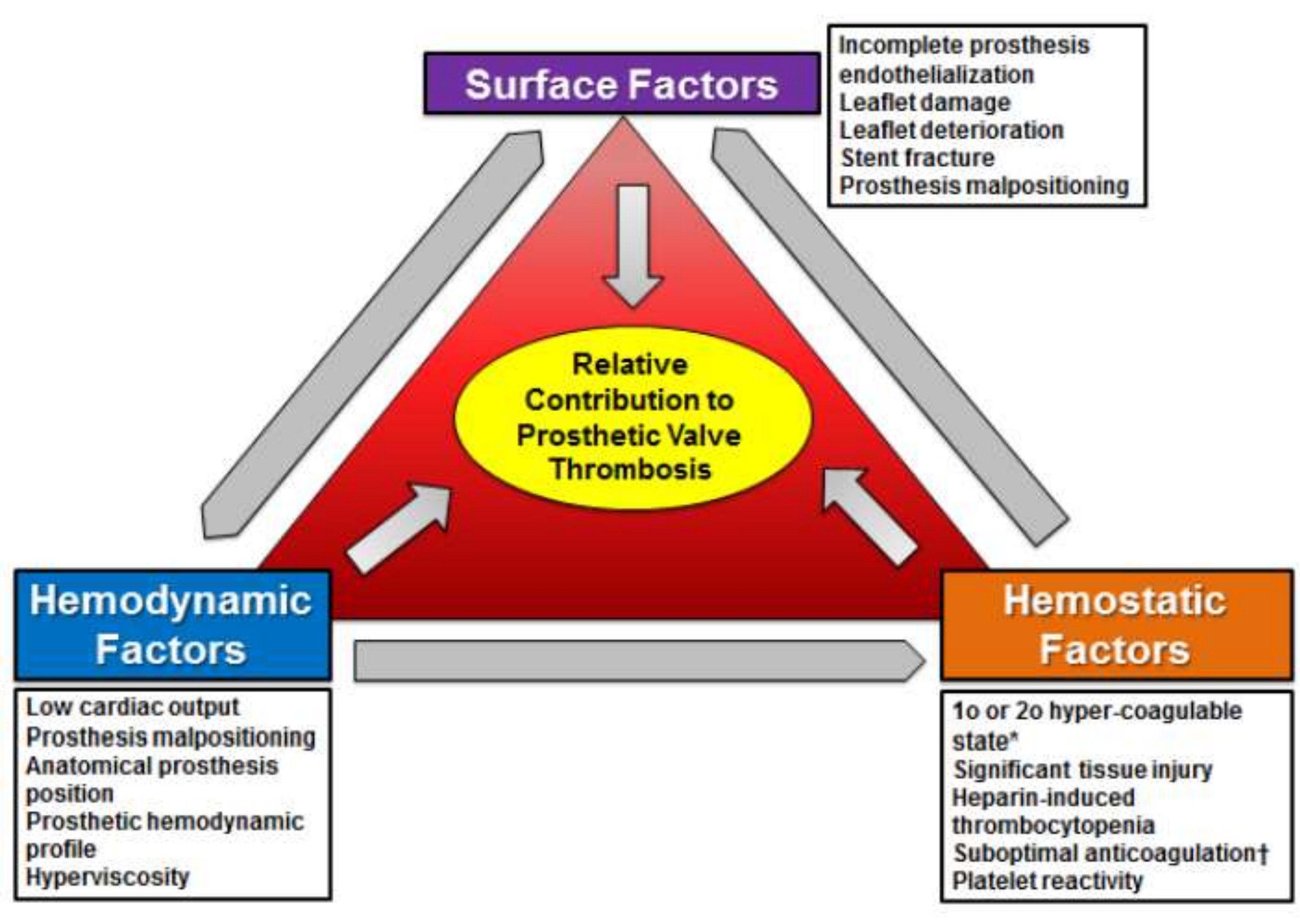
Common Stock (divested): Medtronic

Warfarin/NOAC to prevent/treat HALT/RLM



Makkar, TCT 2017

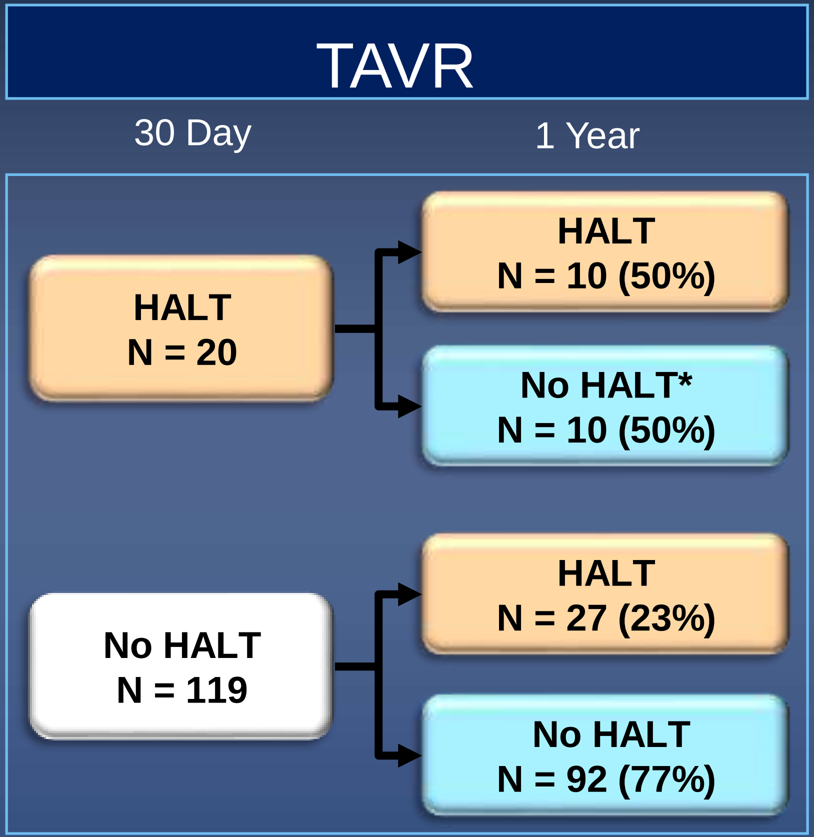
Prosthetic Valve Thrombosis Underlying Pathophysiology

