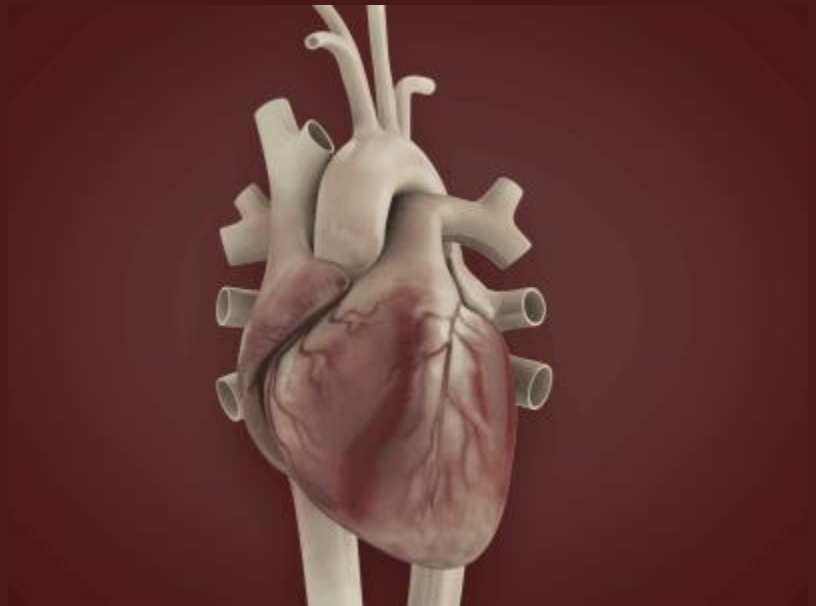
Antithrombotic Therapy post Transcatheter Aortic Valve Replacement (TAVR): Is Less More?



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Conflicts of Interest

There are no conflicts of interest to disclose.

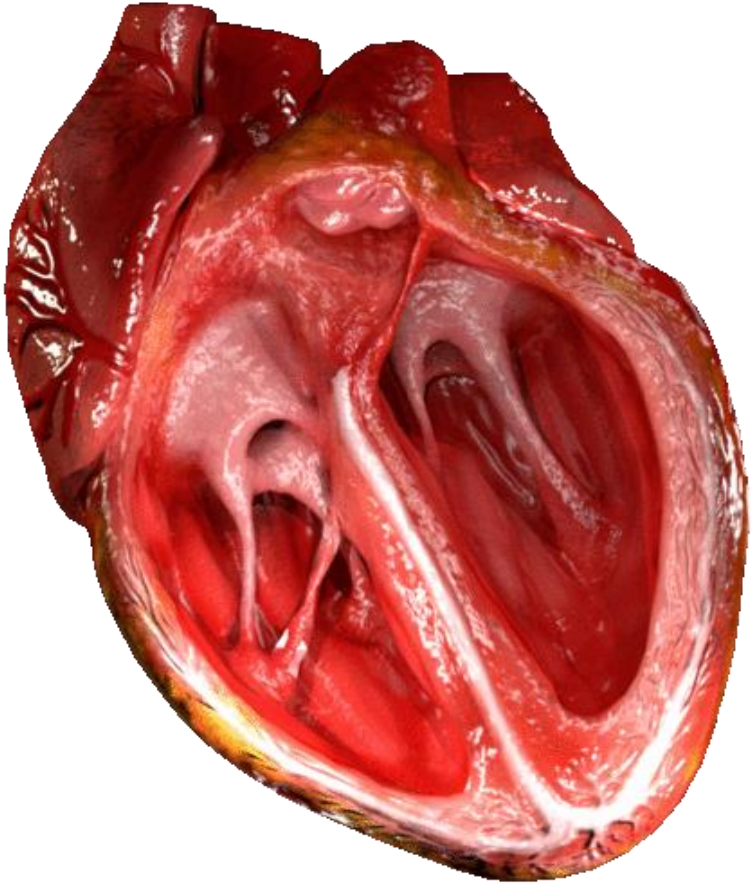
Objectives

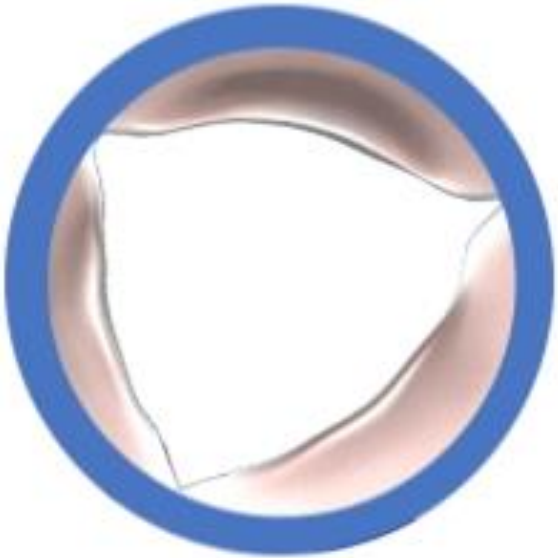
- Describe the risk of ischemic events and bleeding in patients undergoing transcatheter aortic valve replacement (TAVR).
- Assess current guideline recommendations for anti-thrombotic therapy in patients post-TAVR.
- Evaluate the most recent trials investigating the optimal antithrombotic regimen in patients post-TAVR.
- Analyze a given patient and formulate the optimal antithrombotic regimen post-TAVR based on the most recent literature.

Common Abbreviations

- TAVR: Transcatheter Aortic Valve Replacement
- TAVI: Transcatheter Aortic Valve Implantation
- ASA: Aspirin
- DAPT: Dual Antiplatelet Therapy
- SAPT: Single Antiplatelet Therapy
- LD: Loading Dose
- PO: By mouth
- QD: Daily
- PCI: Percutaneous Coronary Intervention
- ACS: Acute Coronary Syndrome
- CAD: Coronary Artery Disease
- HTN: Hypertension
- PE: Pulmonary Embolism

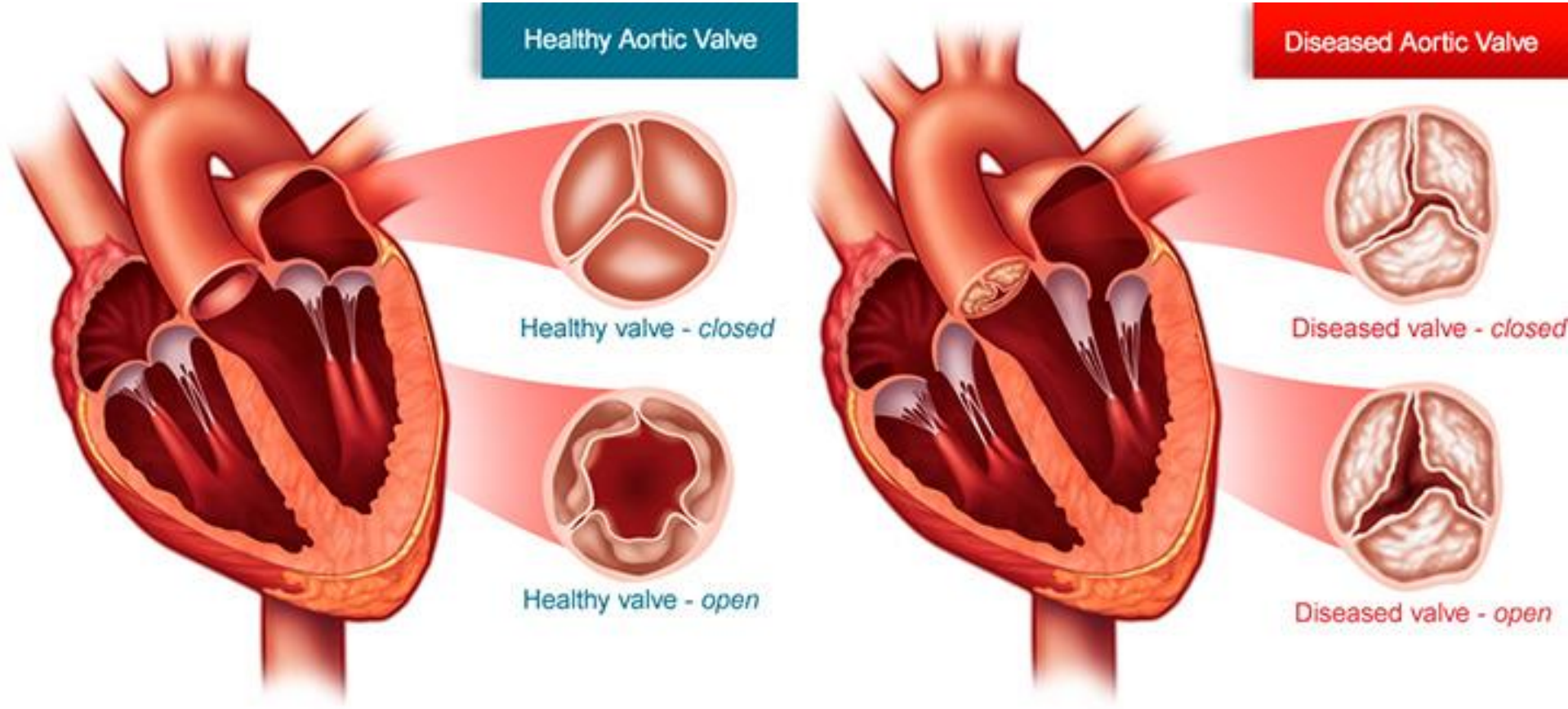
- MI: Myocardial Infarction
- CV: Cardiovascular
- DES: Drug Eluting Stent
- TIA; Transient Ischemic Attack
- VKA: Vitamin K Antagonist
- OAC: Oral Anticoagulant
- BMS: Bare Metal Stent
- STS: Society of Thoracic Surgeons
- NYHA: New York Heart Association
- PAD: Peripheral Artery Disease
- CABG: Coronary Artery Bypass Grafting
- DVT: Deep Vein THrombosis