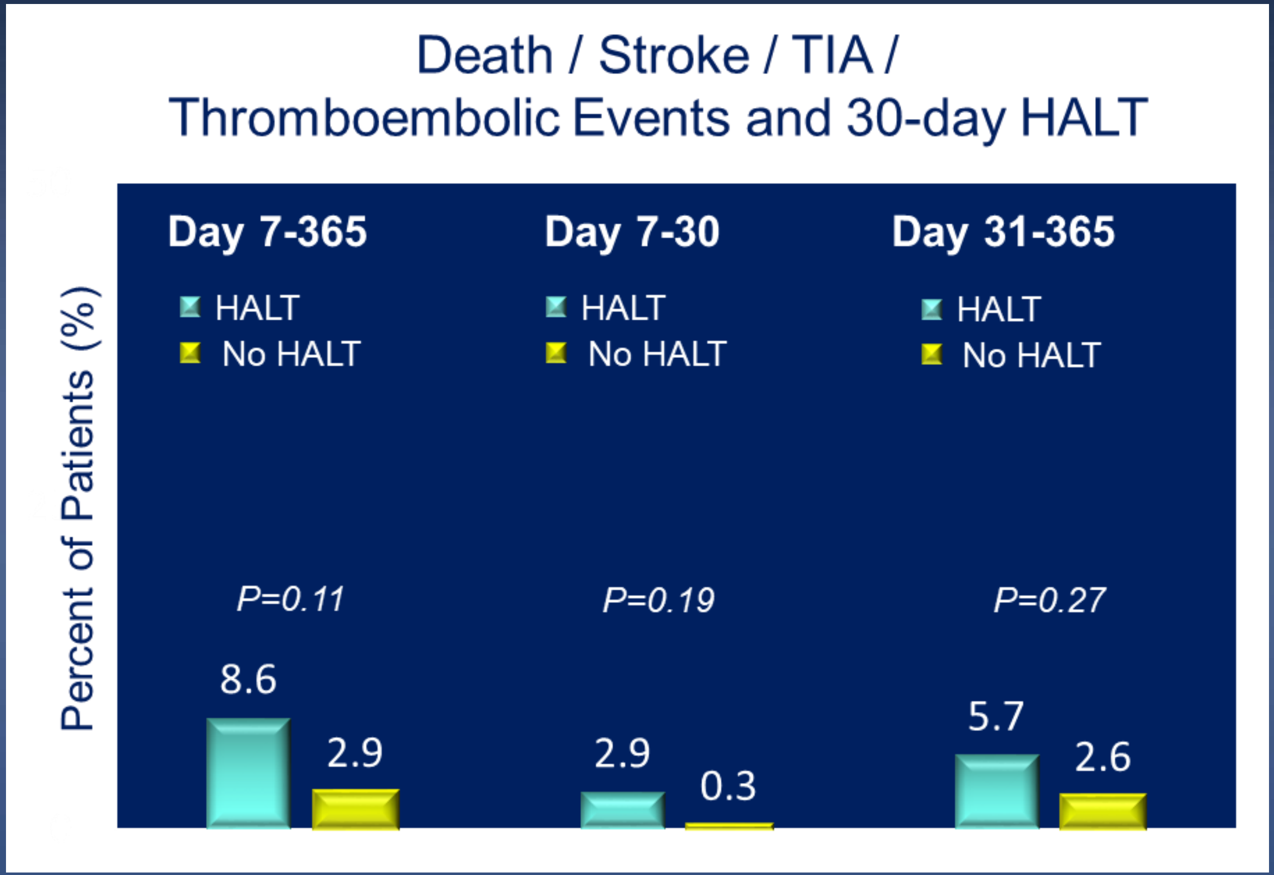


Dangas G, Weitz J, Giustino G, Makkar R, Mehran R. JACC 2016

Incidence and Clinical implications of *Fluctuating* HALT After TAVR/SAVR

PARTNER 3 Low-Risk CT Sub study





Makkar RJ on behalf of the PARTNER 3 Trial Investigators, TCT 2019 and JACC 2020

The Guidelines

2017 AHA/ACC Guidelines

Recommendations	Class	Level
Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily	IIb	C
Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding	IIb	B-NR

2017 ESC/EACTS Guidelines

Recommendations	Class	Level
Oral anticoagulation is recommended lifelong for patients with surgical or transcatheter implanted bioprostheses who have other indications for anticoagulation	I	C
Dual antiplatelet therapy should be considered for the first 3-6 months after TAVI, followed by lifelong single antiplatelet therapy inpatients who do not need oral anticoagulation for other reasons	IIa	C
Single antiplatelet therapy may be considered after		

As large RCTs are still awaited, current guidelines are based on observational studies and expert opinion.

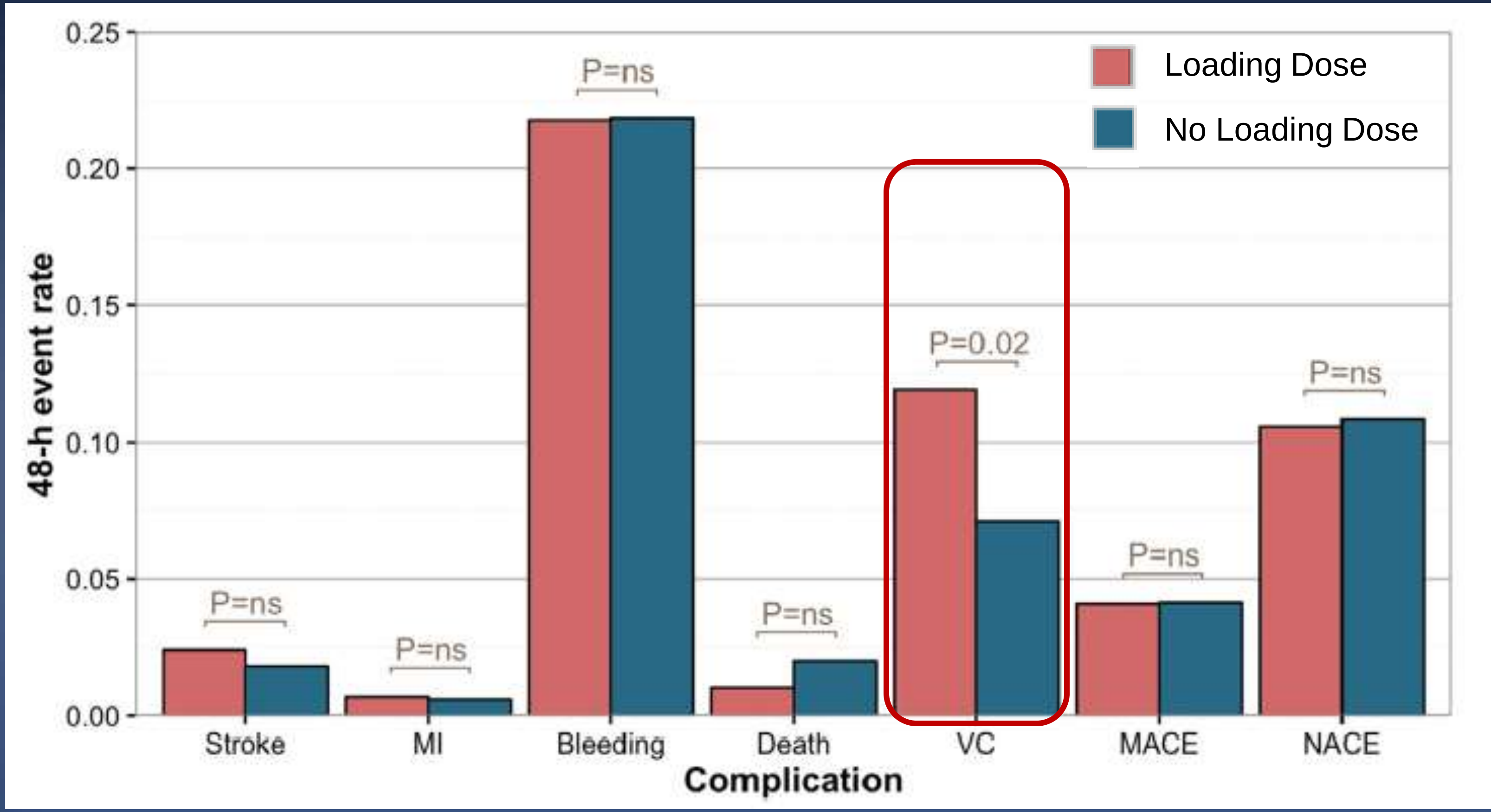
Baumgartner et al, Eur Heart J. 2017 Aug 26 & Eur J Cardiothorac Surg. 2017 Sep 1;52(3):408-417
Nishimura et al, Circulation. 2017 Jun 20;135(25) & J Am Coll Cardiol. 2017 Jul 11;70(2):252-289