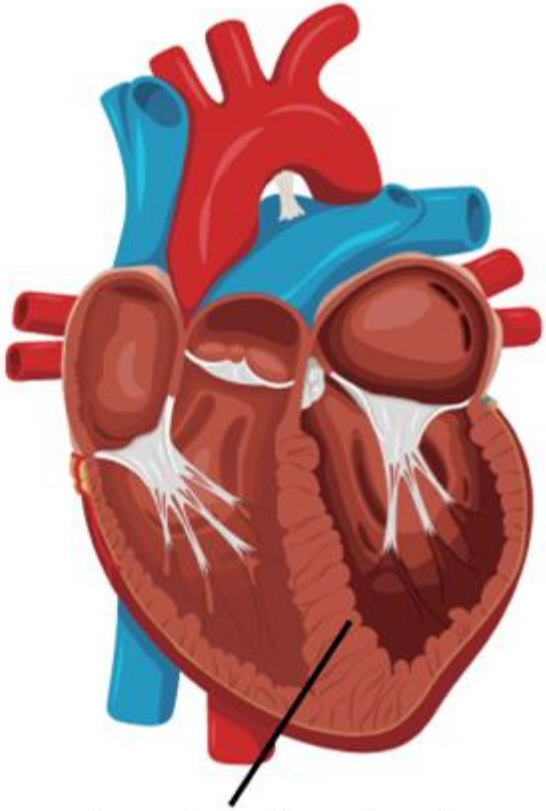


Healthy Aortic Valve

Aortic Stenosis

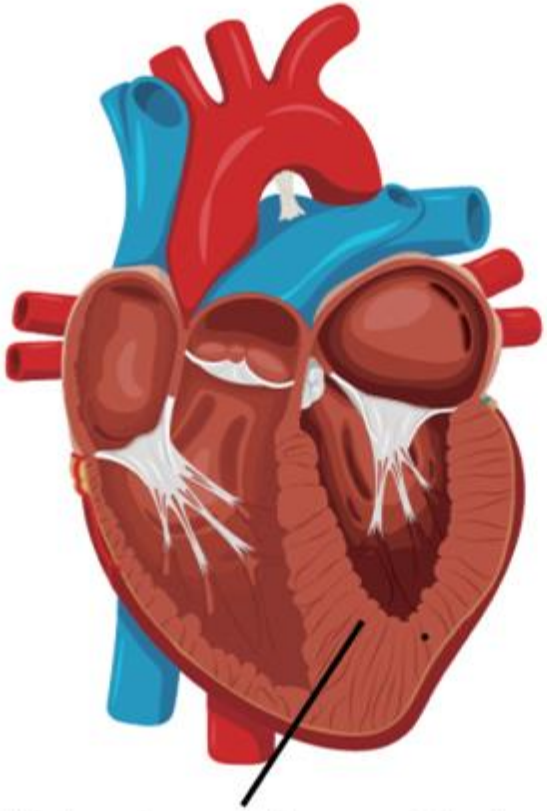


Normal heart

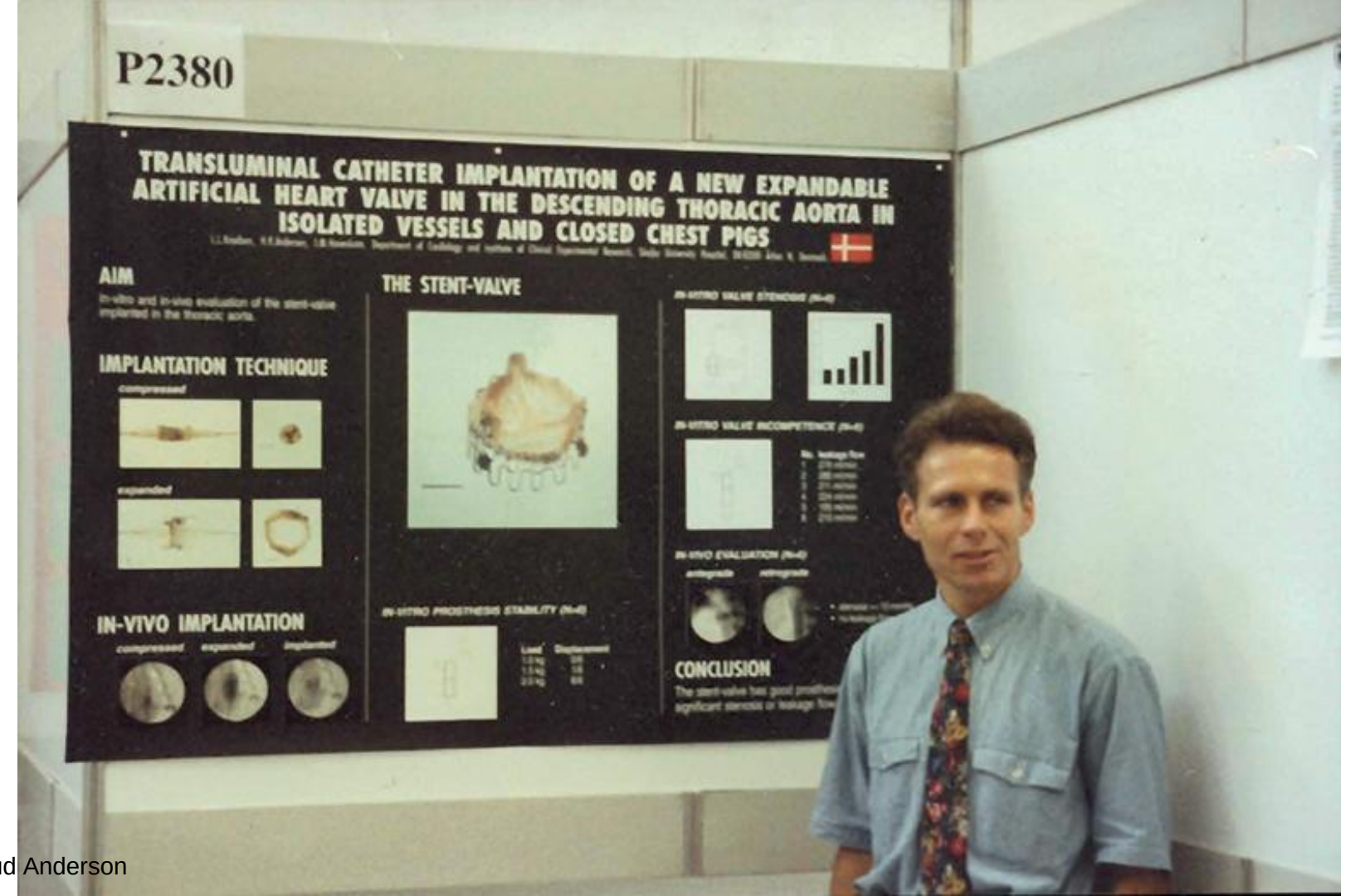


Normal ventricular chambers

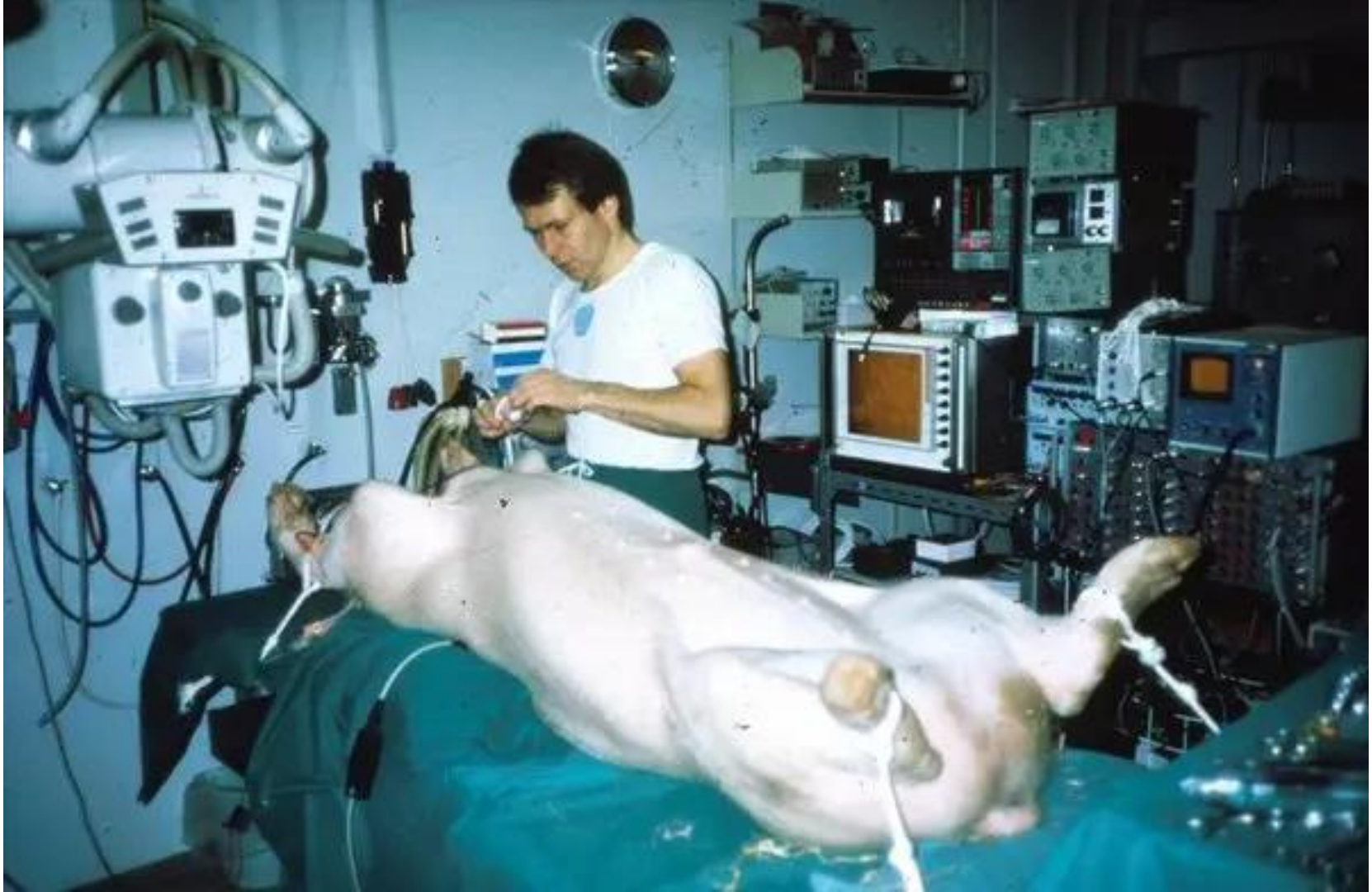
Congestive heart

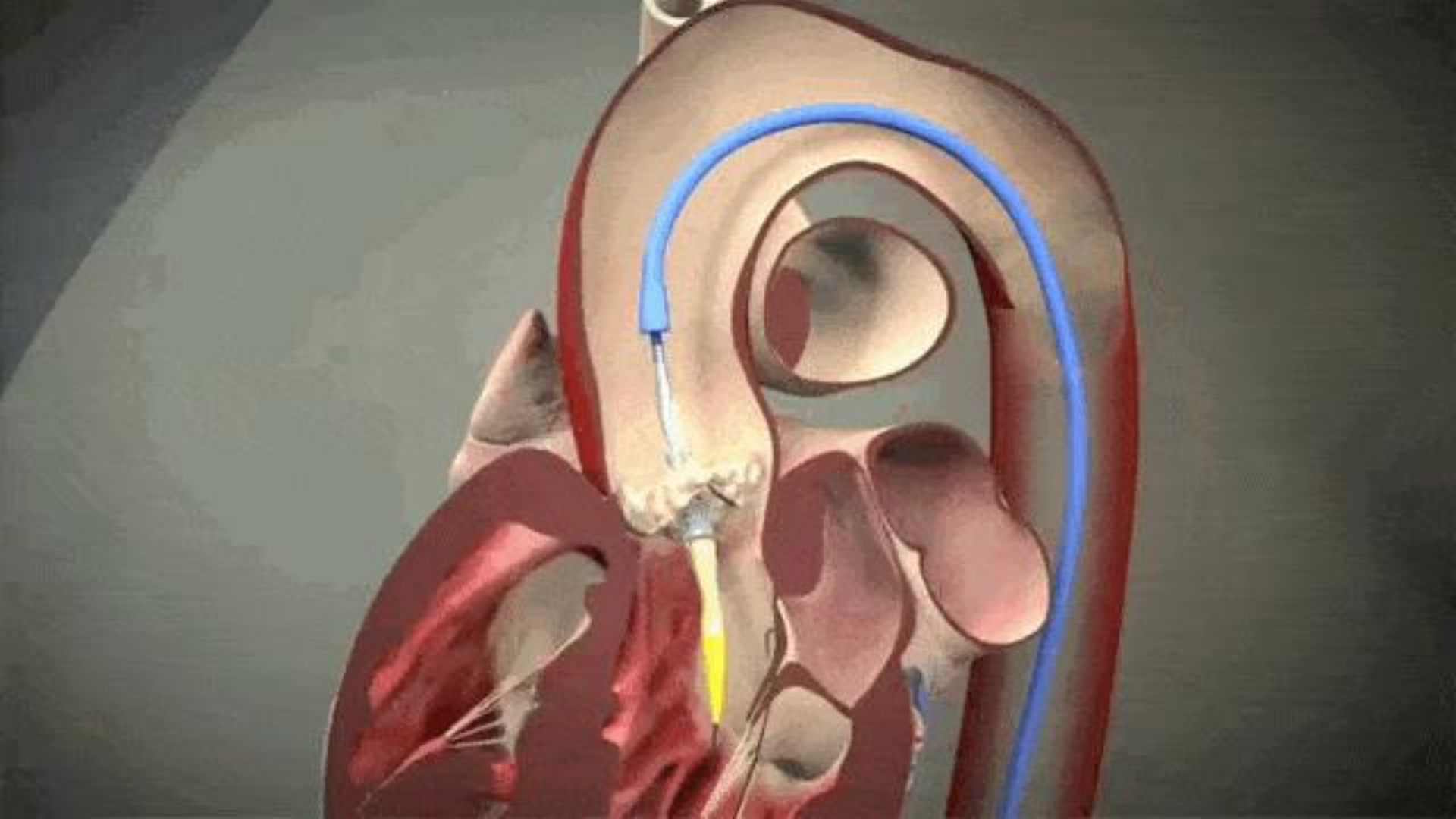


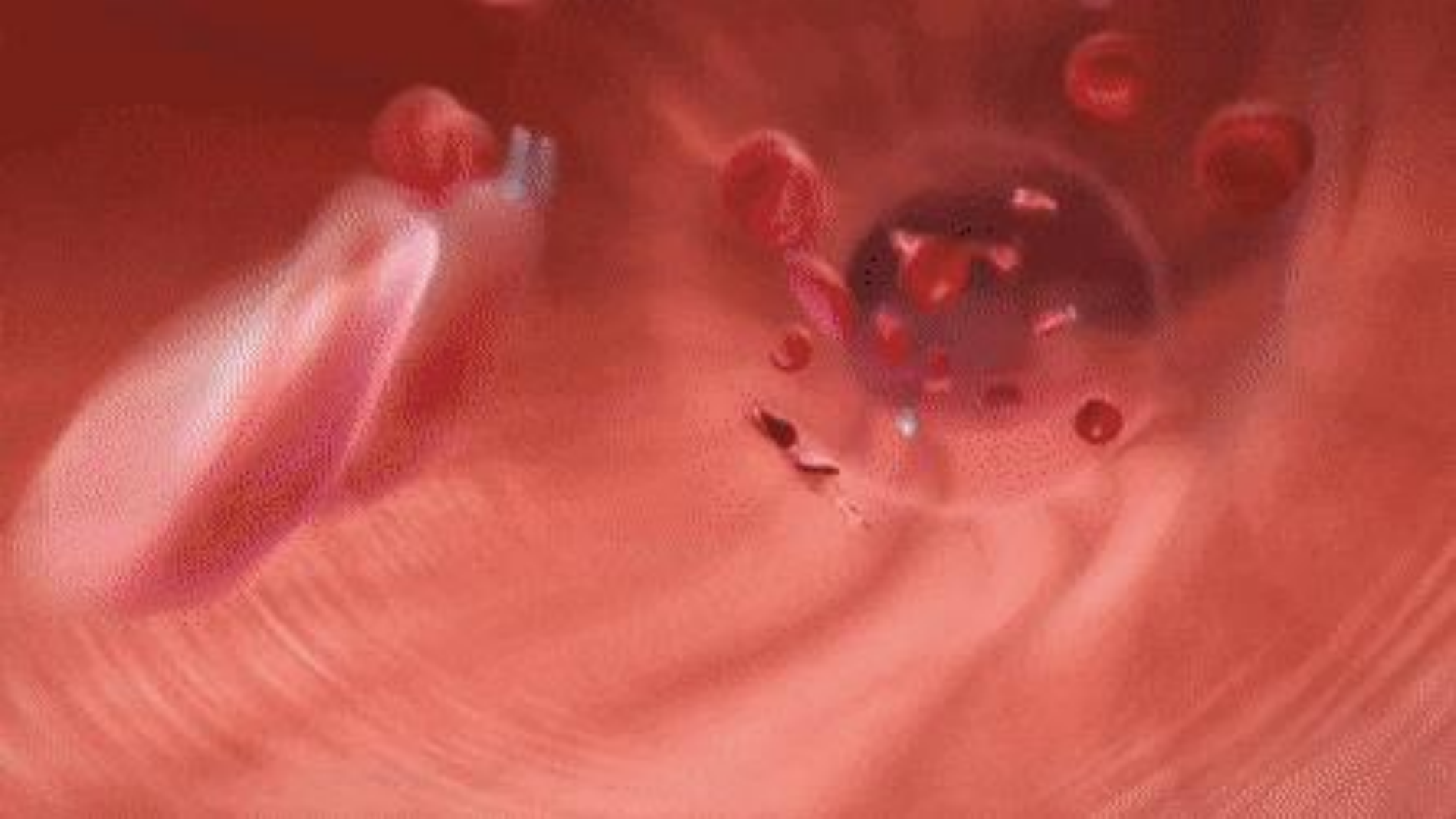
Thickening of the ventricular chambers and smaller filling capacity



Henning Rud Anderson

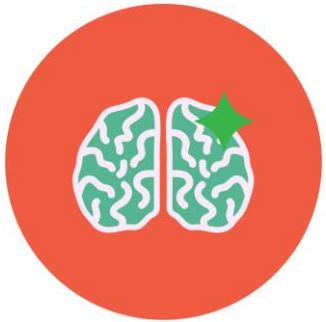






Antithrombotic Optimization

Thrombosis *Bleeding*



7 +/- 1.7%

of patients within first year post TAVR

16 +/- 0.9%

of patients within first year post TAVR

Eur Heart J 2017;38:3341-50.

Major bleeding in up to 15%

of patients at 1 year

N Engl J Med 2016; 374: 1609-20.
N Engl J Med 2019; 380:1695-705.
N Engl J Med 2019; 380: 1706-15.

Standard of Care

DAPT (aspirin and clopidogrel) post TAVR for 3-6 months followed by ASA lifelong

Prevent device-related thromboembolic complications while tissue growth and endothelialization of metallic frame are occuring

N Engl J Med 2010;363:1597-607.
J Am Coll Cardiol 2014;63:1972-81.

Where is the evidence?

- Early trials that evaluated TAVR used DAPT with aspirin and clopidogrel for up to 6 months after the procedure

- Mostly extrapolated data from intra-coronary stenting

N Engl J Med 2010;363:1597-607.
N Engl J Med 2011;364:2187-98.
J Am Coll Cardiol 2014;63:1972-81.
N Engl J Med 2014;371:967-8.

Original Trials

- Grube et al. used extracorporeal bypass for hemodynamic support intra-procedurally and found severe postprocedural thrombocytopenia in patients not on clopidogrel that was thought to be due to platelet activation and consumption
- Histological studies saw that valve incorporation process begins with fibrin deposition and an inflammatory process; after 3 mo, fibrin is replaced by smooth muscle cells and endothelial cells

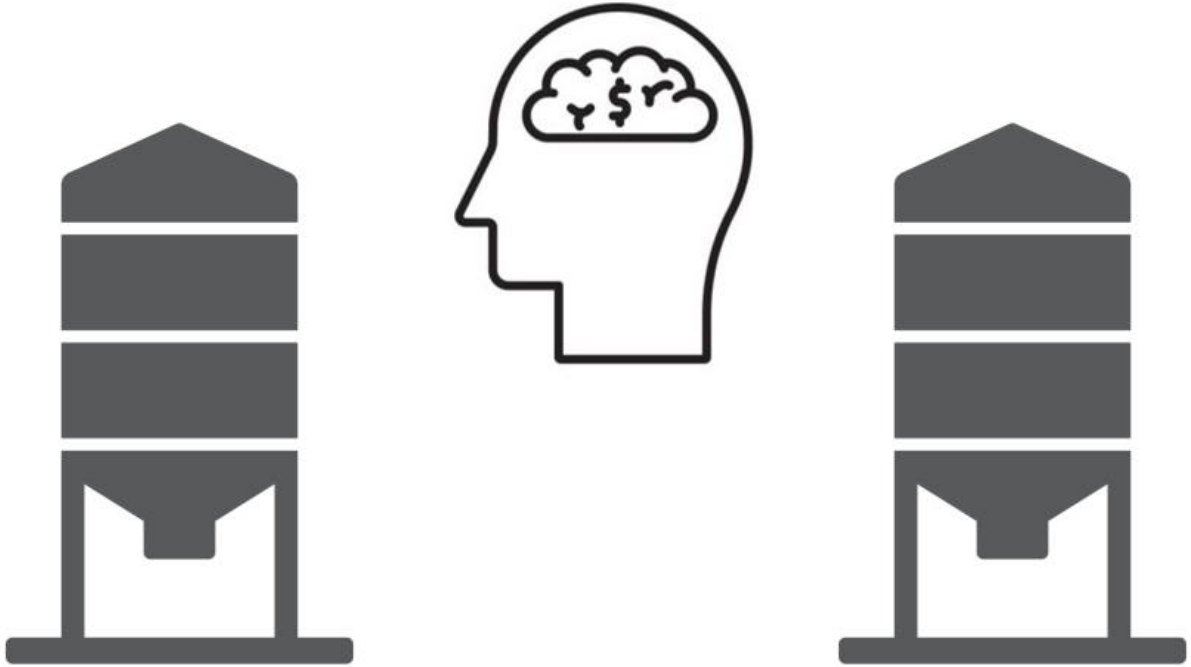
Circulation 2006;114:1616–1624.
Am J Cardiol. 2011 Dec 15;108(12):1772-6.

What we knew at the time...

- SAPT versus DAPT has less bleeding
- Current practice not actually evidence based

EuroIntervention. 2015; 11(suppl W):W92–W95.
EuroIntervention. 2013; 9(suppl):S43–S47.
JACC Cardiovasc Interv. 2017; 10:1366–1369.

Is less more?



Those without an indication for anticoagulation

Those with an indication for anticoagulation

Those without an indication for anticoagulation

2011: PILOT STUDY

USSIA ET AL.

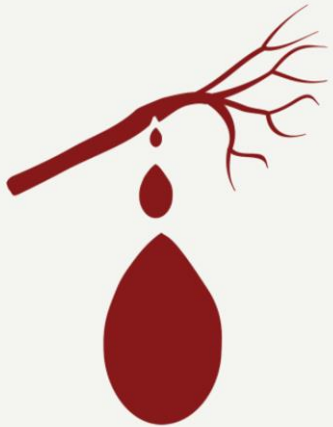
- n= 79
- Randomized, prospective, open-label, single-center study
- DAPT (w/ clopidogrel x3 mo) vs. ASA 100 mg
- Adding clopidogrel to ASA for 3 mo did not reduce MACCE or mortality at 30 days or 6 months. Results did not support strategy of short-term adjunctive use of clopidogrel added to ASA post TAVI.

2014: SAT-TAVI

STABILE ET AL.

- Randomized, double blind controlled trial
- n= 120
- DAPT (w/ clopidogrel or ticlopidine x 6 mo) versus ASA 75-160 mg QD
- No statistically significant differences found between groups except thienopyridine use was linked with a significant increase in the rate of vascular complications

Am J Cardiol. 2011 Dec 15;108(12):1772-6.
Int J Cardiol. 2014 Jul 1;174(3):624-7.
JACC Cardiovasc Interv. 2017 Jul 10;10(13):1357-1365.
Catheter Cardiovasc Interv 2020;96:E177-E186.



2019: META-ANALYIS

KUNO ET AL.

- Meta-analysis
- n= 20,548
- Investigated different antithrombotic strategies post TAVR
- OAC + DAPT had significantly higher rates of mortality.
- SAPT had significantly lower rates of bleeding versus DAPT, OAC+SAPT, OAC+DAPT
- No significant differences in stroke among all regimens

2017: ARTE

RODÉS-CABAU ET AL.

- Prospective, randomized, open label trial
- n= 222
- DAPT (w/ clopidogrel x3 mo) plus ASA 80-100 mg/day versus ASA 80-100 mg/day
- SAPT tended to reduce the occurrence of major adverse events following TAVR.
- Reduced the risk for major or life-threatening events
- No increased risk for MI or stroke

Am J Cardiol. 2011 Dec 15;108(12):1772-6.
Int J Cardiol. 2014 Jul 1;174(3):624-7.
JACC Cardiovasc Interv. 2017 Jul 10;10(13):1357-1365.
Catheter Cardiovasc Interv 2020;96:E177-E186.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation

J. Brouwer, V.J. Nijenhuis, R. Delewi, R.S. Hermanides, W. Holvoet, C.L.F. Dubois, P. Frambach, B. De Bruyne, G.K. van Houwelingen, J.A.S. Van Der Heyden, P. Toušek, F. van der Kley, I. Buysschaert, C.E. Schotborgh, B. Ferdinande, P. van der Harst, J. Roosen, J. Peper, F.W.F. Thielen, L. Veenstra, D.R.P.P. Chan Pin Yin, M.J. Swaans, B.J.W.M. Rensing, A.W.J. van 't Hof, L. Timmers, J.C. Kelder, P.R. Stella, J. Baan, and J.M. ten Berg

POPular TAVI Cohort A

Randomized, open-label, international controlled trial
n= 665

Treatment Arms

DAPT
Clopidogrel 300 mg LOAD followed by 75 mg/day (3 mo) PLUS
ASA 80-100 mg/day (indefinitely)

ASA
ASA 80-100 mg/day (indefinitely)

N Engl J Med 2020; 383:1447-1457

Pertinent Inclusion Criteria

- All patients scheduled to undergo TAVI
- No indication for long-term oral anticoagulation

Pertinent Exclusion Criteria

- Implantation of a DES within 3 months
- Implantation of a BMS within 1 month

N Engl J Med 2020; 383:1447-1457

POPular TAVI Cohort A

Follow up at 12 months

Primary Endpoint:

- All bleeding (including minor, major, and life-threatening or disabling bleeding) and non-procedure-related bleeding over a period of 12 mo

Secondary Endpoint:

- Composite of bleeding or thromboembolic events
  - Death from CV causes, non-procedure-related bleeding, stroke from any cause, MI
- Composite of death from CV causes, ischemic stroke, MI

N Engl J Med 2020; 383:1447-1457

POPular TAVI Cohort A

Statistics:

- If stroke during trial, patients were allowed in the ASA arm to switch to clopidogrel
- If patients developed atrial fibrillation post TAVI, allowed VKA or DOAC
  - Replace ASA
- Hypothesis:
  - SAPT superior to DAPT in bleeding (primary outcome)
  - SAPT noninferior to DAPT in bleeding + thromboembolic events (secondary outcome)
- Non-inferiority margin 7.5 percentage points for absolute between group differences; if met, would test for superiority

N Engl J Med 2020; 383:1447-1457

POPular TAVI Cohort A

Statistics:

- Modified ITT (randomized + TAVI done)
  - Patients who were on clopidogrel prior to randomization were allowed in mITT but excluded from Per Protocol
- Did adjust for multiple testing for all outcomes
- Adherence to clopidogrel 89.2%
- Oral anticoagulation was initiated in 13.3% of the ASA group and 9.6% of the DAPT group

N Engl J Med 2020; 383:1447-1457

POPular TAVI Cohort A: Snapshot of Baseline Characteristics

Characteristic	Aspirin	Aspirin + Clopidogrel
Age - yr	80.4 ± 6.2	79.5 ± 6.4
Female sex - no. (%)	164 (49.5)	160 (47.9)
NYHA Class III or IV - no. (%)	212 (64.0)	220 (65.9)
STS Risk Score - median (IQR)	2.6 (1.6-3.7)	2.4 (1.7-3.7)
Hypertension - no. (%)	243 (73.4)	255 (76.3)
Diabetes - no. (%)	78 (23.6)	85 (25.4)
CAD - no. (%)	134 (40.5)	138 (41.3)
Previous MI - no. (%)	28 (8.5)	31 (9.3)
PAD - no. (%)	47 (14.2)	68 (20.4)
Previous stroke - no. (%)	18 (5.4)	12 (3.6)
Previous CABG - no. (%)	61 (18.4)	65 (19.5)

N Engl J Med 2020; 383:1447-1457

POPular TAVI Cohort A: Primary Outcome

Outcome	Aspirin	Aspirin plus Clopidogrel	RR (95% CI)	P-value
All bleeding	50 (15.1%)	89 (26.6%)	0.57 (0.42 - 0.77)	0.001
Non-procedure-related bleeding	50 (15.1)	83 (24.9%)	0.61 (0.44 - 0.83)	0.005