Successful TAVR
No Underlying OAC indication

No advantages for clopidogrel loading dose in terms of early ischemic and bleeding outcomes

From the BRAVO-3 Randomized Trial

294 LD vs. 508 NLD



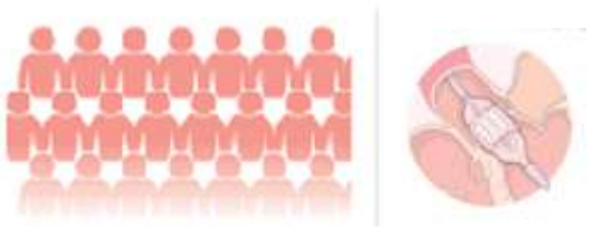
Variable	OR	P-value
MACE	0.75	0.5
Major VC	0.91	0.67
Bleeding (≥ BARC 3b)	0.87	0.65

Observed differences in Major vascular complications were attenuated after adjustment

Results consistent by sensitivity analysis assigning chronic oral clopidogrel preop in the (+) Loading Group

Nijenhuis VJ, Dangas G et al Am J Cardiol. 2019 May 1;123(9):1494-1500.

ARTE: 6-month data for aspirin with or without clopidogrel use in TAVI patients without an indication for long-term anticoagulation



Patients (N = 222) who underwent transcatheter aortic valve implantation. Excluded those with an indication for long-term oral anticoagulation, had received a drug-eluting stent within 1 year or had major bleeding within 3 months of TAVI

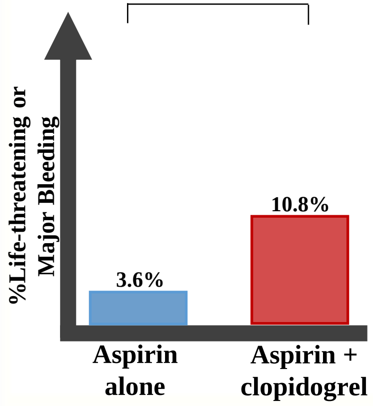
+

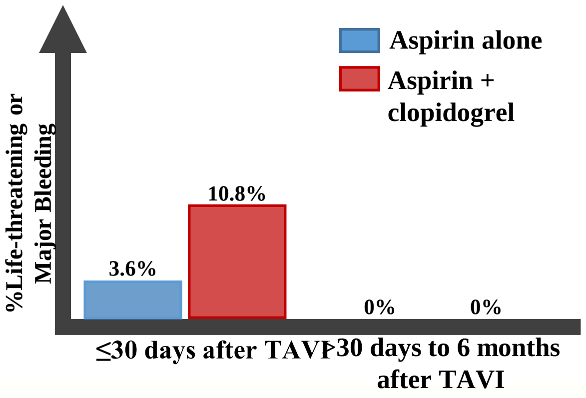
for 3 months (starting before TAVI) with clopidogrel loading dose

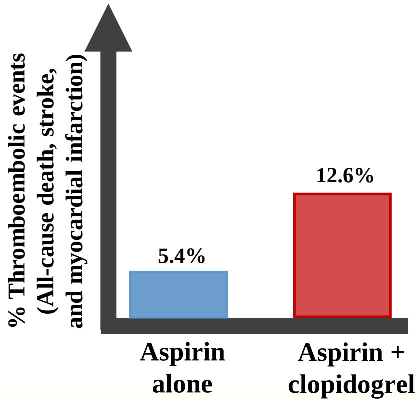
and then aspirin alone for duration of trial and thereafter

Follow-up over a period of 6 months

OR 3.22, 95% CI 1.01-10.34; *P* = 0.038







Pop-TAVI Randomized Trial - Cohort A

PLANNED TAVI (COHORT A)