Severe procedural bleeding: 0% versus 1.8%

N Engl J Med 2020; 383:1447-1457

POPular TAVI Cohort A: Primary Outcome

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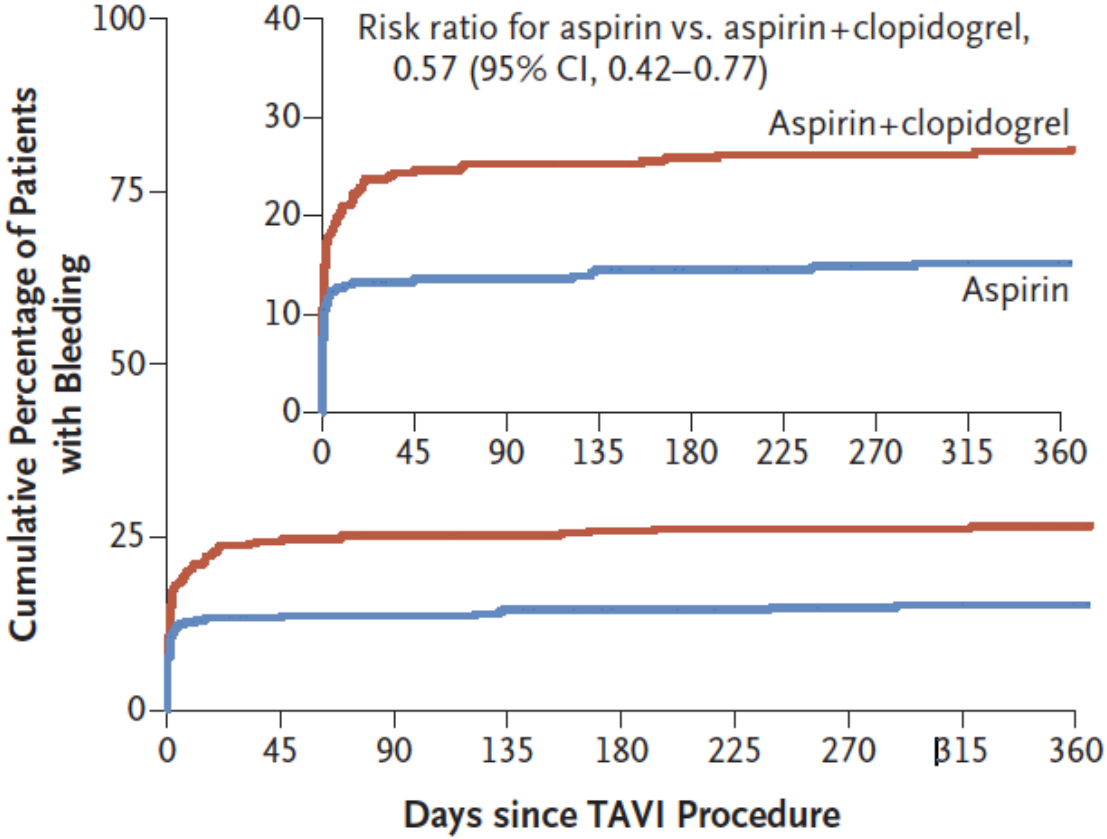
N Engl J Med 2020; 383:1447-1457



No. at Risk

Aspirin+clopidogrel	334	248	244	243	239	238	237	237	234
Aspirin	331	280	279	276	271	269	267	266	264

N Engl J Med 2020; 383:1447-1457

Outcome	Aspirin	Aspirin + Clopidogrel	RR (95% CI)	Absolute Difference (95% CI)	P-value
First Secondary Outcome					
Noninferiority	76 (23.0)	104 (31.1)		-8.2 (-14.9 to -1.5)	<0.001
Superiority	76 (23.0)	104 (31.1)	0.74 (0.57-0.95)		0.04
Second Secondary Outcome					
Noninferiority	32 (9.7)	33 (9.9)		-0.2 (-4.7 to 4.3)	0.004
Superiority	32 (9.7)	33 (9.9)	0.98 (0.62-1.55)		0.93

First Secondary Outcome: Composite of bleeding or thromboembolic events (Death from CV causes, non-procedure-related bleeding, stroke from any cause, MI)
Second Secondary Outcome: Composite of death from CV causes, ischemic stroke, M

N Engl J Med 2020; 383:1447-1457

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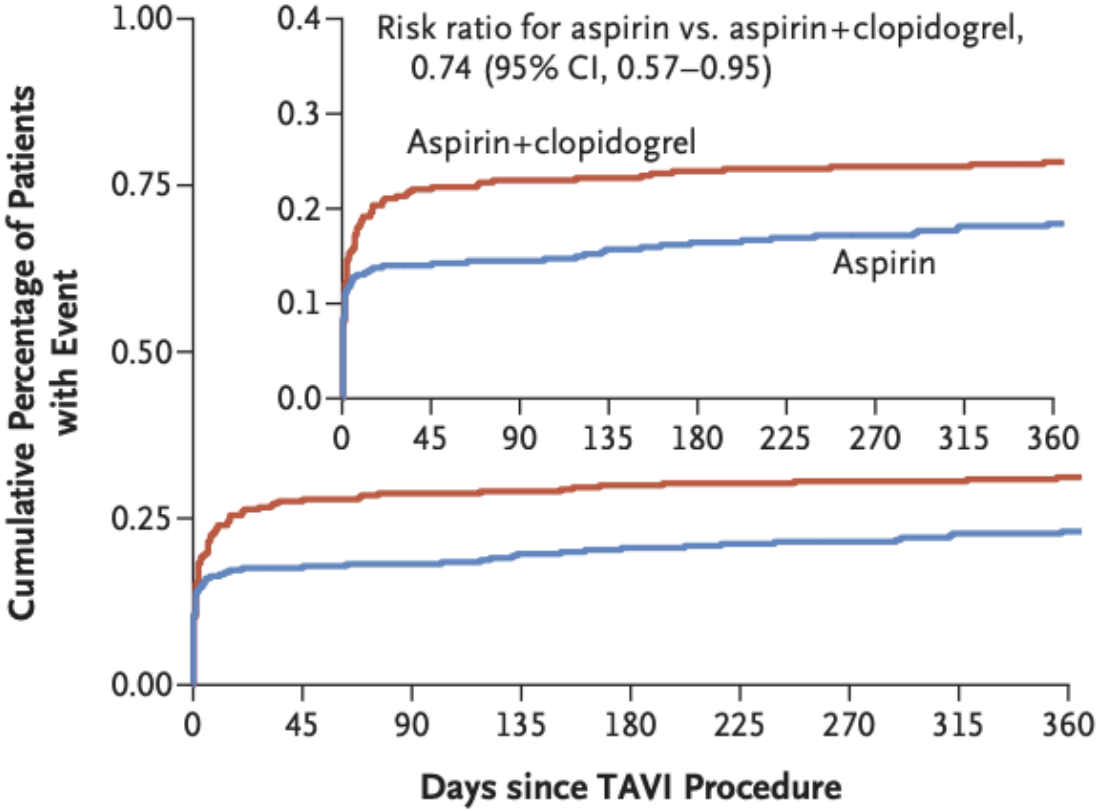
Second Secondary Outcome: Composite of death from CV causes, ischemic stroke, M

N Engl J Med 2020; 383:1447-1457

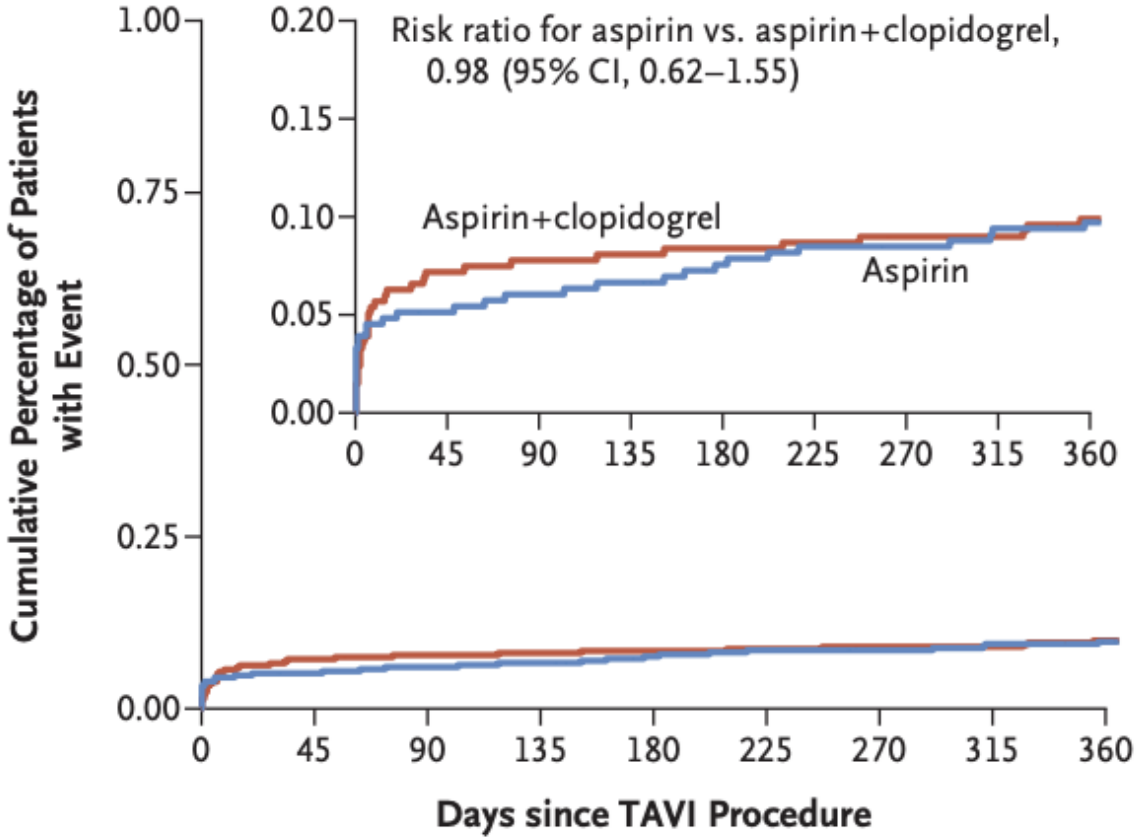
A **Death from Cardiovascular Causes, Non–Procedure-Related Bleeding, Stroke from Any Cause, or MI**



No. at Risk									
Aspirin+clopidogrel	334	242	238	237	232	231	229	229	226
Aspirin	331	272	270	265	259	257	255	251	249

N Engl J Med 2020; 383:1447-1457

B **Death from Cardiovascular Causes, Ischemic Stroke, or MI**



No. at Risk

Aspirin+clopidogrel	334	310	307	306	303	302	300	300	296
Aspirin	331	313	310	308	302	299	298	295	293

POPular TAVI Cohort A

Conclusion:

ASA monotherapy had lower rates of all bleeding and non-procedural bleeding at 1 year without sacrificing thromboembolic protection

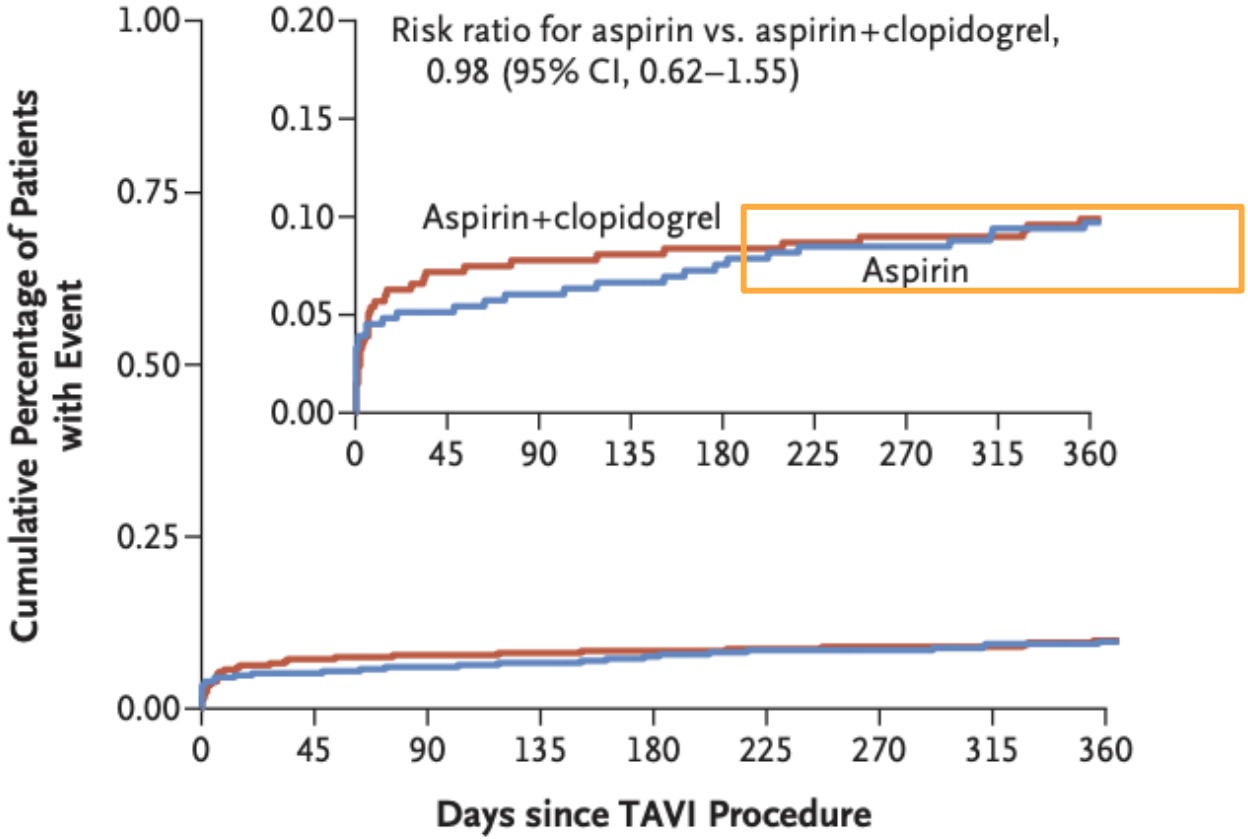
N Engl J Med 2020; 383:1447-1457

- Fairly large, randomized controlled trial
- Patient population representative of what is typically seen in practice
- Captured bleeding and thromboembolic events

- Procedural bleeding defined by BARC Type 4 - not for TAVR; 54-58% of “non-procedural” bleeding was access site bleeding
- Open-label
- Powered for composite of bleeding AND thrombotic events
- Did not detect subclinical CT valve thrombosis

N Engl J Med 2020; 383:1447-1457

B **Death from Cardiovascular Causes, Ischemic Stroke, or MI**



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N Engl J Med 2020; 383:1447-1457

Those without an indication for anticoagulation - SAPT > DAPT

What about using anticoagulation???

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

G.D. Dangas, J.G.P. Tijssen, J. Wöhrle, L. Søndergaard, M. Gilard, H. Möllmann, R.R. Makkar, H.C. Herrmann, G. Giustino, S. Baldus, O. De Backer, A.H.C. Guimarães, L. Gullestad, A. Kini, D. von Lewinski, M. Mack, R. Moreno, U. Schäfer, J. Seeger, D. Tchétché, K. Thomitzek, M. Valgimigli, P. Vranckx, R.C. Welsh, P. Wildgoose, A.A. Volkl, A. Zazula, R.G.M. van Amsterdam, R. Mehran, and S. Windecker, for the GALILEO Investigators*

N Engl J Med 2020; 382:120-129

GALILEO Trial

Randomized, open-label, event-driven, multicenter
n= 1644
Those **without** indication for anticoagulation

Treatment Arms

Rivaroxaban Group
Rivaroxaban 10 mg PO QD PLUS
ASA 75-100 mg x 3 months

DAPT
ASA 75-100 mg PO QD PLUS
Clopidogrel 75 mg PO QD x 3 months

N Engl J Med 2020; 382:120-129

Pertinent Inclusion Criteria

- 18 years or older
- Undergone successful TAVR for treatment of aortic stenosis

Pertinent Exclusion Criteria

- Established indication for long term anticoagulation
- Absolute indication for dual antiplatelet therapy

N Engl J Med 2020; 383:1447-1457

GALILEO Trial

Statistics:

- If patients established atrial fibrillation would get rivaroxaban 20 mg or 15 mg depending on renal function in rivaroxaban group and in antiplatelet group, would get a VKA to replace clopidogrel with a targeted INR 2.0-3.0
- Hypothesis that rivaroxaban would be superior to antiplatelet group

N Engl J Med 2020; 383:1447-1457

GALILEO Trial

Event driven - planned follow up at 1, 3, 6 month and then q6 mo

Primary Efficacy Endpoint:

- Composite of death from any cause or thromboembolic events
  - Stroke, MI, symptomatic valve thrombosis, systemic embolism, DVT, PE

Primary Safety Endpoint:

- Major, disabling, or life threatening bleeding

N Engl J Med 2020; 382:120-129

GALILEO Trial

Characteristic	Rivaroxaban Group	Antiplatelet Group
Age - yr	80.4 ± 7.1	80.8 ± 6.0
Male sex - no. (%)	426 (51.6)	405 (49.5)
HTN - no. (%)	720 (87.2)	697 (85.2)
Diabetes mellitus - no. (%)	236 (28.6)	235 (28.7)
STS risk score	4.0 ± 3.2	4.3 ± 3.5
Congestive Heart Failure - no (%)	394 (47.7)	380 (46.5)
NYHA class III or IV - no (%)	250 (30.3)	222 (27.1)
Previous stroke - no. (%)	51 (6.2)	35 (4.3)
Peripheral Artery Disease - no. (%)	83 (10.0)	82 (10.0)
Previous DVT - no. (%)	18 (2.2)	15 (1.8)

GALILEO Trial

Results

Trial terminated prematurely by data and safety monitoring board because of safety concerns

N Engl J Med 2020; 382:120-129

GALILEO Trial - Safety Outcome

Outcome	Rivaroxaban	Antiplatelet	Difference (95% CI)	HR (95% CI)
Primary Safety Outcome*	46 (5.6)	31 (3.8)	1.5 (-0.1 to 3.1)	1.50 (0.95 to 2.37)
VARC life-threatening or disabling bleeding	18 (2.2)	17 (2.1)	0.1 (-1.0 to 1.2)	1.06 (0.55 to 2.06)
Fatal Bleeding	2 (0.2)	1 (0.1)	0.1 (-0.2 to 0.4)	2.01 (0.18 to 22.19)
VARC major bleeding	30 (3.6)	15 (1.8)	1.4 (0.2 to 2.6)	2.02 (1.09 to 3.76)
TIMI major or minor bleeding	42 (5.1)	24 (2.9)	1.7 (0.3 to 3.2)	1.78 (1.08 to 2.94)
ISTH major bleeding	49 (5.9)	30 (3.7)	1.9 (0.2 to 3.5)	1.66 (1.05 to 2.62)
BARC type 2, 3, or 5 bleeding	148 (17.9)	85 (10.4)	7.2 (4.2 to 10.3)	1.84 (1.41 to 2.41)

*Primary Safety Outcome: composite of life-threatening, disabling, or major bleeding

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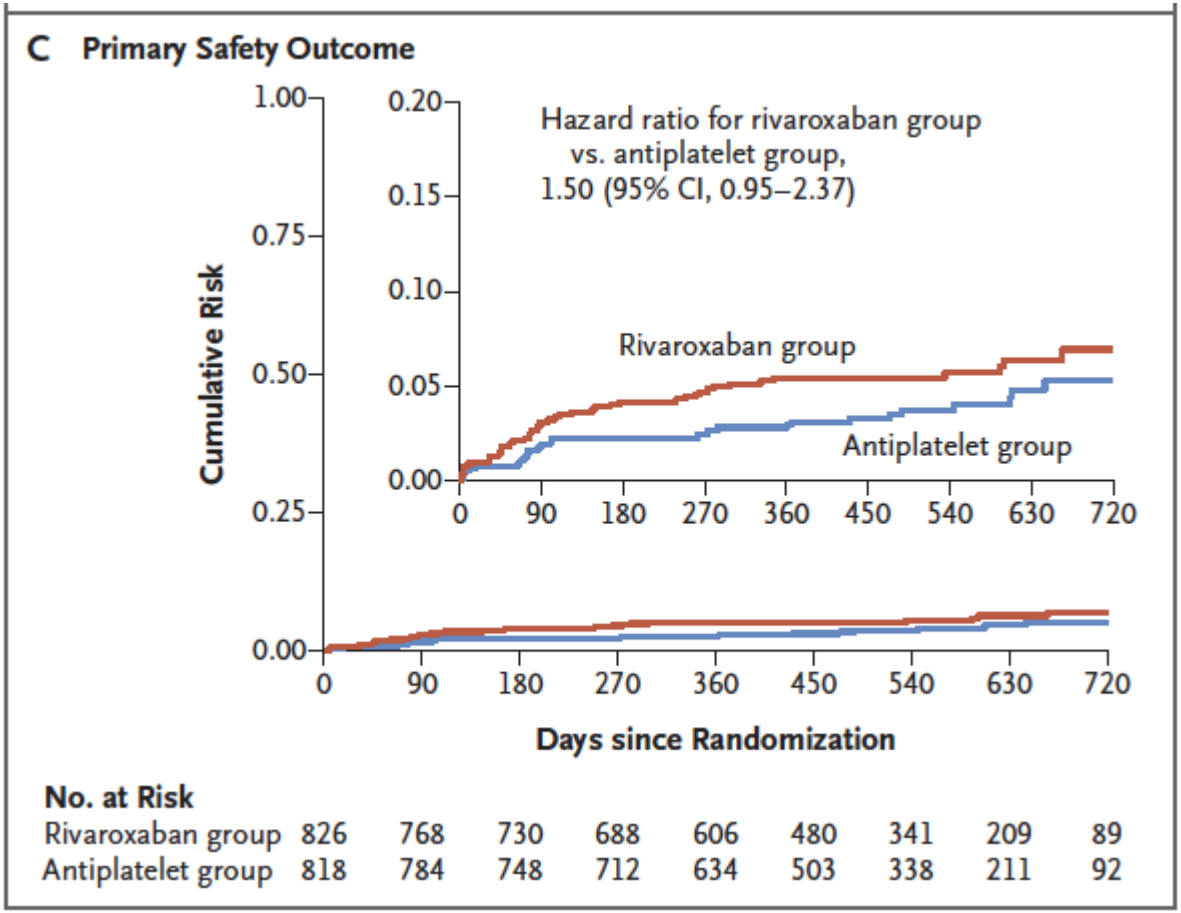
Fatal Bleeding	2 (0.2)	1 (0.1)	0.1 (-0.2 to 0.4)	2.01 (0.18 to 22.19)
VARC major bleeding	30 (3.6)	15 (1.8)	1.4 (0.2 to 2.6)	2.02 (1.09 to 3.76)
TIMI major or minor bleeding	42 (5.1)	24 (2.9)	1.7 (0.3 to 3.2)	1.78 (1.08 to 2.94)
ISTH major bleeding	49 (5.9)	30 (3.7)	1.9 (0.2 to 3.5)	1.66 (1.05 to 2.62)
BARC type 2, 3, or 5 bleeding	148 (17.9)	85 (10.4)	7.2 (4.2 to 10.3)	1.84 (1.41 to 2.41)