RANDOMIZATION 1:1
PRIOR TO TAVI
N=690

ASPIRIN ALONE
N=343

12 EXCLUDED
- 5 Screen failure
- 4 Died before TAVI procedure
- 2 TAVI not initiated/completed
- 1 Withdrew consent

Modified ITT ANALYSIS
N=331

ASPIRIN + 3M CLOPIDOGREL
N=347

13 EXCLUDED
- 6 TAVI not initiated/completed
- 4 Screen failure
- 3 Withdrew consent

Modified ITT ANALYSIS
N=334

FOLLOW-UP: 1 YEAR

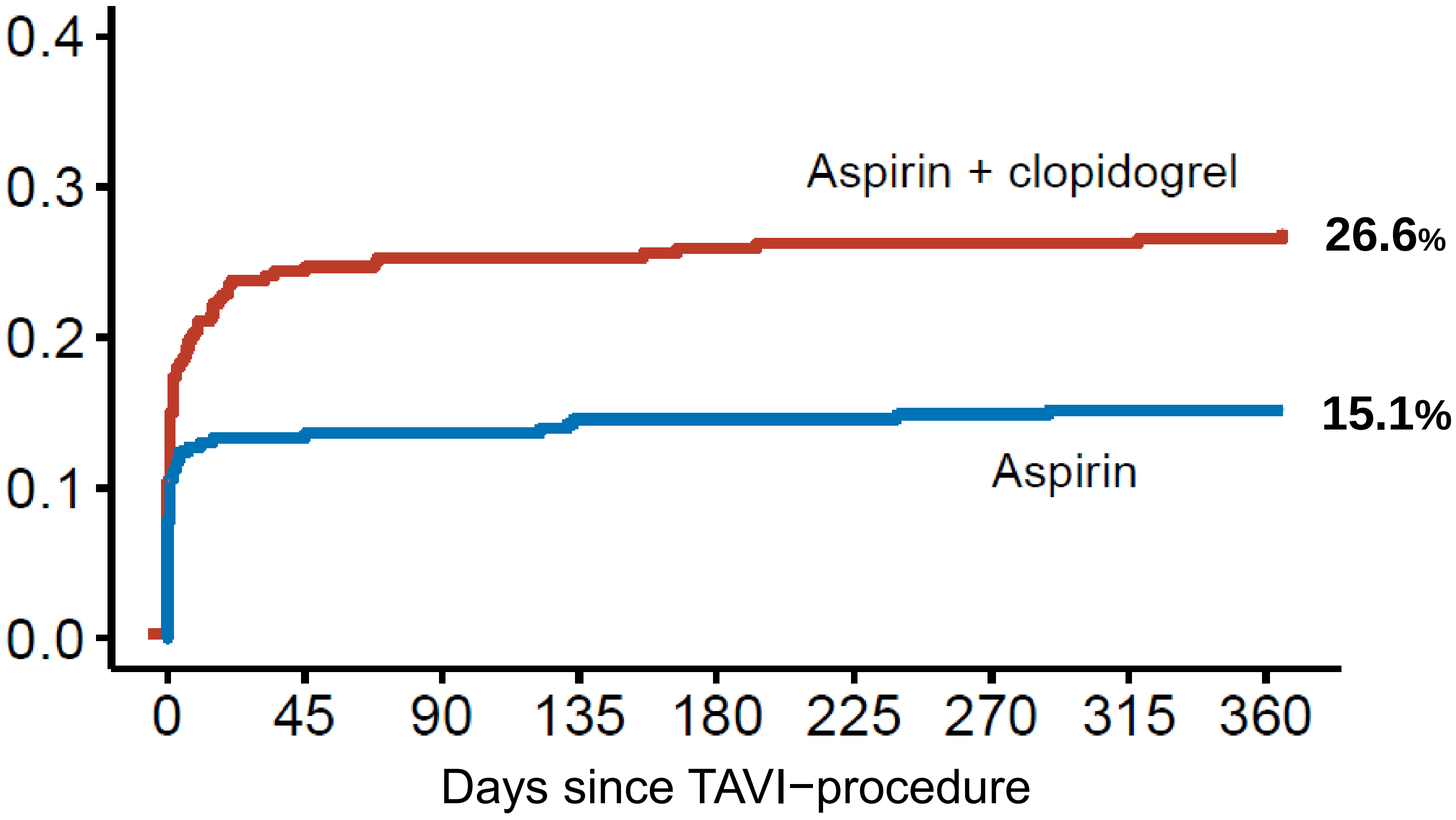
CO-PRIMARY OUTCOMES:
1. All bleeding (VARC-2)
2. Non-procedural bleeding (BARC)

CO-SECONDARY OUTCOMES:
1. CV mortality, non-procedural bleeding, stroke, or MI
2. CV mortality, ischemic stroke, or MI

Jorn Brouwer, Jurrien ten Berg, et al; ESC 2020

Pop-TAVI Randomized Trial - Cohort A

All Bleeding

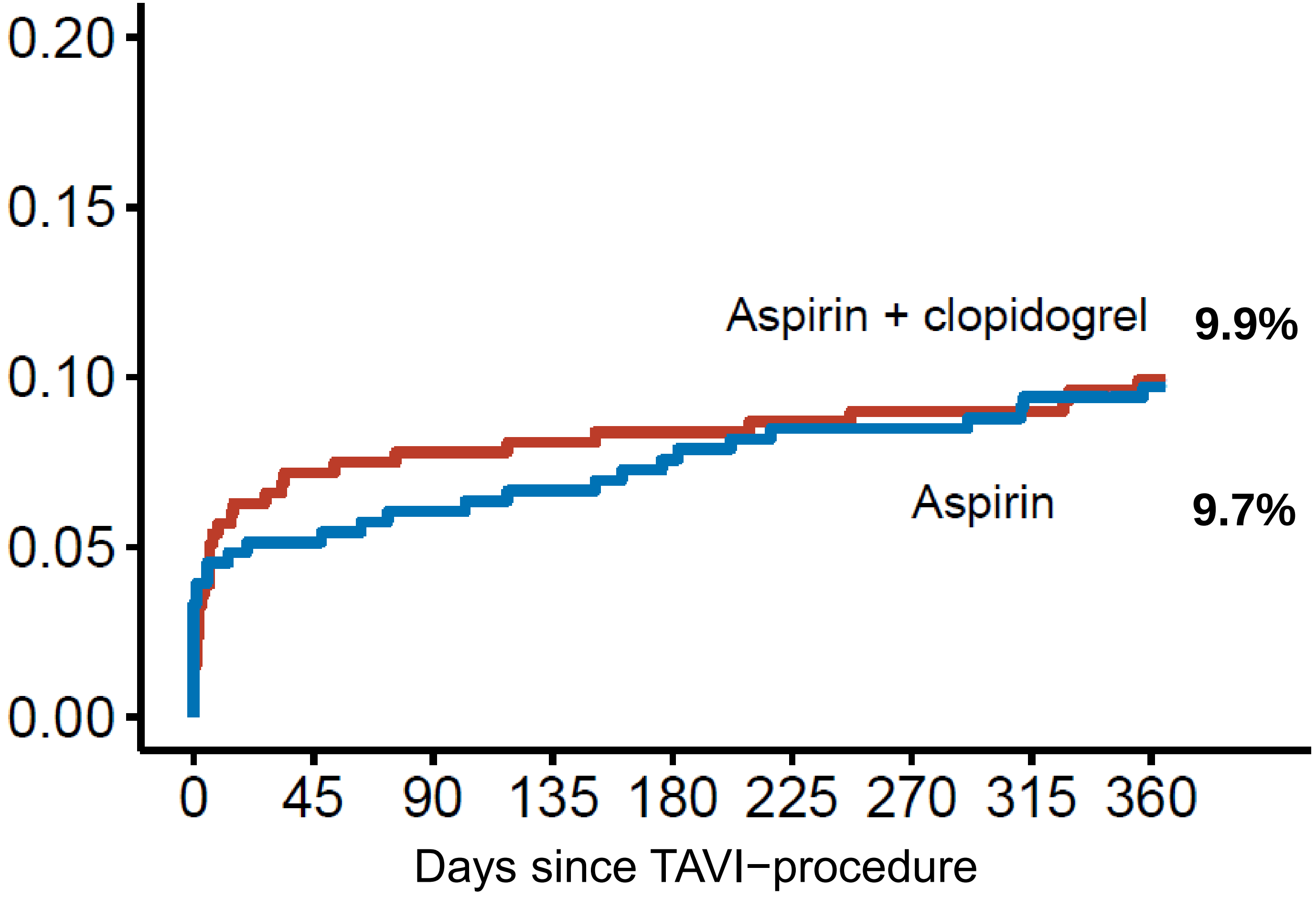


RR 0.57
95% CI 0.42 to 0.77
P = 0.001

Jorn Brouwer, Jurrien ten Berg, et al; ESC 2020

Pop-TAVI Randomized Trial - Cohort A

CV Mortality, Ischemic Stroke, MI



RR 0.98
95% CI 0.62 to 1.55
-0.2% (-4.7 to 4.3)
Non-inferiority margin +7.5%
P = 0.04 (noninferiority)
P = 0.93 (superiority)

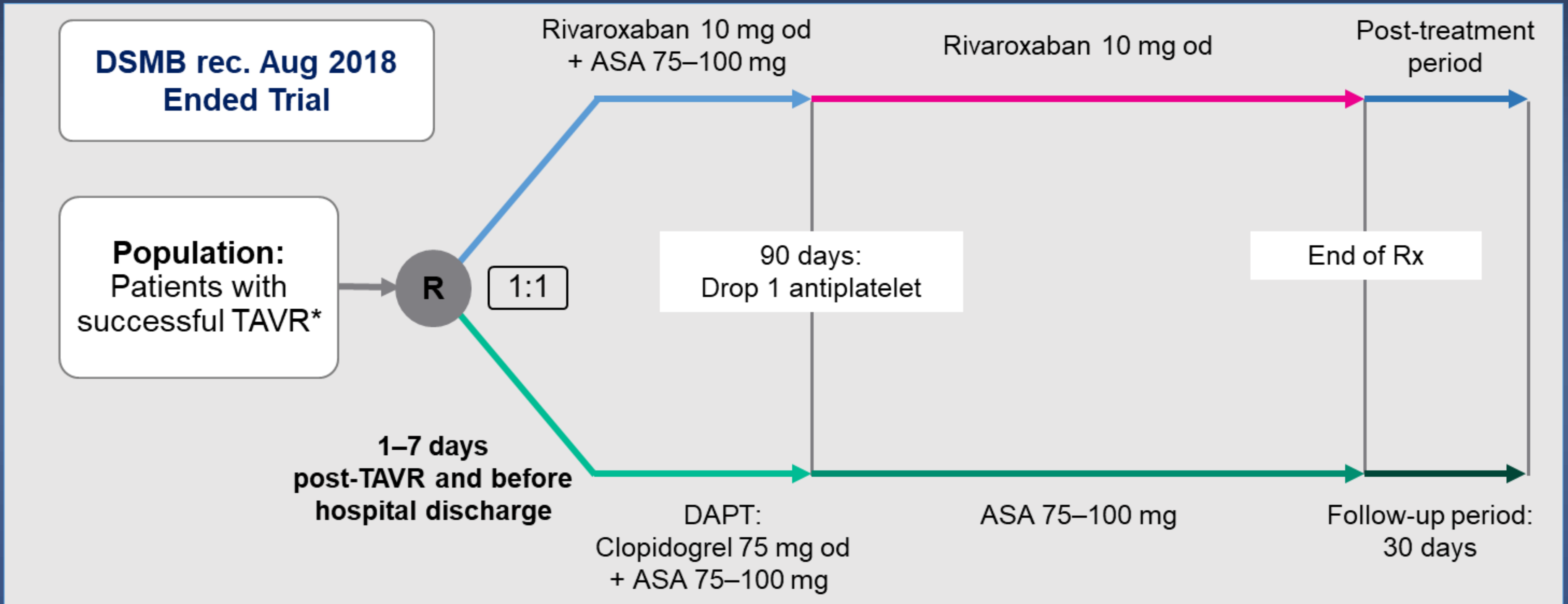
Jorn Brouwer, Jurrien ten Berg, et al; ESC 2020

Global PIs G. Dangas and S. Windecker

Official study title: Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter AortIc Valve Replacement to Optimize Clinical Outcomes

Primary Efficacy Endpoint

Composite: Death-Stroke-MI-Symptomatic Valve Thrombosis-Systemic Thromboembolism-Major VTE