*Primary Safety Outcome: composite of life-threatening, disabling, or major bleeding

N Engl J Med 2020; 382:120-129


C Primary Safety Outcome
Hazard ratio for rivaroxaban group vs. antiplatelet group, 1.50 (95% CI, 0.95–2.37)
Rivaroxaban group
Antiplatelet group
Cumulative Risk
1.00
0.75
0.50
0.25
0.00
0.20
0.15
0.10
0.05
0.00
0 90 180 270 360 450 540 630 720
Days since Randomization
No. at Risk
Rivaroxaban group 826 768 730 688 606 480 341 209 89
Antiplatelet group 818 784 748 712 634 503 338 211 92

GALILEO Trial - Efficacy Outcomes

Outcome	Rivaroxaban	Antiplatelet	Difference (95% CI)	HR (95% CI)
Primary Efficacy Outcome*	105 (12.7)	78 (9.5)	2.6 (0.1 to 5.1)	1.35 (1.01 to 1.81)
Death	64 (7.7)	38 (4.6)	2.4 (0.6 to 4.1)	1.69 (1.13 to 2.53)
Stroke	30 (3.6)	25 (3.1)	0.5 (-0.8 to 1.8)	1.20 (0.71 to 2.05)
Myocardial infarction	23 (2.8)	17 (2.1)	0.6 (-0.6 to 1.7)	1.37 (0.73 to 2.56)
Symptomatic valve thrombosis	3 (0.4)	7 (0.9)	-0.4 (-0.9 to 0.2)	0.43 (0.11 to 1.66)
Pulmonary embolism	3 (0.4)	2 (0.2)	0.1 (-0.3 to 0.5)	1.49 (0.25 to 8.93)
DVT	1 (0.1)	4 (0.5)	-0.3 (-0.8 to 0.1)	0.25 (0.03 to 2.23)
Systemic embolism	1 (0.1)	1 (0.1)	0.0 (-0.3 to 0.3)	0.98 (0.06 to 15.69)
Secondary efficacy outcome+	83 (10.0)	68 (8.3)	1.5 (-0.8 to 3.7)	1.22 (0.89 to 1.69)

*Primary Efficacy Outcome: Composite of death from any cause or thrombotic events, including stroke, MI, systemic embolism, DVT, PE
+Secondary efficacy outcome: primary efficacy outcome with death from CV causes replacing death from any cause

N Engl J Med 2020; 382:120-129

GALILEO Trial - Efficacy Outcomes

Outcome	Rivaroxaban	Antiplatelet	Difference (95% CI)	HR (95% CI)
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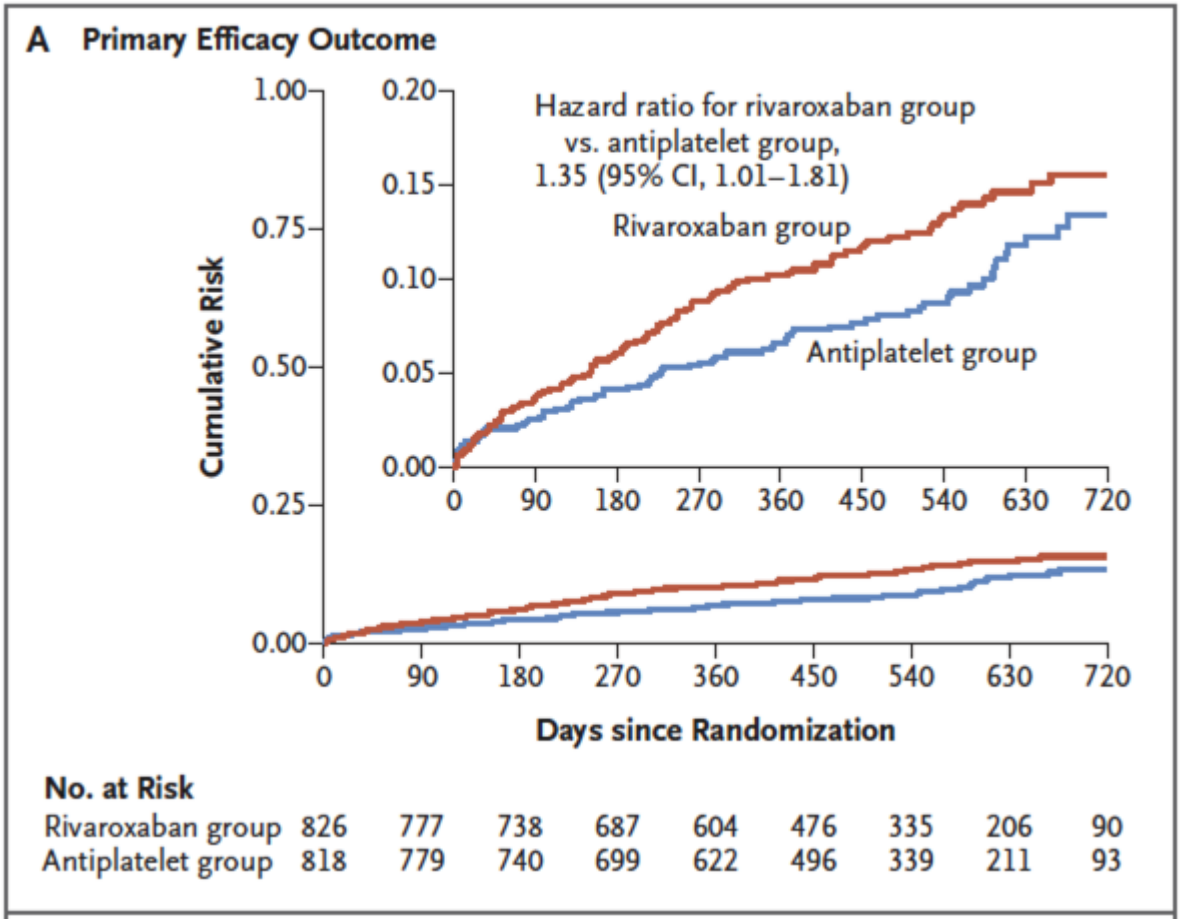
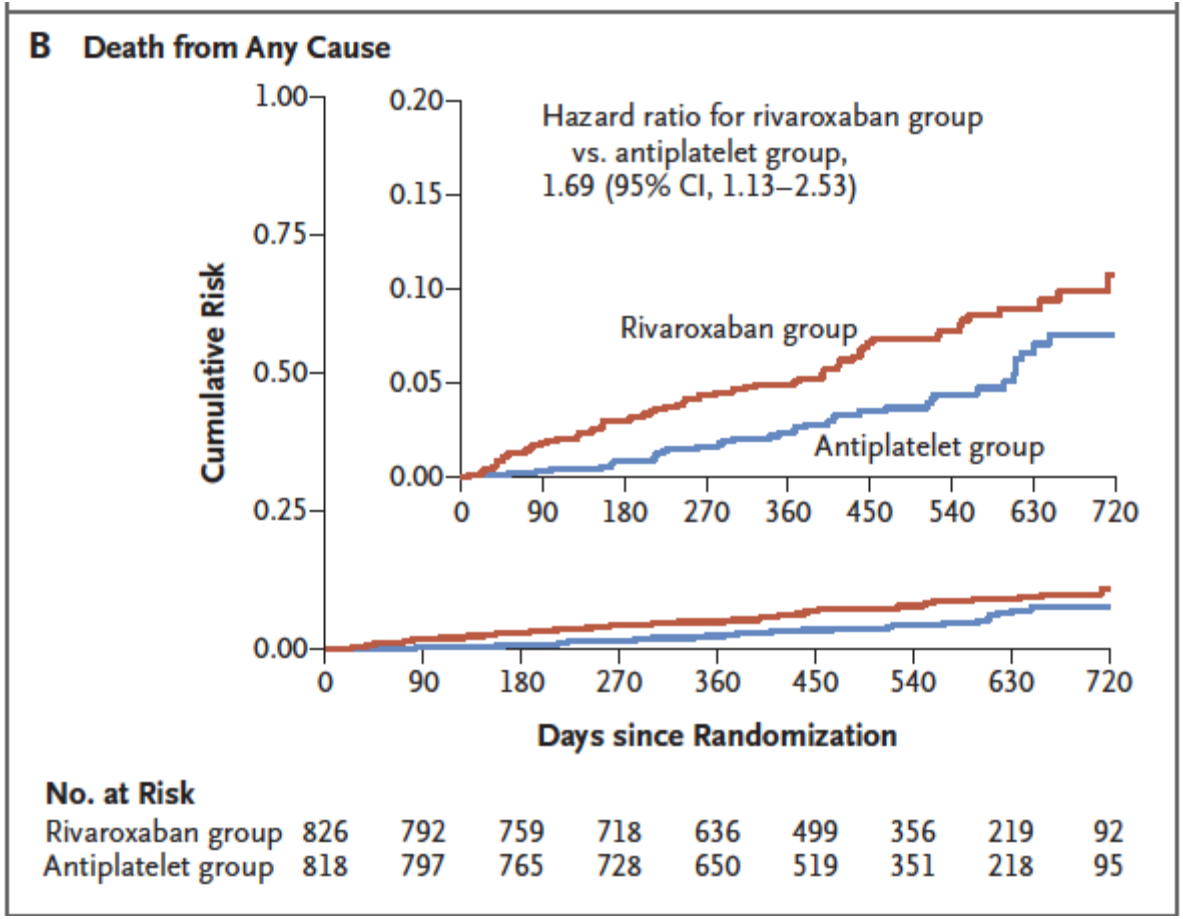
DVT	1 (0.1)	4 (0.5)	-0.3 (-0.8 to 0.1)	0.25 (0.03 to 2.23)
Systemic embolism	1 (0.1)	1 (0.1)	0.0 (-0.3 to 0.3)	0.98 (0.06 to 15.69)
Secondary efficacy outcome+	83 (10.0)	68 (8.3)	1.5 (-0.8 to 3.7)	1.22 (0.89 to 1.69)

*Primary Efficacy Outcome: Composite of death from any cause or thrombotic events, including stroke, MI, systemic embolism, DVT, PE
+Secondary efficacy outcome: primary efficacy outcome with death from CV causes replacing death from any cause

N Engl J Med 2020; 382:120-129


A Primary Efficacy Outcome
Hazard ratio for rivaroxaban group vs. antiplatelet group, 1.35 (95% CI, 1.01–1.81)
Rivaroxaban group
Antiplatelet group
Cumulative Risk
1.00
0.75
0.50
0.25
0.00
0.20
0.15
0.10
0.05
0.00
0 90 180 270 360 450 540 630 720
Days since Randomization
No. at Risk
Rivaroxaban group 826 777 738 687 604 476 335 206 90
Antiplatelet group 818 779 740 699 622 496 339 211 93


B Death from Any Cause
Hazard ratio for rivaroxaban group vs. antiplatelet group, 1.69 (95% CI, 1.13–2.53)
Rivaroxaban group
Antiplatelet group
Cumulative Risk
1.00
0.75
0.50
0.25
0.00
0.20
0.15
0.10
0.05
0.00
0 90 180 270 360 450 540 630 720
Days since Randomization
No. at Risk
Rivaroxaban group 826 792 759 718 636 499 356 219 92
Antiplatelet group 818 797 765 728 650 519 351 218 95

GALILEO Trial

Conclusion: Rivaroxaban use was found to be harmful in those without an indication for anticoagulation in both bleeding and thromboembolic protection.

N Engl J Med 2020; 382:120-129

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.[30]

Those with an indication for anticoagulation

What is done in coronary stenting...

ORIGINAL ARTICLE

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

Renato D. Lopes, M.D., Ph.D., Gretchen Heizer, M.S., Ronald Aronson, M.D., Amit N. Vora, M.D., M.P.H., Tyler Massaro, Ph.D., Roxana Mehran, M.D., Shaun G. Goodman, M.D., Stephan Windecker, M.D., Harald Darius, M.D., Jia Li, Ph.D., Oleg Averkov, M.D., Ph.D., M. Cecilia Bahit, M.D., Otavio Berwanger, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Ziad Hijazi, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Peter Sinnaeve, M.D., Ph.D., Robert F. Storey, M.D., Holger Thiele, M.D., Dragos Vinereanu, M.D., Ph.D., Christopher B. Granger, M.D., and John H. Alexander, M.D., M.H.S., for the AUGUSTUS Investigators*

N Engl J Med 2019; 380:1509-1524

What is done in coronary stenting...

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

Lancet. 2013 Mar 30;381(9872):1107-15.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation

V.J. Nijenhuis, J. Brouwer, R. Delewi, R.S. Hermanides, W. Holvoet, C.L.F. Dubois, P. Frambach, B. De Bruyne, G.K. van Houwelingen, J.A.S. Van Der Heyden, P. Toušek, F. van der Kley, I. Buysschaert, C.E. Schotborgh, B. Ferdinande, P. van der Harst, J. Roosen, J. Peper, F.W.F. Thielen, L. Veenstra, D.R.P.P. Chan Pin Yin, M.J. Swaans, B.J.W.M. Rensing, A.W.J. van 't Hof, L. Timmers, J.C. Kelder, P.R. Stella, J. Baan, and J.M. ten Berg

N Engl J Med 2020; 382:1696-1707

POPular TAVI Cohort B

Randomized, open-label, international controlled trial
n= 313

Treatment Arms

OAC Alone
Allowed for VKA or DOAC, depending on what the patient was on prior to randomization

OAC + Clopidogrel
Allowed for VKA or DOAC, depending on what the patient was on prior to randomization PLUS 300 mg LD followed by 75 mg clopidogrel x3 mo

N Engl J Med 2020; 382:1696-1707

Pertinent Inclusion Criteria

- 18 years or older
- Undergone successful TAVR for treatment of aortic stenosis
- Had an established indication for long-term oral anticoagulation

Pertinent Exclusion Criteria

- DES implantation within 3 months
- BMS within 1 month

N Engl J Med 2020; 382:1696-1707

POPular TAVI Cohort B

Follow up at 12 months

Primary Endpoint:

- All bleeding and non-procedure-related bleeding

Secondary Endpoint #1

- Composite of death from CV causes, non-procedure-related bleeding, stroke from any cause or MI

Secondary Endpoint #2

- Composite of death from CV causes, ischemic stroke, MI (excluded bleeding)

N Engl J Med 2020; 382:1696-1707

POPular TAVI Cohort B

Statistics:

- Modified Intention to Treat
  - All patient who were randomized and underwent TAVI
- Set a noninferiority margin of 7.5% points for the absolute difference with 80% power and a one-sided alpha of 0.025
- If noninferior, tested for superiority

N Engl J Med 2020; 382:1696-1707

Characteristic	Oral Anticoagulation	Oral Anticoagulation + Clopidogrel
Age - yr	80.9 ± 6.2	81.0 ± 5.5
Female Sex - no. (%)	69 (43.9)	73 (46.8)
NYHA Class III or IV - no (%)	119 (75.8)	110 (70.5)
STS Score - Median (IQR)	3.2 (2.2-4.8)	3.1 (2.3-4.5)
Atrial Fibrillation - no (%)	150 (95.5)	147 (94.2)
Hypertension - no (%)	115 (73.2)	105 (67.3)
Diabetes - no (%)	43 (27.4)	46 (29.5)
Coronary Artery Dx - no (%)	65 (41.4)	69 (44.2)
Previous MI - no (%)	14 (8.9)	20 (12.8)
Peripheral artery dx - no (%)	30 (19.1)	28 (17.9)
Previous stroke - no (%)	15 (9.6)	15 (9.6)
Previous CABG - no (%)	30 (19.1)	30 (19.2)

N Engl J Med 2020; 382:1696-1707

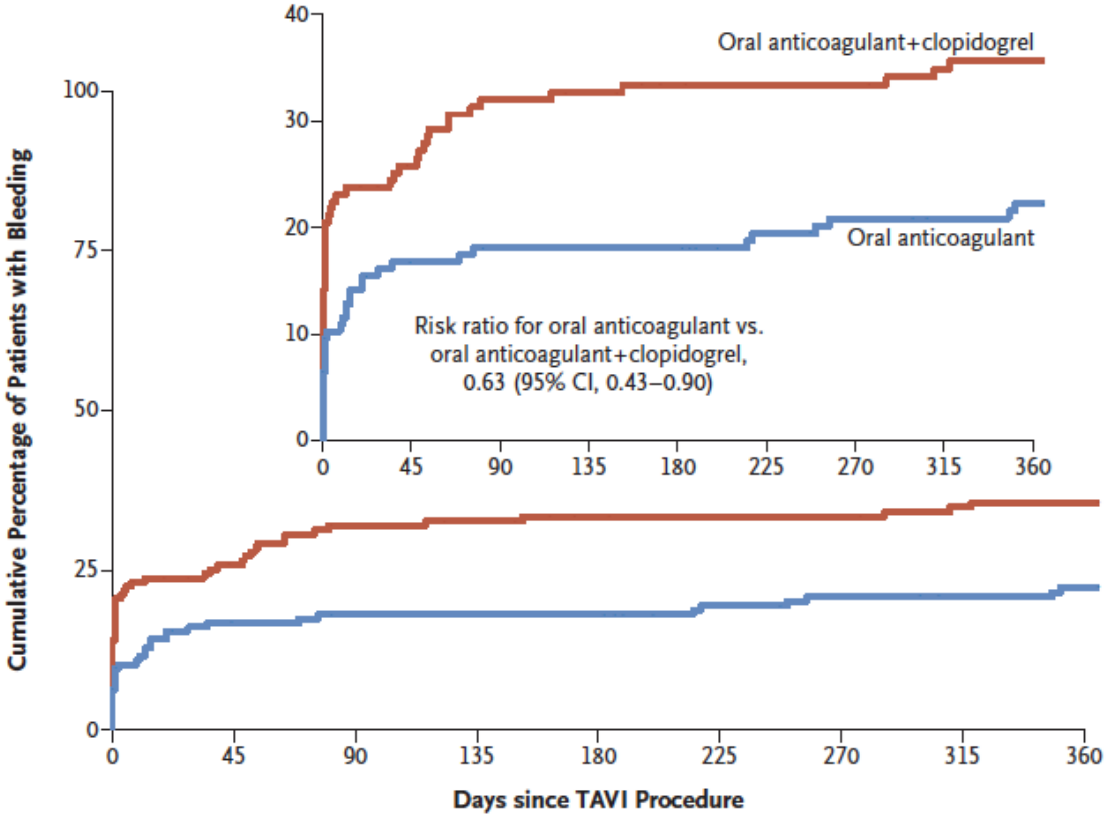
POPular TAVI Cohort B

Outcome	Anticoagulation	Anticoagulation + Clopidogrel	Risk Ratio (95% CI)	P-value
Primary Outcomes				
All bleeding	34 (21.7)	54 (34.6)	0.63 (0.43 to 0.90)	0.01
Non-procedure related bleeding	34 (21.7)	53 (34.0)	0.64 (0.44 to 0.92)	0.02