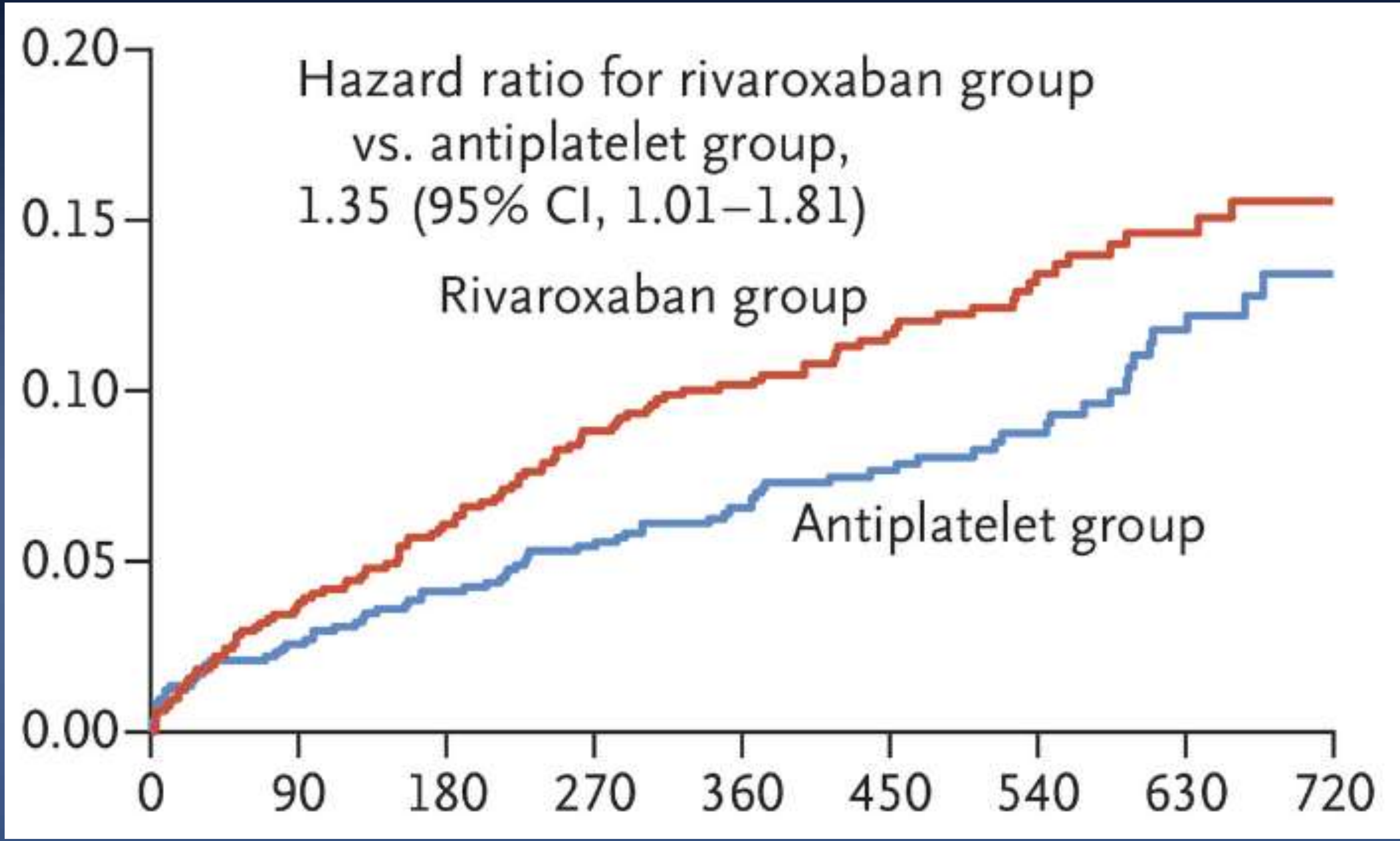


*136 sites in Europe and N. America (16 countries); gastroprophylaxis recommended throughout study

Windecker S et al, Am Heart J 2017:184:81–87

A Randomized Controlled Trial of Rivaroxaban after TAVR

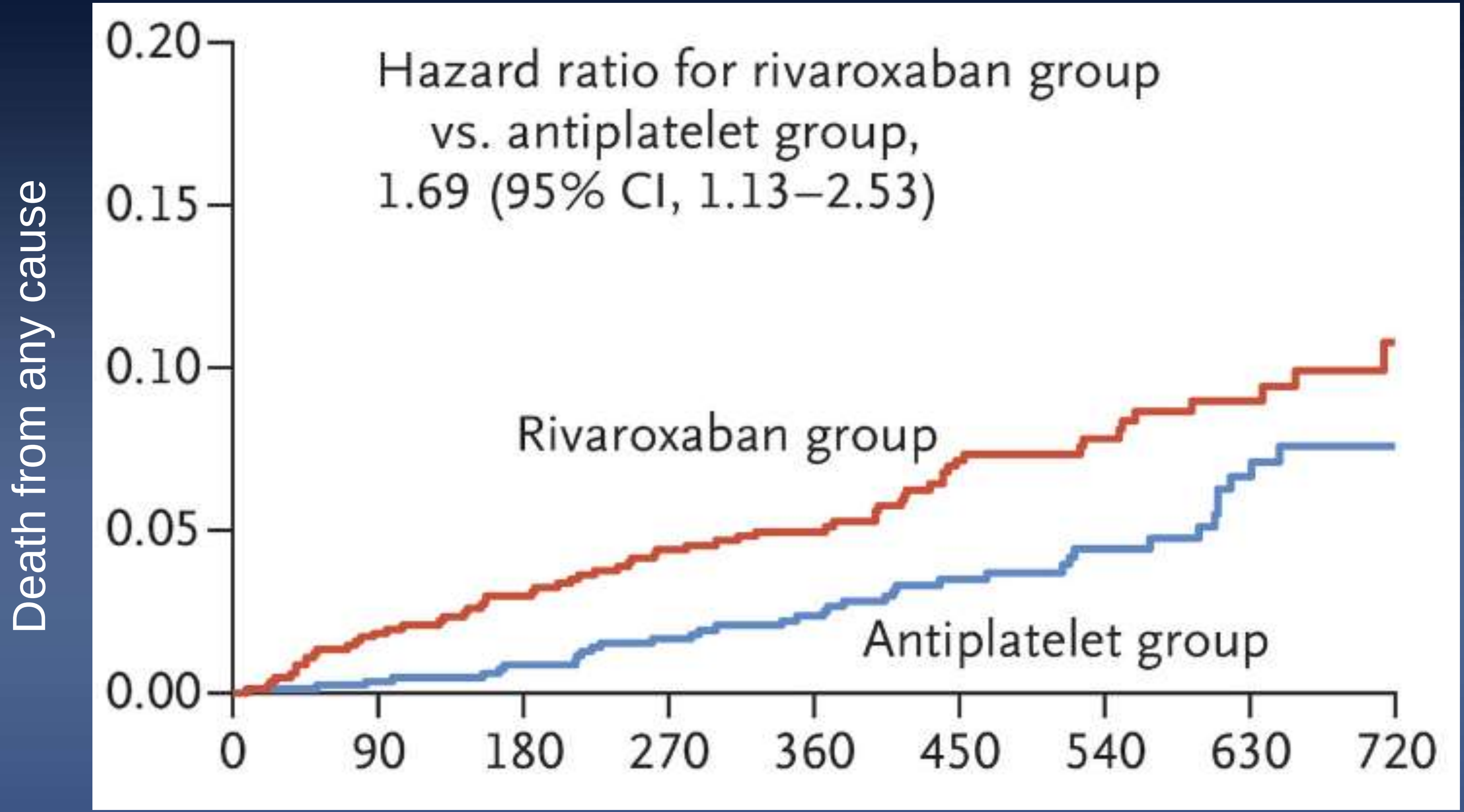
Death, Stroke, MI, symptomatic valve thrombosis, PE, DVT, or systemic embolism



Dangas GD et al N Engl J Med. 2020 and AHA 2019.