Access site made up 44% vs. 50%

Severe procedure bleeding: 1 in OAC + clopidogrel versus 0 in OAC alone

N Engl J Med 2020; 382:1696-1707



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

POPular TAVI Cohort B

Outcome	Anticoagulation	Anticoagulation plus Clopidogrel	Risk Ratio	Absolute Difference
First Secondary Composite*				
Noninferiority	49 (31.2)	71 (45.5)		-14.3 (-25.0 to -3.6)
Superiority	49 (31.2)	71 (45.5)	0.69 (0.51 to 0.92)	
Second Secondary Composite+				
Noninferiority	21 (13.4)	27 (17.3)		-3.9 (-11.9 to 4.0)
Superiority	21 (13.4)	27 (17.3)	0.77 (0.46 to 1.31)	

*First secondary endpoint: Composite of death from CV causes, non-procedure-related bleeding, stroke from any cause or MI
+Second secondary endpoint: Composite of death from CV causes, ischemic stroke, MI (excluded bleeding)

N Engl J Med 2020; 382:1696-1707

POPular TAVI Cohort B

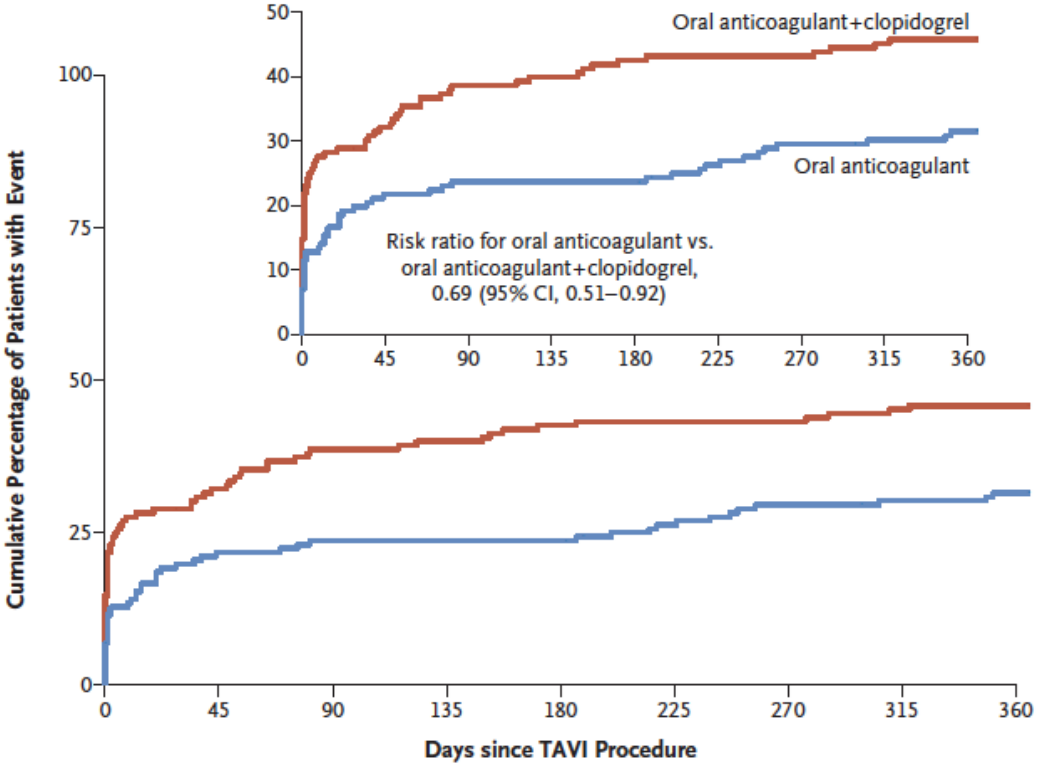
Outcome	Anticoagulation	Anticoagulation plus Clopidogrel	Risk Ratio	Absolute Difference
First Secondary Composite*				
Noninferiority	49 (31.2)	71 (45.5)		-14.3 (-25.0 to -3.6)
Superiority	49 (31.2)	71 (45.5)	0.69 (0.51 to 0.92)	
Second Secondary Composite+				
Noninferiority	21 (13.4)	27 (17.3)		-3.9 (-11.9 to 4.0)
Superiority	21 (13.4)	27 (17.3)	0.77 (0.46 to 1.31)	

*First secondary endpoint: Composite of death from CV causes, non-procedure-related bleeding, stroke from any cause or MI
+Second secondary endpoint: Composite of death from CV causes, ischemic stroke, MI (excluded bleeding)

N Engl J Med 2020; 382:1696-1707

Outcome	Anticoagulation	Anticoagulation plus Clopidogrel	Risk Ratio
Death from any cause	21 (13.4)	24 (15.4)	0.87 (0.51 to 1.50)
Death from CV causes	13 (8.3)	20 (12.8)	0.65 (0.33 to 1.25)
Stroke	9 (5.7)	9 (5.8)	0.99 (0.41 to 2.44)
Ischemic	8 (5.1)	9 (5.8)	0.88 (0.35 to 2.23)
Hemorrhagic	1 (0.6)	0	
Myocardial Infarction	1 (0.6)	1 (0.6)	0.99 (0.06 to 15.75)
VARC-2 bleeding			
Life-threatening or disabling bleeding	6 (3.8)	13 (8.3)	0.46 (0.18 to 1.18)
Major bleeding	8 (5.1)	13 (8.3)	0.61 (0.26 to 1.43)
Major, life-threatening, or disabling bleeding	14 (8.9)	26 (16.7)	0.54 (0.29 to 0.99)
Minor bleeding	20 (12.7)	28 (17.9)	0.71 (0.42 to 1.21)

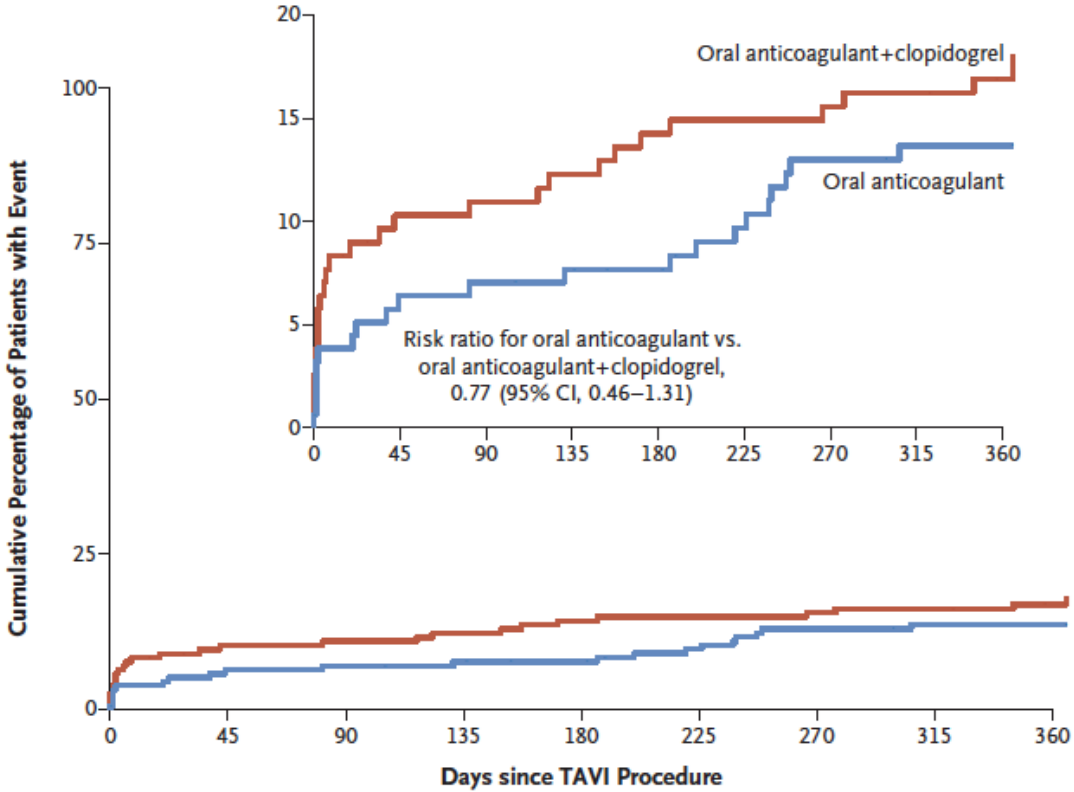
A **Death from Cardiovascular Causes, Non–Procedure-Related Bleeding, Stroke, or MI (Secondary Composite 1)**



No. at Risk

Oral anticoagulant+clopidogrel	156	104	94	92	88	87	87	84	83
Oral anticoagulant	157	122	119	119	119	113	108	106	104

B **Death from Cardiovascular Causes, Ischemic Stroke, or MI (Secondary Composite 2)**



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

POPular TAVI Cohort B

Conclusion:

Among patients with an indication for anticoagulation, OAC alone was associated with a lower incidence of serious bleeding over 1 year versus OAC + clopidogrel and was noninferior in terms of adverse ischemic outcomes.

N Engl J Med 2020; 382:1696-1707

- Fairly large, randomized controlled trial
- Patient population representative of what is typically seen in practice
- Ischemic events were non-inferior on rivaroxaban alone

- Time in therapeutic range not reported
- Indication for anticoagulation mostly driven by atrial fibrillation
- 75.2% of patients on VKA
- CHADSVASC not reported
- DOAC dosing not reported

N Engl J Med 2020; 382:1696-1707

Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS)

ClinicalTrials.gov Identifier: NCT02664649

Recruitment Status : Completed
First Posted : January 27, 2016
Last Update Posted : February 25, 2021

ATLANTIS

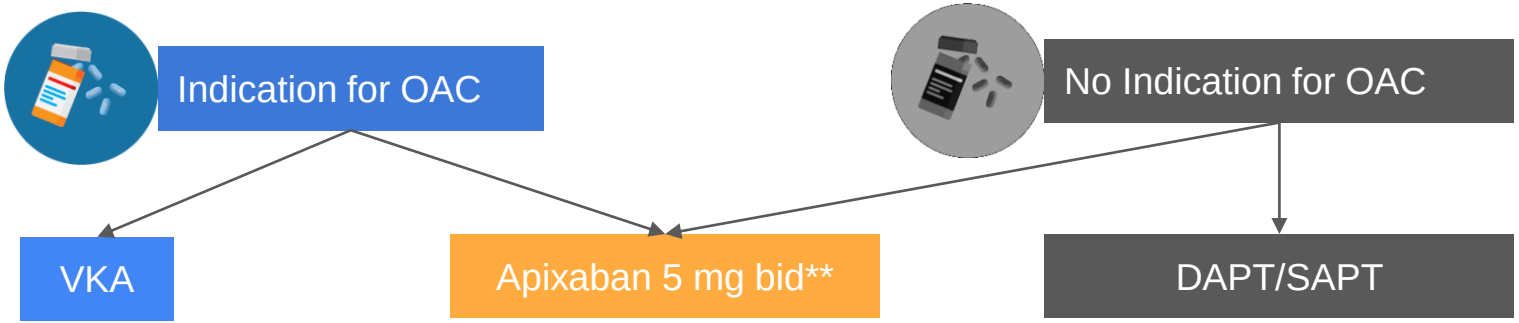
Two Strata:

- In patients **with** an indication for OACs, is apixaban better than warfarin?
- In patients **without** an indication for anticoagulation, is apixaban 5 mg better than SAPT or DAPT?

ATLANTIS

Randomized, open-label, international controlled trial
n= 1510

Treatment Arms



**allowed for 2.5 mg bid if 2 of three metr SCr >=1.5mg/dL, age >=80 years, weight <=60 kilo or if on concomitant antiplatelet therapy (ACS or recent stenting) or physician's choice

ATLANTIS

Follow up at 12 months

Primary Endpoint:

- Composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of DVT or PE, major bleed

ATLANTIS

4D-CT scan protocol to identify subclinical valve thrombosis (defined as visible thrombus on TTE or CT scan **and** mean transprosthetic gradient >=10 mmHg change from baseline or 20mmHg OR reduced leaflet mobility grade 3-4 on at least one leaflet

- > 18 yo
- Successful TAVI
- Irrespective of prior antithrombotic therapy
- With any approved TAVR device

- CrCl <15 mL/min or dialysis
- Mechanical valves
- Severe mitral valve stenosis requiring intervention
- Unsuccessful TAVI
- Ongoing major bleeding or vascular complication
- Prior hx of intracranial hemorrhage
- Recent stroke/TIA on anticoagulant therapy (<6 weeks)
- Planned major surgery during follow up
- Expected survival <1 year
- Concomitant use of prasugrel or ticagrelor
- Coronary stent implantation <2 weeks prior
- Taking CYP3A4 inhibitors
- Any coagulopathy with significant risk of bleeding

ATLANTIS - Primary Endpoint

	Apixaban	SOC	P-value for interaction	HR (95% CI)
Primary Outcome	138 (18.4%)	151 (20.1%)	0.57	0.92 (0.73-1.16)
No indication for OAC	89 (16.9%)	101 (19.3%)		0.88 (0.66-1.17)
Indication for OAC	49 (21.9%)	50 (21.9%)		1.02 (0.68-1.51)

ATLANTIS - Primary Endpoint without valve thrombosis

	Apixaban	SOC	P-value for interaction	HR (95% CI)
Primary Outcome	133 (17.8%)	121 (16.1%)	0.70	1.12 (0.88-1.44)
No indication for OAC	84 (16.9%)	73 (13.9%)		1.16 (0.85-1.60)
Indication for OAC	49 (21.9%)	48 (21.9%)		1.06 (0.71-1.58)

ATLANTIS - Secondary Endpoints

	Apixaban	SOC	HR (95% CI)
Death, MI, any stroke/TIA	79 (10.5%)	62 (8.26%)	1.31 (0.95-1.85)
Death, any stroke/TIA or systemic embolism	78 (10.4%)	60 (8.0%)	1.35 (0.96-1.90)
Death - From CV causes - From non-CV causes	54 (7.2%) 38 (5.1%) 16 (2.1%)	41 (5.5%) 28 (3.7%) 13 (1.8%)	1.39 (0.92-2.09) 1.42 (0.87-2.32) 1.33 (0.63-2.77)
MI	6 (0.8%)	5 (0.7%)	1.22 (0.37-4.00)
Stroke or TIA	28 (3.7%)	21 (2.8%)	1.38 (0.78-2.44)
Systemic Embolism	2 (0.3%)	3 (0.4%)	0.65 (0.11-3.91)
Bioprosthetic thrombosis	8 (1.1%)	35 (4.7%)	0.23 (0.11-0.50)
Intracardiac thrombus	3 (0.4%)	3 (0.4%)	1.11 (0.22-5.54)
DVT or PE	1 (0.1%)	11 (1.5%)	0.09 (0.01-0.72)

ATLANTIS - Secondary Endpoints

	Apixaban	SOC	HR (95% CI)
Death, MI, any stroke/TIA	79 (10.5%)	62 (8.26%)	1.31 (0.95-1.85)
Death, any stroke/TIA or systemic embolism	78 (10.4%)	60 (8.0%)	1.35 (0.96-1.90)
Death - From CV causes - From non-CV causes	54 (7.2%) 38 (5.1%) 16 (2.1%)	41 (5.5%) 28 (3.7%) 13 (1.8%)	1.39 (0.92-2.09) 1.42 (0.87-2.32) 1.33 (0.63-2.77)
MI	6 (0.8%)	5 (0.7%)	1.22 (0.37-4.00)
Stroke or TIA	28 (3.7%)	21 (2.8%)	1.38 (0.78-2.44)
Systemic Embolism	2 (0.3%)	3 (0.4%)	0.65 (0.11-3.91)
Bioprosthetic thrombosis	8 (1.1%)	35 (4.7%)	0.23 (0.11-0.50)
Intracardiac thrombus	3 (0.4%)	3 (0.4%)	1.11 (0.22-5.54)
DVT or PE	1 (0.1%)	11 (1.5%)	0.09 (0.01-0.72)

ATLANTIS - Safety Analysis

	Apixaban	SOC	HR (95% CI)
Primary safety endpoint	6.4 (8.5%)	64 (8.5%)	1.02 (0.72-1.44)
Life-threatening bleeding	19 (2.5%)	18 (2.4%)	1.06 (0.55-2.02)
Major bleeding	50 (6.7%)	48 (6.4%)	1.07 (0.72-1.59)
Minor bleeding (BARC 2 or 3a)	70 (9.3%)	78 (10.4%)	0.91 (0.66-1.26)
Any bleeding	174 (23.2%)	170 (22.6%)	1.05 (0.85-1.30)

Indication for oral anticoagulation (post-hoc)

	Apixaban	SOC	HR (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 bleeding
+life threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, b, and 3c as defined by VARC-2)

No Indication for oral anticoagulation (post-hoc)

	Apixaban	SOC	HR (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)
- CV death	17 (3.2%)	13 (2.5%)	1.42 (0.69-2.94)
- Non CV 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 bleeding
+life threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, b, and 3c as defined by VARC-2)

ATLANTIS

Conclusion:

- Apixaban after TAVR is not superior to SOC antithrombotic treatment (VKA in OAC group, APT in no OAC group) globally and in each stratum though there was a reduction in subclinical valve leaflet thrombosis; however this didn’t translate into improved clinical outcomes
- The bleeding with apixaban is similar to that of the current SOC, globally and in each stratum.
- In those without an indication for OAC, apixaban was associated with higher non-CV mortality versus APT use (similar to GALILEO Trial)

Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions (1:1) (AVATAR)

ClinicalTrials.gov Identifier: NCT02735902

Recruitment Status : Recruiting
First Posted : April 13, 2016
Last Update Posted : January 29, 2021

See **Contacts and Locations**

AVATAR

In patients with indication for long-term OAC, what is the 12-mo clinical benefit of OAC monotherapy with VKA or DOAC versus double therapy with ASA plus OAC?

Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (ENVISAGE-TAVI AF)

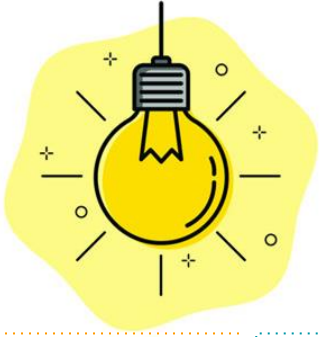
ClinicalTrials.gov Identifier: NCT02943785

Recruitment Status : Completed
First Posted : October 25, 2016
Last Update Posted : July 7, 2021

ENVISAGE-TAVI AF

In patients with an indication for anticoagulation, is edoxaban 60 mg better to warfarin in terms of net adverse events and major bleeds?

SAPT or DAPT can be administered at investigator’s discretion



In patients **without** an indication for anticoagulation:

- Rivaroxaban 10 mg QD PLUS aspirin 75-100 mg QD is harmful (GALILEO)
- Apixaban 5 mg BID PO appears harmful (ATLANTIS)

SAPT results in less bleeding than DAPT without an increase in thromboembolic events (POPULAR-TAVI, Cohort A)

In the majority of these patients: I would recommend SAPT alone.

In patients **with** an indication for anticoagulation:

- Most data supports long term VKA
  - Apixaban may be considered (ATLANTIS)
  - Edoxaban not recommended (ENVISAGE-TAVI AF)

Anticoagulation alone results in less bleeding than anticoagulation PLUS clopidogrel without an increase in thromboembolic events (POPULAR TAVI Cohort B)

What we know now....

Future Directions

In patients **<u>without</u>** an indication for anticoagulation *AND recent coronary stenting*:

?? Likely DAPT

In patients **<u>with</u>** an indication for anticoagulation *AND recent coronary stenting*:

?? (OAC + P2Y12 inhibitor) versus (OAC + ASA)

In patients **<u>with</u>** an indication for anticoagulation:

?? OAC alone versus (OAC + ASA)


Thank you

Appendix Slides

Valve Academic Research Consortium (VARC)-2 bleeding

- VARC-2 life threatening or disabling bleeding
  - Fatal bleeding (BARC type 5)
  - Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c).
  - Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b).
  - Overt source of bleeding with drop in hemoglobin > 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units * (BARC type 3b).
- VARC-2 major bleeding:
  - Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBCs, or causing hospitalization or permanent injury, or requiring surgery (BARC type 3a) AND
  - Does not meet the criteria of life-threatening or disabling bleeding.
- VARC-2 minor bleeding: Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major (BARC type 2 or 3a, depending on the severity).