The NEW ENGLAND JOURNAL of MEDICINE

Increased mortality in the Rivaroxaban arm



Dangas GD et al N Engl J Med. 2019 and AHA 2019

Bleeding rate post TAVR

Outcome	Rivaroxaban Group (N=826)		Antiplatelet Group (N=818)		Difference (95% CI)	Hazard Ratio (95% CI)
	no. (%)	*incidence rate/100 person-yr*	*no. (%)*	*incidence rate/100 person-yr*	*incidence rate/100 person-yr*	
Safety outcomes						
Primary safety outcome¶	46 (5.6)	4.3	31 (3.8)	2.8	1.5 (−0.1 to 3.1)	1.50 (0.95 to 2.37)
VARC life-threatening or disabling bleeding	18 (2.2)	1.6	17 (2.1)	1.5	0.1 (−1.0 to 1.2)	1.06 (0.55 to 2.06)
Fatal bleeding	2 (0.2)	0.2	1 (0.1)	0.1	0.1 (−0.2 to 0.4)	2.01 (0.18 to 22.19)
VARC major bleeding	30 (3.6)	2.8	15 (1.8)	1.4	1.4 (0.2 to 2.6)	2.02 (1.09 to 3.76)
TIMI major or minor bleeding	42 (5.1)	3.9	24 (2.9)	2.2	1.7 (0.3 to 3.2)	1.78 (1.08 to 2.94)
ISTH major bleeding	49 (5.9)	4.6	30 (3.7)	2.7	1.9 (0.2 to 3.5)	1.66 (1.05 to 2.62)
BARC type 2, 3, or 5 bleeding	148 (17.9)	15.4	85 (10.4)	8.2	7.2 (4.2 to 10.3)	1.84 (1.41 to 2.41)

Dangas GD et al N Engl J Med 2019 2020 and AHA 2019

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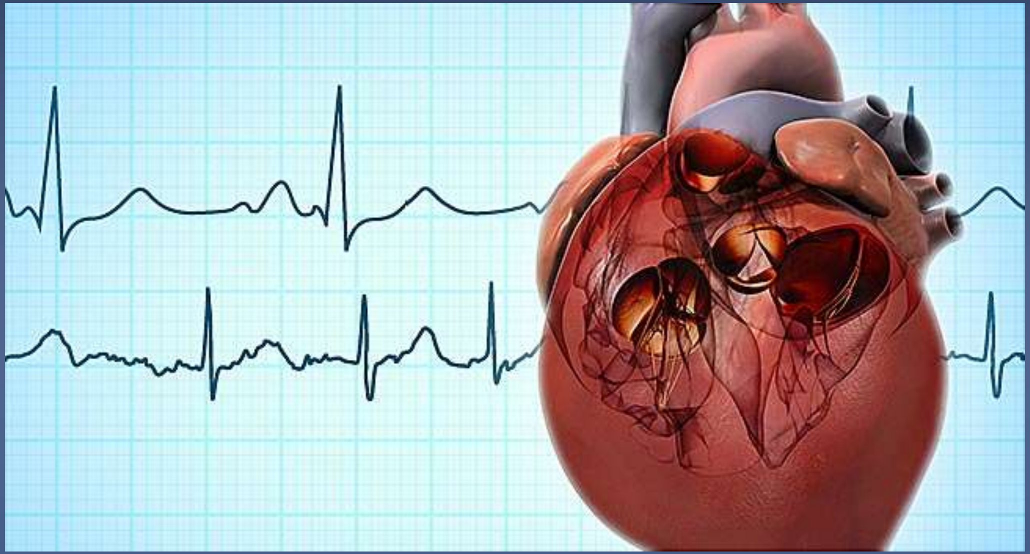
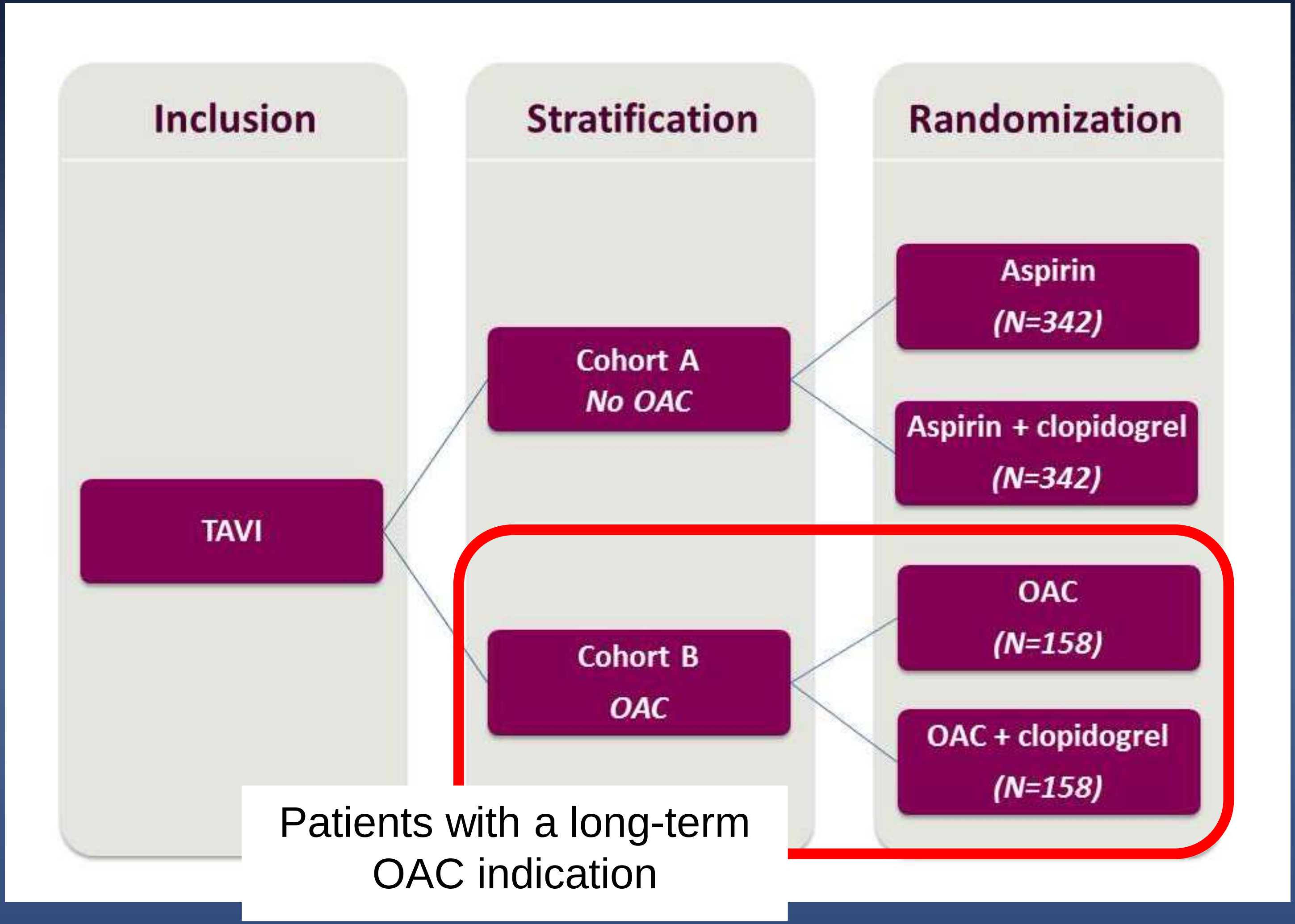
TAVR With Underlying OAC indication