Bleeding Academic Research Consortium Definition for Bleeding (BARC) bleeding

- Type 1:
  - Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional.
- Type 2:
  - Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:
    - Requiring nonsurgical, medical intervention by a health-care professional.
    - Leading to hospitalization or increased level of care.
    - Prompting evaluation

Bleeding Academic Research Consortium Definition for Bleeding (BARC) bleeding

- Type 3:
  - Type 3a:
    - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL.
    - Any transfusion with overt bleeding
  - Type 3b:
    - Overt bleeding plus hemoglobin drop ≥5 g/dL.
    - Cardiac tamponade.
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid).
    - Bleeding requiring intravenous vasoactive agents.
  - Type 3c:
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal).
    - Subcategories confirmed by autopsy or imaging or lumbar puncture.
    - Intraocular bleed compromising vision

Bleeding Academic Research Consortium Definition for Bleeding (BARC) bleeding

- Type 4: CABG-related bleeding:
  - Perioperative intracranial bleeding within 48 h.
  - Reoperation after closure of sternotomy for the purpose of controlling bleeding.
  - Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period.
  - Chest tube output more than or equal to 2L within a 24-h period.
- Type 5: Fatal bleeding

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.[12–14]
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.[12,13,29]
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.[30]

Circulation. Volume 143, Issue 5, 2 February 2021; Pages e72-e227

Dual Antiplatelet Therapy Versus Aspirin Alone in Patient Undergoing Transcatheter Aortic Valve Implantation (Ussia et al)

Ussia et al.

Randomized, open-label, single-center study
n=79 (mean age 81, cohorts balanced)

Treatment Arms

DAPT
Clopidogrel 300 mg LD (day before TAVI) +
Clopidogrel 75 mg PO QD x3 mo + ASA 100 mg PO QD indefinitely

ASA
ASA 100 mg PO QD indefinitely

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

Ussia et al.

Randomized, open-label, single-center study
n=79 (mean age 81, cohorts balanced)

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ASA
ASA 100 mg PO QD indefinitely

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

Ussia et al.

Pertinent Exclusion Criteria

- Liver Cirrhosis
- Recurrent pulmonary embolism
- Porcelain aorta
- Severe connective tissue dx
- Previous PCI or ACS requiring DAPT
- Need for oral anticoagulation
- Allergy or intolerance to study drugs

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

Ussia et al.

Follow up at 30 days and 6 mo

Primary Endpoint: composite of major adverse cardiac and cerebrovascular events

- Death from any cause
- MI
- Major stroke
- Urgent or emergency conversion to surgery
- Life-threatening bleeding

Ussia et al.

Results:

- Intention to Treat
- The cumulative incidence of major adverse cardiac and cerebrovascular events at 30 days and 6 months 14% versus 16%
- No significant differences between the DAPT and ASA groups noted at both 30 days (13% vs. 15%, p=0.71) and 6 mo (18% vs 15%, p=0.85).

Conclusion: Adding clopidogrel to ASA for 3 mo did **not** reduce MACCE or mortality at 30 days or 6 months. Results do not support strategy of short-term adjunctive use of clopidogrel added to ASA post TAVI.

Variable	Overall (n=79)	DAPT (n=40)	ASA (n=39)	p-value
All-cause	3 (4%)	1 (3%)	2 (5%)	0.49
CV death	1 (1%)	1 (3%)	0	0.51
Major stroke	3 (4%)	1 (3%)	2 (5%)	0.49
Minor stroke	0	0	0	--
TIA	2 (3%)	1 (3%)	1 (3%)	0.75
MI	0	0	0	--
Conversion to open heart sx	0	0	0	--
Life-threatening bleeding	4 (5%)	2 (5%)	2 (5%)	0.92
Major bleeding	3 (4%)	2 (5%)	1 (3%)	0.61
Minor bleeding	7 (9%)	3 (8%)	4 (10%)	0.55
MACCE	7 (9%)	3 (8%)	4 (10%)	0.49
Cardiac tamponade	1 (1%)	1 (3%)	0	0.51
Major vascular complications	6 (10%)	3 (8%)	2 (5%)	0.65
Minor vascular complications	5 (6%)	3 (8%)	2 (5%)	0.51
Percutaneous management	8 (9%)	3 (10%)	2 (5%)	0.97
Surgical management	1 (1%)	1 (3%)	0	0.53

In-Hospital Outcomes

SAT-TAVI (Stabile et al.)

Stabile et al.

Randomized, double blind controlled trial
n=120

Treatment Arms

DAPT
Clopidogrel 75 mg/d OR ticlopidine 500 mg/bid (6 months) PLUS
ASA 75-160 mg/day (indefinitely)

ASA
ASA 75-160 mg/day (indefinitely)

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

Stabile et al.

Pertinent Exclusion Criteria

- Untreated CAD requiring revascularization
- Acute MI within 1 mo
- GIB within 3 mo
- DES or BAV
- Indication for oral anticoagulation therapy

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

Stabile et al.

Follow up at 30 days and 6 mo

Primary Endpoint:

- Adverse Cardiovascular events at 30 days
  - CV death
  - Major vascular complication
  - Minor vascular complication
  - Major and minor vascular complication
  - Major stroke
  - Minor stroke

Stabile et al.

Results (ASA vs DAPT)

- All NS at 30 days except:
  - **Major and minor vascular complication 3% versus 13.3%, p<0.05**
- No differences at 6 mo

Conclusion: Thienopyridine use was linked with a significant increase in the rate of vascular complications

ARTE Trial (Rodes-Cabau et al.)

ARTE Trial

Prospective, randomized, open label trial
n= 222

Treatment Arms

DAPT
Clopidogrel 300 mg LOAD followed by 75 mg/day (3 mo) PLUS
ASA 80-100 mg/day (indefinitely)

ASA
ASA 80-100 mg/day (indefinitely)

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

ARTE Trial

Pertinent Exclusion Criteria

- Chronic anticoagulation treatment
- Major bleeding within 3 months prior
- Prior intracranial bleeding
- DES within past year

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

ARTE Trial

Follow up at 3 months

Primary Endpoint:

- Occurrence of death, MI, stroke or TIA, or major life threatening bleeding within 3 months following the procedure

ARTE Trial

Results (DAPT vs ASA)

- Primary endpoint occurred more in DAPT group (15.3% vs 7.2%, p=0.065)
- No differences in occurrence of:
  - Death (DAPT, 6.3%; SAPT, 3.6% p=0.37)
  - MI (DAPT, 3.6%; SAPT 0.9%, p=0.18)
  - Stroke or TIA (DAPT, 2.7%; SAPT, 0.9%; p=0.31)
- DAPT had a **higher rate of major or life-threatening bleeding** (10.8% vs. 3.6% in the SAPT group, p=0.038)

Conclusion: SAPT tended to reduce the occurrence of major adverse events following TAVR.

- Reduced the risk for major or life-threatening events
- No increased risk for MI or stroke

Antithrombotic Strategies after Transcatheter Aortic Valve Implantation: Insights from a Network Meta-Analysis (Kuno et al.)

Kuno et al.

Meta-analysis
n=20,548

Target

To investigate the efficacy and safety of different antithrombotic strategies in patients undergoing TAVI

J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

Kuno et al.

Primary Endpoint:

- All cause mortality, major or life-threatening bleeding events, and stroke
- All included anticoagulants were VKAs

Kuno et al.

Results

- No differences in mortality except OAC + DAPT had significantly higher rates of mortality vs. other regimens ($P<0.05$, $I^2 = 0$)
- SAPT had significantly lower rates of bleeding versus DAPT, OAC+SAPT, OAC+DAPT.
  - HR: 0.59 [0.46-0.77], p <.001
  - HR: 0.58 0.34-0.99], p = .045
  - HR: 0.41 [0.18-0.93], p = .033, respectively, $I^2 = 0\%$).
- No significant difference in stroke among all regimens

Kuno et al.

Conclusion:

- If DAPT or anticoagulation indicated, avoid DAPT + OAC
- If no indication for OAC or DAPT post-TAVI, SAPT recommended
- When DAPT or OAC indicated, should avoid triple therapy or minimize duration

Table 1
Baseline clinical and echocardiographic characteristics

Variable	Overall (n = 79)	DAPT (n = 40)	Aspirin (n = 39)	p Value
Age (years)	81 ± 4	80 ± 6	81 ± 4	0.68
Women	43 (54%)	20 (50%)	23 (59%)	0.44
Hypertension	66 (84%)	35 (88%)	31 (80%)	0.96
Diabetes mellitus	21 (27%)	13 (33%)	8 (21%)	0.35
Peripheral vascular disease	7 (9%)	3 (8%)	4 (10%)	0.43
Porcelain aorta	2 (3%)	1 (3%)	1 (3%)	0.72
Congestive heart failure*	32 (41%)	18 (45%)	14 (36%)	0.65
Previous myocardial infarction	11 (14%)	7 (18%)	4 (10%)	0.31
Previous stroke	6 (8%)	2 (5%)	4 (10%)	0.28
Previous transient ischemic attack	4 (5%)	2 (5%)	2 (5%)	0.68
Previous coronary artery bypass grafting	6 (8%)	2 (5%)	4 (10%)	0.28
Previous cardiac surgery†	3 (4%)	2 (5%)	1 (3%)	0.55
Previous percutaneous coronary intervention	21 (27%)	12 (30%)	9 (23%)	0.35
Chronic obstructive pulmonary disease	17 (22%)	10 (25%)	7 (18%)	0.60
Liver cirrhosis	1 (1%)	0	1 (3%)	0.47
Chronic kidney failure	11 (14%)	6 (15%)	5 (13%)	0.92
Permanent atrial fibrillation	10 (13%)	4 (10%)	6 (15%)	0.29
Previous aortic valvuloplasty	42 (53%)	24 (60%)	18 (46%)	0.45
Previous pacemaker	5 (6%)	4 (10%)	1 (3%)	0.22
New York Heart Association class III and IV	49 (62%)	26 (65%)	23 (59%)	0.60
Echocardiographic findings				
Mean gradient (mm Hg)	53 ± 17	52 ± 6	57 ± 18	0.23
Aortic valve area (cm^2)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.3	0.70
Left ventricular ejection fraction (%)	52 ± 12	51 ± 12	54 ± 8	0.49
Logistic EuroSCORE (%)	21 ± 13	23 ± 15	21 ± 16	0.60
Society of Thoracic Surgeons score (%)	7.3 ± 4	8 ± 5	7 ± 3	0.37

Table 2
Procedural variables

Variable	Overall (n = 79)	DAPT (n = 40)	Aspirin (n = 39)	p Value
Procedural variables				
Procedure time (minutes)	45 ± 26	44 ± 23	47 ± 23	0.70
Fluoroscopy time (minutes)	22 ± 13	22 ± 13	22 ± 13	0.48
Approach				
Transfemoral	77 (97%)	38 (95%)	39 (100%)	
Trans-subclavian	2 (3%)	2 (5%)	0	
Device				
CoreValve Revalving system 26-mm	35 (44%)	23 (56%)	12 (31%)	
CoreValve Revalving system 29-mm	44 (56%)	17 (43%)	27 (69%)	
Procedural success	74 (94%)	38 (95%)	36 (92%)	0.49
Postdilation	4 (5%)	1 (3%)	3 (8%)	0.30
Valve-on-valve	3 (4%)	2 (5%)	1 (3%)	0.51
Valve-in-valve	0	0	0	—

Table 3
In-hospital outcomes

Variable	Overall (n = 79)	DAPT (n = 40)	Aspirin (n = 39)	p Value
All-cause death	3 (4%)	1 (3%)	2 (5%)	0.49
Cardiovascular death	1 (1%)	1 (3%)	0	0.51
Major stroke	3 (4%)	1 (3%)	2 (5%)	0.49
Minor stroke	0	0	0	—
Transient ischemic attack	2 (3%)	1 (3%)	1 (3%)	0.75
Myocardial infarction	0	0	0	—
Conversion to open heart surgery	0	0	0	—
Life-threatening bleeding	4 (5%)	2 (5%)	2 (5%)	0.92
Major bleeding	3 (4%)	2 (5%)	1 (3%)	0.61
Minor bleeding	7 (9%)	3 (8%)	4 (10%)	0.55
Major adverse cardiac and cerebrovascular events	7 (9%)	3 (8%)	4 (10%)	0.49
Cardiac tamponade	1 (1%)	1 (3%)	0	0.51
Major vascular complications	6 (10%)	3 (8%)	3 (8%)	0.65
Minor vascular complications	5 (6%)	3 (8%)	2 (5%)	0.51
Vascular intervention				
Percutaneous management	8 (9%)	4 (10%)	4 (10%)	0.97
Surgical management	1 (1%)	1 (3%)	0	0.53

Table 4
Outcomes at 30 days and 6 months

Variable	Overall (n = 79)	DAPT (n = 40)	Aspirin (n = 39)	p Value
30 Days				
All-cause death	8 (10%)	4 (10%)	4 (10%)	0.63
Cardiovascular death	1 (1%)	1 (3%)	0	0.51
Major stroke	3 (4%)	1 (3%)	2 (5%)	0.49
Minor stroke	0	0	0	—
Transient ischemic attack	2 (3%)	1 (3%)	1 (3%)	0.75
Spontaneous myocardial infarction	0	0	0	—
Conversion to open heart surgery	0	0	0	—
Life-threatening bleeding	4 (5%)	2 (5%)	2 (5%)	0.92
Major bleeding	3 (4%)	2 (5%)	1 (3%)	0.61
Minor bleeding	7 (9%)	3 (8%)	4 (10%)	0.55
Major adverse cardiac and cerebrovascular events	11 (14%)	5 (13%)	6 (15%)	0.71
6 Months				
All-cause death	9 (11%)	4 (10%)	5 (13%)	0.50
Cardiovascular death	1 (1%)	1 (3%)	0	0.51
Major stroke	3 (4%)	1 (3%)	2 (5%)	0.49
Minor stroke	0	0	0	—
Transient ischemic attack	2 (3%)	1 (3%)	1 (3%)	0.75
Spontaneous myocardial infarction	1 (3%)	1 (3%)	0	0.51
Conversion to open heart surgery	0	0	0	—
Life-threatening bleeding	4 (5%)	2 (5%)	2 (5%)	0.92
Major bleeding	3 (4%)	2 (5%)	1 (3%)	0.61
Minor bleeding	7 (9%)	3 (8%)	4 (10%)	0.55
Major adverse cardiac and cerebrovascular events	13 (16%)	7 (18%)	6 (15%)	0.85

Table 2
Procedural characteristics.

	ASA ($N = 60$)	DAPT ($N = 60$)	P
Device success (%)	60 (100.0)	60 (100.0)	ns
23 mm size valve (%)	34 (56.7)	34 (56.7)	ns
26 mm size valve (%)	26 (43.3)	23 (43.3)	ns
MLD of Ileofemoral vessels on the therapeutic side (mm)	6.72 ± 0.6	6.69 ± 0.5	ns
Outer sheath diameter/MLD Ileofemoral vessel on the therapeutic side	1.07 ± 0.1	1.06 ± 0.1	ns
Surgical access closure at first intention (%)	6 (10.0)	5 (8.3)	ns
Percutaneous closure at first intention (%)	54 (90.0)	55 (91.7)	ns
PCI before index procedure (%)	14 (23.3)	13 (21.3)	ns
Actual significant CAD (%)	5 (8.3)	5 (8.3)	ns
General anesthesia (%)	1 (1.7)	2 (3.3)	ns
Clopidogrel (%)	–	53 (88.3)	–

Table 3
Adverse cardiovascular events at 30 days.

	ASA ($N = 60$)	DAPT ($N = 60$)	P
CV death (n/%)	2 (3.3)	1 (1.7)	ns
Major vascular complication	0 (0)	3 (5)	ns
Minor vascular complication	3 (5)	5 (8.3)	ns
Major and minor vascular complication	3 (5)	8 (13.3)	<0.05
Major stroke	1 (1.7)	1 (1.7)	ns
Minor stroke	1 (1.7)	0 (0)	ns

Stabile et al.

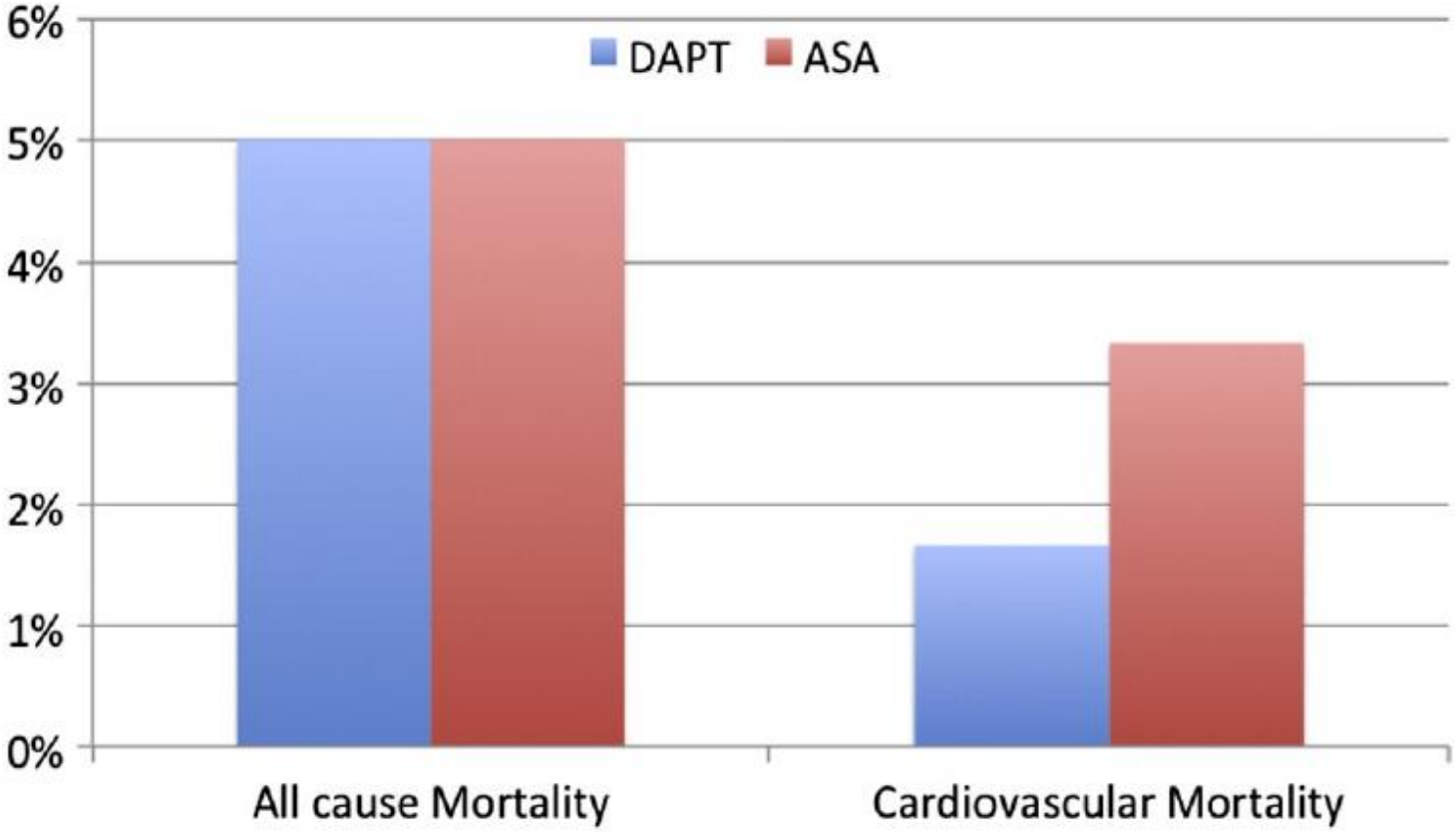


Fig. 2. All cause and cardiovascular mortality at 6 months (p = NS). DAPT = Dual antiplatelet therapy group. ASA = Aspirin group.

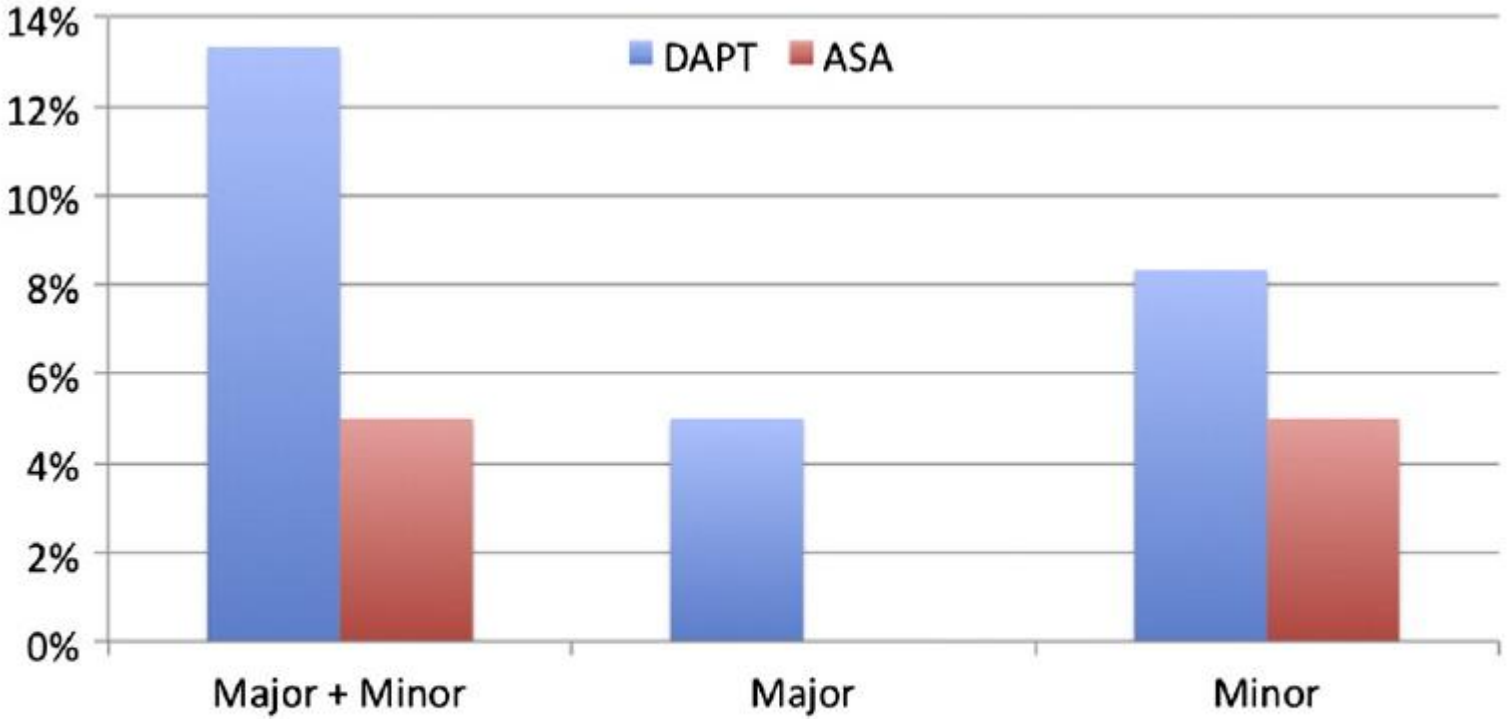
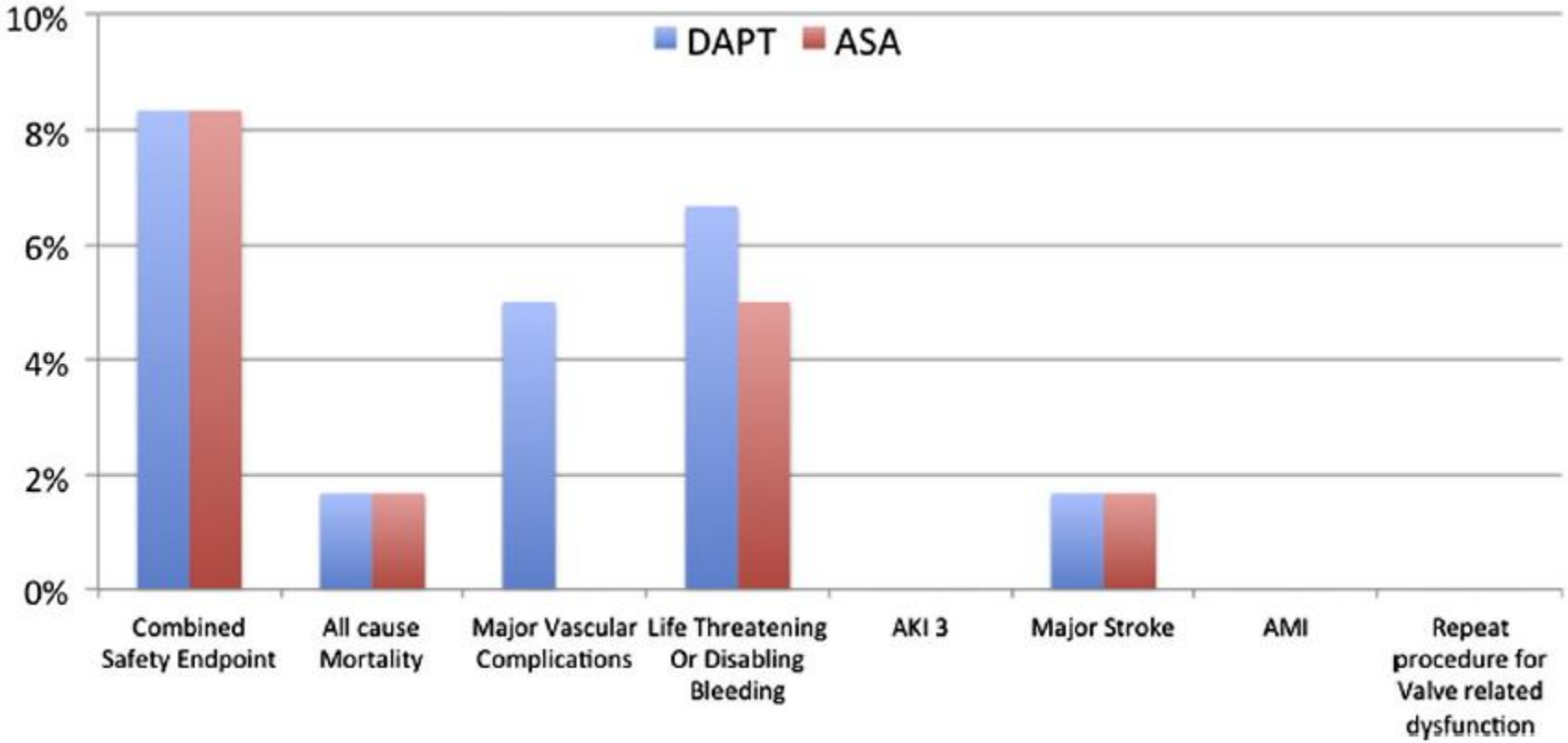


Fig. 3. Vascular complications at 30 days (major + minor $p < 0.05$, major $p =$ Ns, minor $p =$ ns). DAPT = Dual antiplatelet therapy group. ASA = Aspirin group.

Stabile et al.



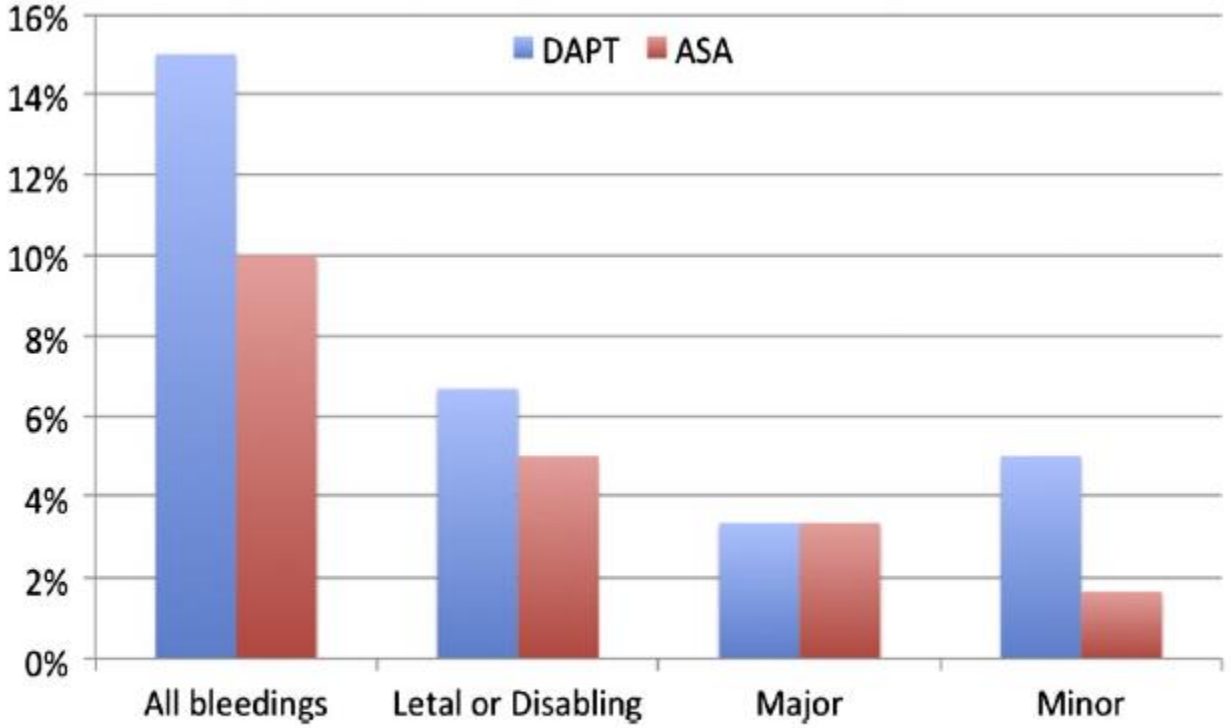


Fig. 4. Incidence of bleedings at 30 days post TAVI (p = ns). DAPT = Dual antiplatelet therapy group. ASA = Aspirin group.

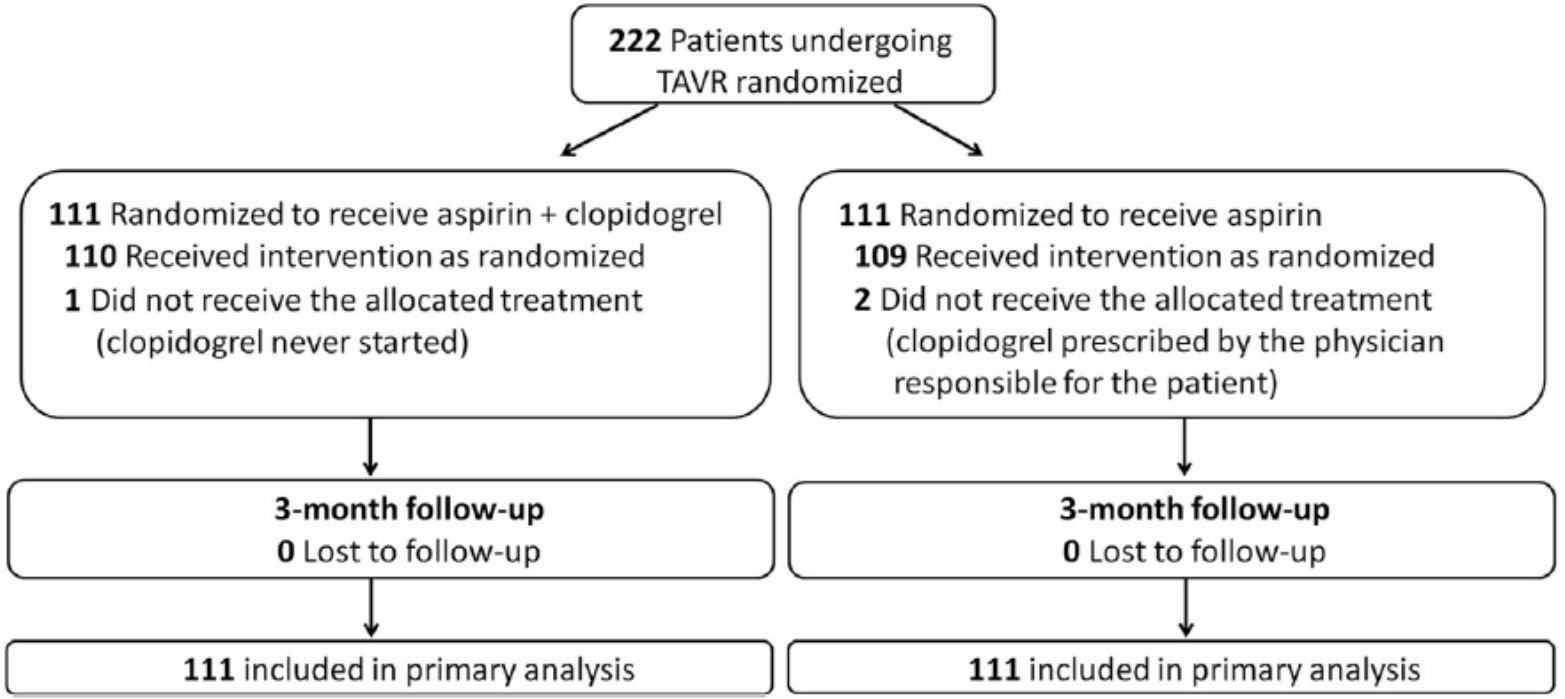
TABLE 1 Baseline Characteristics of the Study Population According to Treatment Allocation

	Treatment		
	Aspirin Plus Clopidogrel (n = 111)	Aspirin (n = 111)	p Value
Baseline characteristics			
Age (yrs)	79 ± 9	79 ± 9	0.716
Male	70 (63.1)	59 (53.2)	0.174
Diabetes	41 (36.9)	36 (32.7)	0.573
Hypertension	86 (77.5)	87 (79.8)	0.743
Current smokers	3 (2.7)	2 (1.8)	0.504
Previous myocardial infarction	26 (23.4)	20 (18.4)	0.409
Previous coronary artery bypass graft	39 (35.1)	42 (38.5)	0.886
Peripheral vascular disease	28 (25.2)	22 (20.0)	0.422
COPD	28 (25.2)	33 (30.0)	0.455
Chronic renal failure (GFR <60 ml/min)	70 (63.1)	70 (63.1)	0.999
Porcelain aorta	18 (16.2)	11 (10.1)	0.232
STS-PROM score (%)	6.2 ± 4.4	6.4 ± 4.6	0.769
Echocardiographic variables			
Mean gradient (mm Hg)	43 ± 16	43 ± 15	0.713
Indexed AVA (cm^2/m^2)	0.42 ± 0.13	0.40 ± 0.11	0.095
Ejection fraction (%)	55 ± 12	54 ± 13	0.675
Aortic regurgitation			
None/trace	51 (48.1)	47 (45.6)	0.409
Mild	30 (28.3)	40 (38.8)	
Moderate/severe	25 (23.6)	16 (15.6)	

Values are mean ± SD or n (%).

AVA = aortic valve area; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

FIGURE 1 **Flowchart of the Study Population**



TAVR = transcatheter aortic valve replacement.

TABLE 2 Procedural Characteristics of the Study Population According to Treatment Allocation

	Treatment		
	Aspirin Plus Clopidogrel (n = 111)	Aspirin (n = 111)	p Value
Procedural characteristics			
Approach			
Femoral	80 (72.1)	73 (65.8)	0.788
Transapical	18 (16.2)	20 (18.0)	
Transaortic	10 (9.0)	14 (12.6)	
Transcarotid	3 (2.7)	4 (3.6)	
Valve type			
SAPIEN XT	104 (93.7)	101 (90.9)	0.615
SAPIEN 3	7 (6.3)	10 (9.0)	
Need for second valve	3 (2.7)	1 (0.9)	0.623
Conversion to open heart surgery	2 (1.8)	3 (2.7)	0.683
Major vascular complications	10 (9.0)	7 (6.4)	0.615
New-onset atrial fibrillation	12 (10.8)	12 (10.8)	0.999
Procedural success	101 (90.9)	94 (86.2)	0.294
Echocardiography at discharge			
Mean gradient (mm Hg)	10.8 ± 5.3	10.3 ± 5.7	0.539
Indexed AVA (cm^2/m^2)	0.95 ± 0.34	0.99 ± 0.34	0.991
Ejection fraction (%)	54 ± 11	54 ± 12	0.999
Aortic regurgitation			
None/trace	59 (61.4)	66 (68.7)	0.571
Mild	28 (29.2)	24 (25.0)	
Moderate/severe	9 (9.4)	6 (6.3)	

Values are n (%) or mean ± SD.
AVA = aortic valve area.

TABLE 3 Study Outcomes According to Treatment Allocation

	Aspirin Plus Clopidogrel (n = 111)	Aspirin (n = 111)	OR (95% CI)	p Value
30-day outcomes				
Combined endpoint*	16 (14.4)	7 (6.3)	2.48 (0.98–6.31)	0.056
Life-threatening/major bleeding	12 (10.8)	4 (3.6)	3.22 (1.01–10.34)	0.038
Major bleeding	5 (4.5)	3 (2.7)	1.68 (0.39–7.21)	0.484
Life-threatening bleeding	7 (6.3)	1 (0.9)	7.34 (0.89–60.71)	0.065
Myocardial infarction	4 (3.6)	1 (0.9)	4.13 (0.45–37.60)	0.175
Stroke/TIA	3 (2.7)	1 (0.9)	3.11 (0.32–30.43)	0.313
Nondisabling stroke	2 (1.8)	0	—	—
Disabling stroke	1 (0.9)	1 (0.9)	0.97 (0.06–15.81)	0.983
TIA	0	0	—	—
Death	6 (5.4)	3 (2.7)	2.04 (0.50–8.37)	0.307
90-day outcomes				
Combined endpoint* (primary endpoint)	17 (15.3)	8 (7.2)	2.31 (0.95–5.62)	0.065
Life-threatening/major bleeding	12 (10.8)	4 (3.6)	3.22 (1.01–10.34)	0.038
Major bleeding	5 (4.5)	3 (2.7)	1.68 (0.39–7.21)	0.484
Life-threatening bleeding	7 (6.3)	1 (0.9)	7.34 (0.89–60.71)	0.065
Myocardial infarction	4 (3.6)	1 (0.9)	4.13 (0.45–37.60)	0.175
Stroke/TIA	3 (2.7)	1 (0.9)	3.11 (0.32–30.43)	0.313
Disabling stroke	1 (0.9)	1 (0.9)	0.97 (0.06–15.81)	0.983
Nondisabling stroke	2 (1.8)	0	—	—
TIA	0	0		
Death	7 (6.3)	4 (3.6)	1.78 (0.51–6.27)	0.370

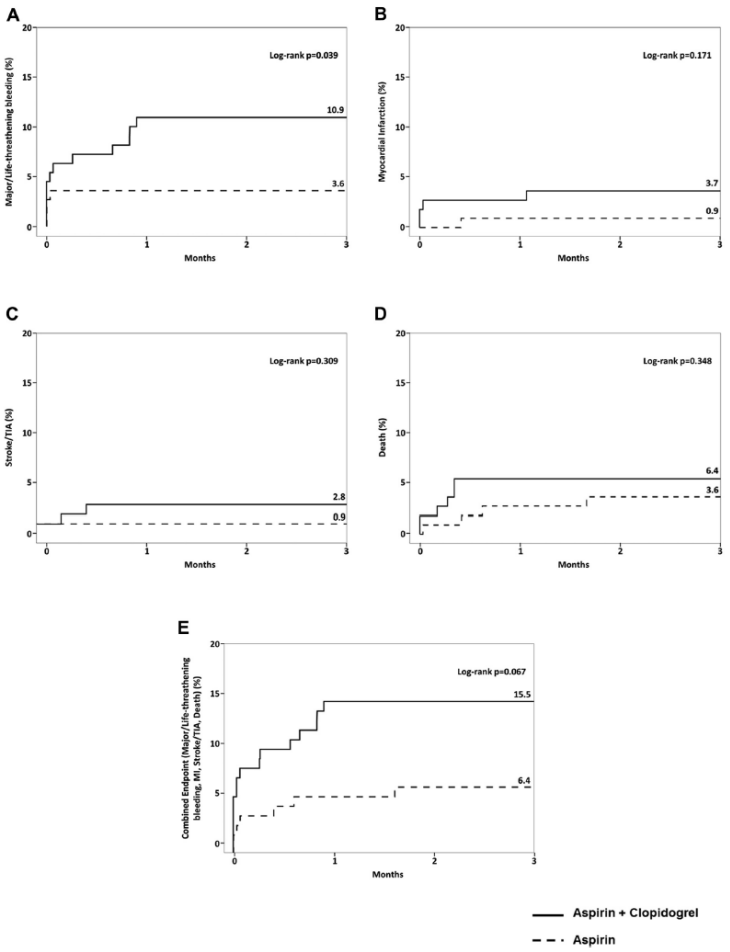
Values are n (%). *Death, myocardial infarction, stroke or TIA, or major or life-threatening bleeding.
CI = confidence interval; OR = odds ratio; TIA = transient ischemic attack.