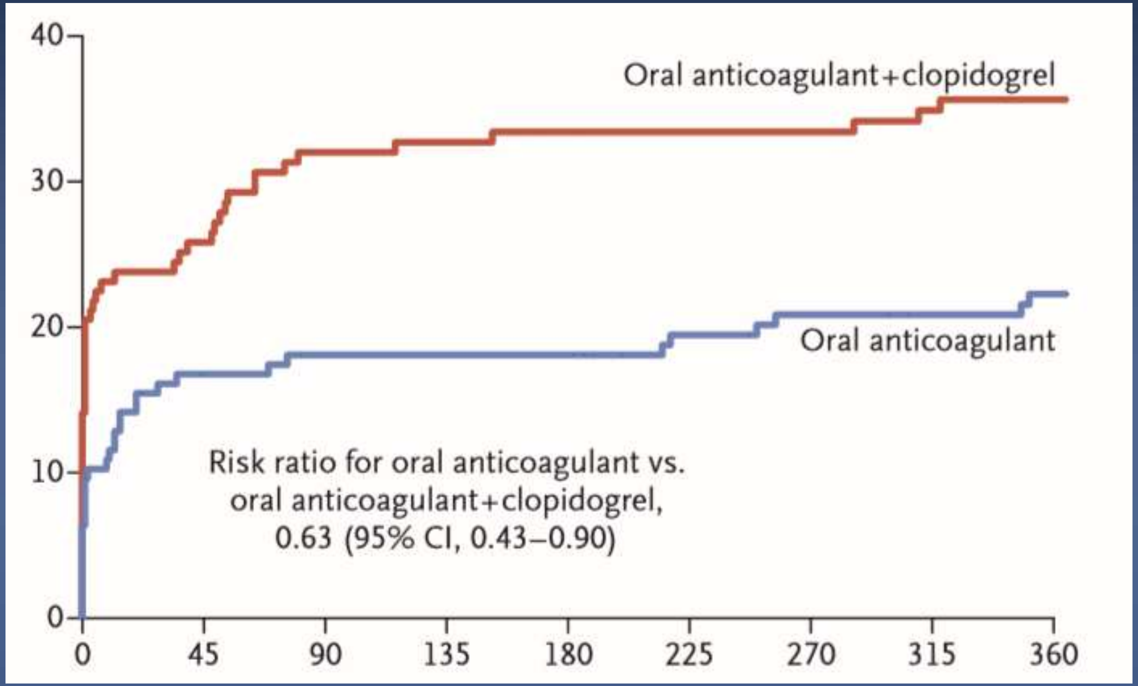
POPULAR TAVI trial Design in 2 Cohorts (on/off OAC)



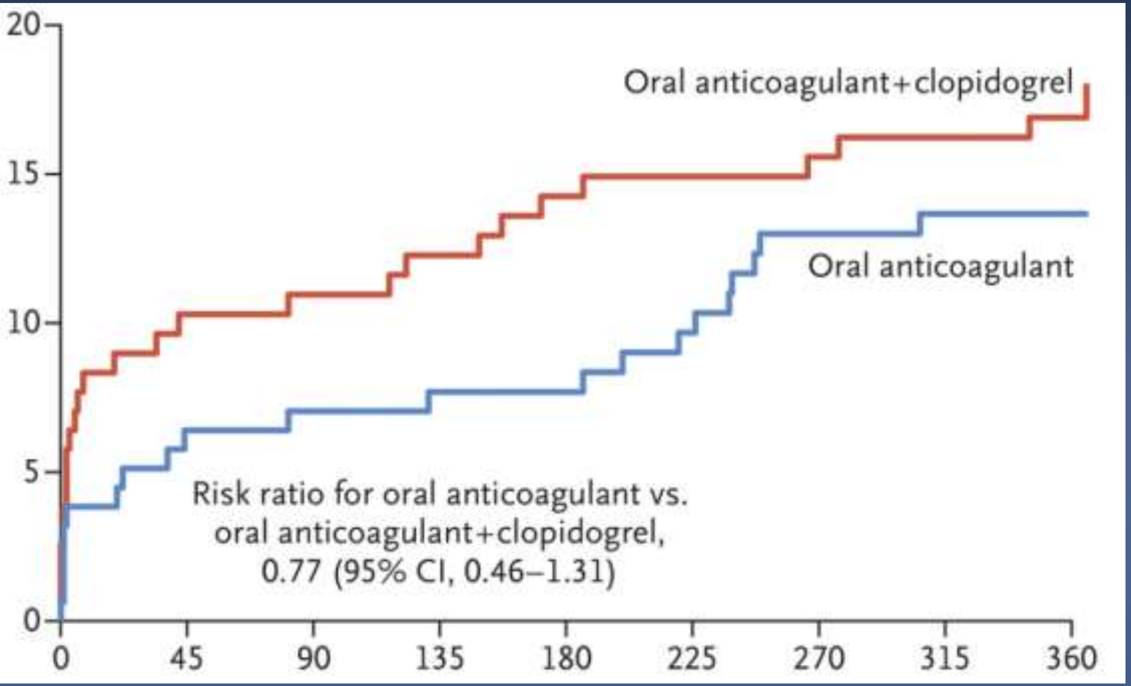
Nijenhuis VJ, ten Berg J et al. Am Heart J. 2016 Mar;173:77-85.

Pop-TAVI Cohort B: Ischemic and Bleeding outcomes

Primary Bleeding Endpoint



Ischemic composite of CV death, ischemic stroke, or MI



Clopidogrel administration on top of OAC increased bleeding without providing ischemic benefit

Most TAVI performed on uninterrupted OAC

Nijenhuis VJ, ten Berg J et al NEJM 2020 Apr 30;382(18):1696-1707.

Conclusions

- The incidence of leaflet thrombosis post-TAVR is high but its clinical implications are not well understood.
  - No immediate Stroke/TIA risk
  - ? Contribution to Limited/shorter Valve Durability
- Clopidogrel loading before TAVR is associated with more bleeding and vascular complications without obvious benefits in stroke prevention.
- In GALILEO trial Rivaroxaban was associated with increased mortality despite reducing the incidence of Reduced Leaflet Motion and Leaflet Thickening by all 4DCT-imaging definitions.
- Among Patients with A-fib OAC monotherapy was shown to be superior to OAC + clopidogrel in the POPULAR TAVI trial.
  - With the caveat that most TAVI performed on uninterrupted OAC and most outcome differences occurred in-hospital
- Additional LARGE-SCALE randomized evidence basis is required to properly inform guideline recommendations!