TABLE 4 Major or Life-Threatening Bleeding Events During the Study Period

Patient #	Treatment Allocation	Severity	Days From Procedure	Cause
1	Aspirin plus clopidogrel	Life-threatening	Periprocedural	Annular rupture
2	Aspirin plus clopidogrel	Life-threatening	27	GI bleeding
3	Aspirin plus clopidogrel	Major	Periprocedural	Femoral hematoma
4	Aspirin plus clopidogrel	Major	8	GI bleeding
5	Aspirin plus clopidogrel	Life-threatening	1	GI bleeding
6	Aspirin plus clopidogrel	Major	20	Access-site bleeding
7	Aspirin plus clopidogrel	Major	2	Femoral hematoma
8	Aspirin plus clopidogrel	Life-threatening	25	GI bleeding
9	Aspirin plus clopidogrel	Life-threatening	Periprocedural	Annular rupture
10	Aspirin plus clopidogrel	Major	Periprocedural	Femoral hematoma
11	Aspirin plus clopidogrel	Life-threatening	Periprocedural	Conversion to open heart surgery
12	Aspirin plus clopidogrel	Life-threatening	25	GI bleeding
13	Aspirin	Major	Periprocedural	Left ventricular perforation
14	Aspirin	Major	Periprocedural	Aortic hematoma
15	Aspirin	Major	1	Access-site bleeding
16	Aspirin	Life-threatening	Periprocedural	Annular rupture

GI = gastrointestinal.

FIGURE 2 Kaplan-Meier Curves Regarding Major Ischemic and Bleeding Events, According to the Allocated Treatment



(A) Major or life-threatening bleeding. **(B)** Stroke or transient ischemic attack (TIA). **(C)** Myocardial infarction (MI). **(D)** Death. **(E)** Combined endpoint (death, stroke or TIA, MI, or major or life-threatening bleeding).

TABLE 5 Main Outcomes at 90 Days (as-Treated Population)

	Aspirin Plus Clopidogrel (n = 110)	Aspirin (n = 109)	OR (95% CI)	p Value
90-day outcomes				
Combined endpoint*	17 (15.5)	8 (7.3)	2.27 (0.93–5.52)	0.060
Life-threatening/major bleeding	12 (10.9)	4 (3.7)	3.16 (1.00–10.14)	0.040
Major bleeding	5 (4.6)	3 (2.8)	1.64 (0.38–7.06)	0.484
Life-threatening bleeding	7 (6.4)	1 (0.9)	7.21 (0.87–59.69)	0.067
Myocardial infarction	4 (3.6)	1 (0.9)	4.12 (0.45–37.58)	0.178
Stroke/TIA	3 (2.7)	1 (0.9)	3.12 (0.32–30.74)	0.317
Disabling stroke	1 (0.9)	1 (0.9)	0.95 (0.06–15.43)	0.970
Nondisabling stroke	2 (1.8)	0	—	—
TIA	0	0	—	—
Death	7 (6.4)	4 (3.7)	1.75 (0.50–6.16)	0.381

Values are n (%). *Death, myocardial infarction, stroke or TIA, or major or life-threatening bleeding.
Abbreviations as in Table 3.

GALILEO Trial

GALILEO Trial

- Sponsored by Bayer and Janssen Pharmaceuticals
- Patients not previously on aspirin or clopidogrel in the DAPT group were loaded (80-100 mg; greater than or equal to 300 mg)
- Patients who developed atrial fibrillation:
  - Rivaroxaban group: 20 mg PO QD (versus renal adjustment of 15 mg PO QD)
  - DAPT group: VKA (INR 2-3) to replace clopidogrel within 3 months or to replace aspirin after those 3 months
- Looked at patients from December 2016 - May 2018

GALILEO Trial

- Discontinuation rate:
  - 307 in the rivaroxaban group vs. 194 in the antiplatelet group
- New onset atrial fibrillation occurred in 11% of population

Table 1. (Continued.)

Characteristic	Rivaroxaban Group (N=826)	Antiplatelet Group (N=818)
Post-TAVR echocardiographic characteristics		
Aortic valve area — cm^2	1.8±0.6	1.9±0.5
Mean aortic valve gradient — mm Hg	10.0±4.7	10.1±4.6
Left ventricular ejection fraction — %	57.4±10.9	58.2±11.2
Paravalvular aortic regurgitation — no. (%)		
Mild	157 (19.0)	168 (20.5)
Moderate or severe	10 (1.2)	10 (1.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NYHA denotes New York Heart Association, and TAVR transcatheter aortic-valve replacement.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), which measure patient risk at the time of cardiovascular surgery, are calculated by means of logistic-regression equations. A score of greater than 10% indicates high risk, 5 to 10% intermediate risk, and less than 5% low risk.
§ Society of Thoracic Surgeons (STS) risk scores, which measure patient risk at the time of cardiovascular surgery, are calculated by means of logistic-regression equations. A score of greater than 8% indicates high risk, 3 to 8% intermediate risk, and less than 3% low risk.
¶ Coronary artery disease was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary-artery bypass grafting.

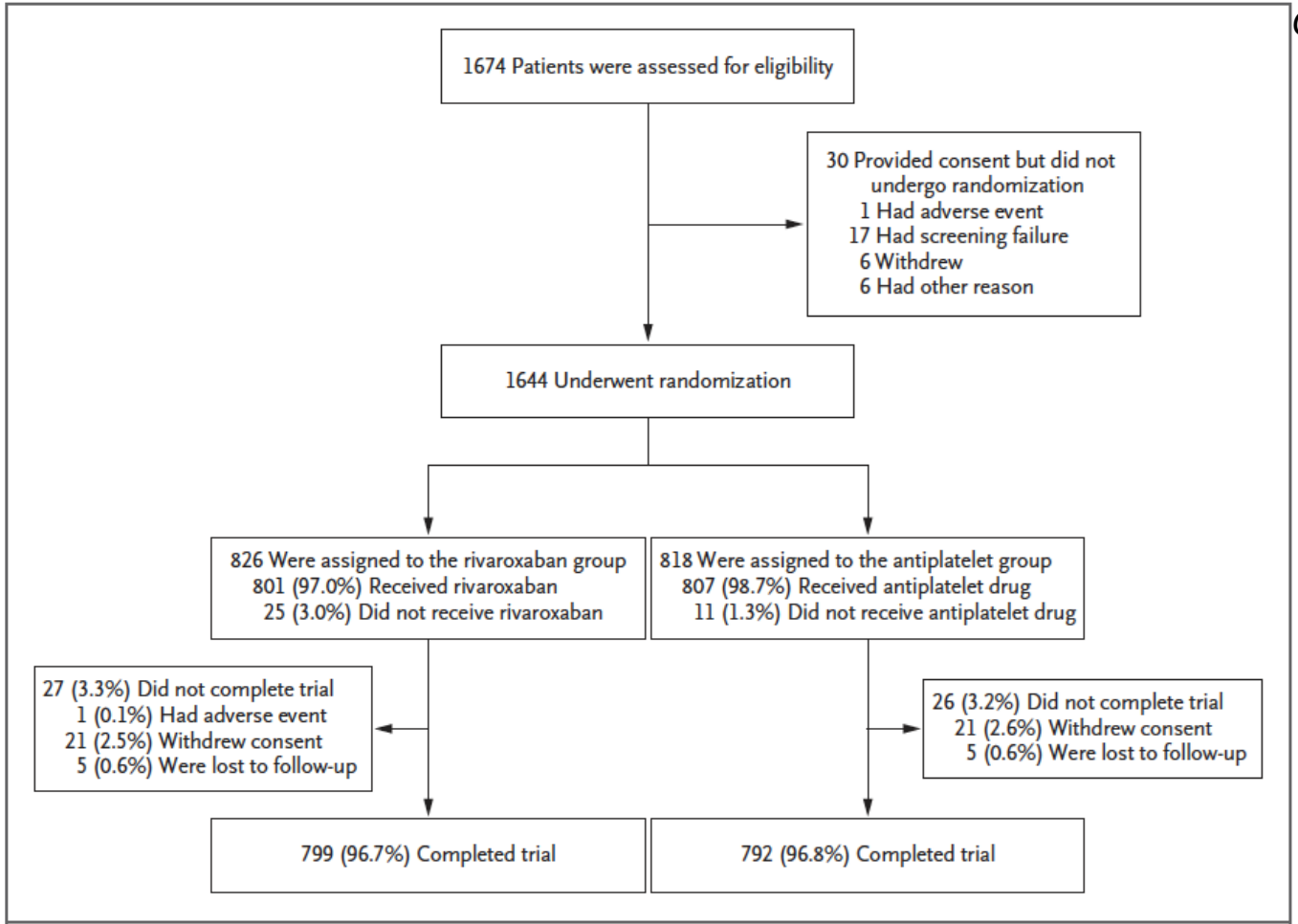
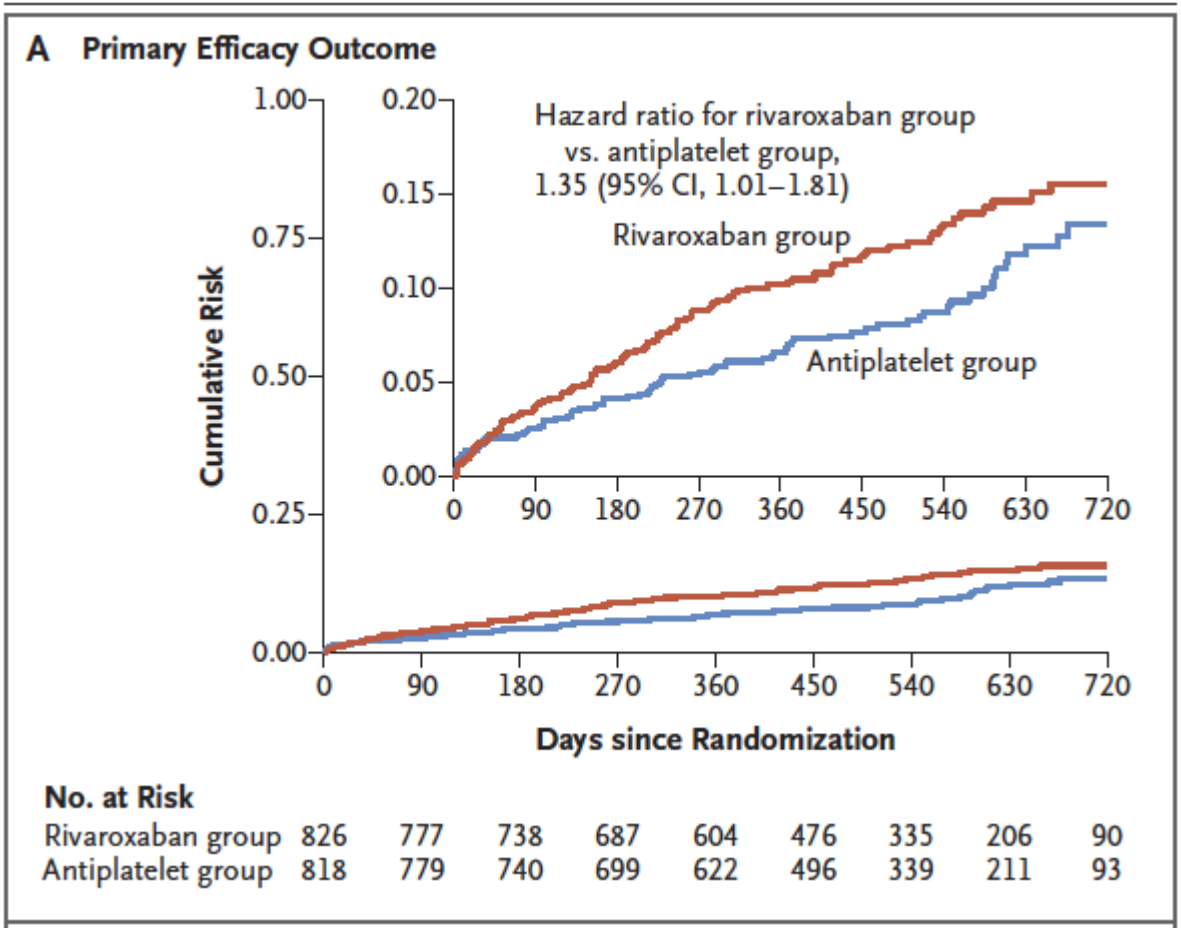
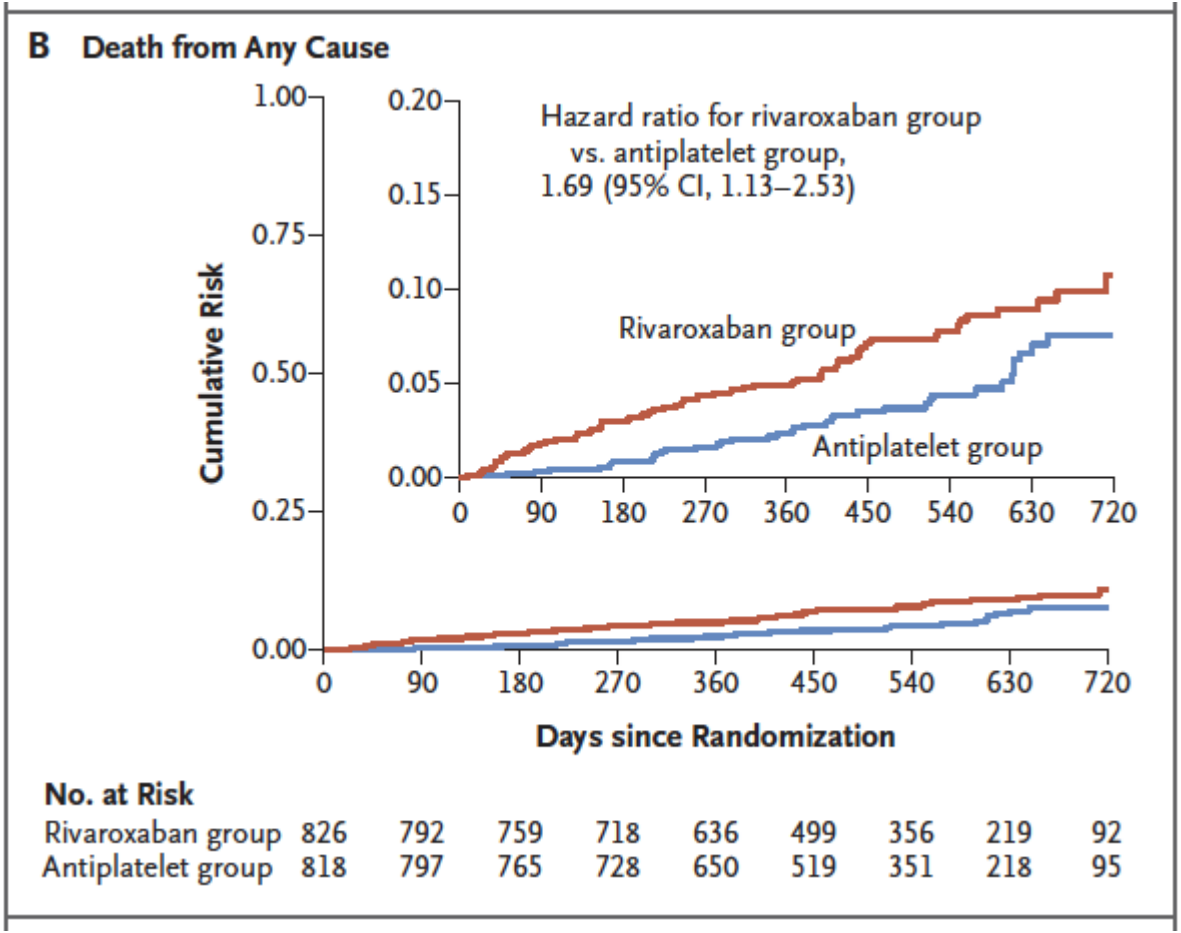
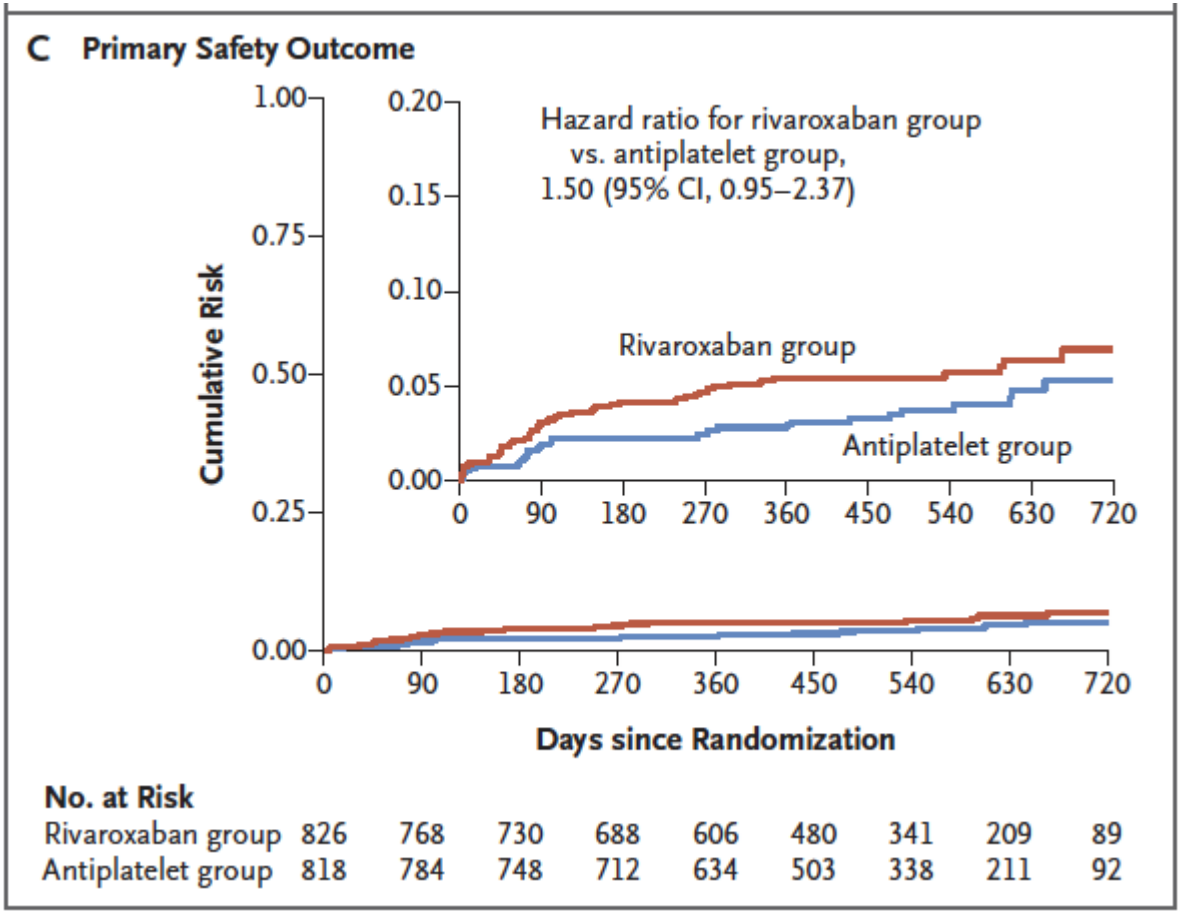


Figure 1. Screening, Randomization, and Follow-up.


A Primary Efficacy Outcome
Cumulative Risk
1.00
0.75
0.50
0.25
0.00
0.20
0.15
0.10
0.05
0.00
Hazard ratio for rivaroxaban group vs. antiplatelet group, 1.35 (95% CI, 1.01–1.81)
Rivaroxaban group
Antiplatelet group
0 90 180 270 360 450 540 630 720
Days since Randomization
No. at Risk
Rivaroxaban group 826 777 738 687 604 476 335 206 90
Antiplatelet group 818 779 740 699 622 496 339 211 93


B Death from Any Cause
Hazard ratio for rivaroxaban group vs. antiplatelet group, 1.69 (95% CI, 1.13–2.53)
Rivaroxaban group
Antiplatelet group
Cumulative Risk
1.00
0.75
0.50
0.25
0.00
0.20
0.15
0.10
0.05
0.00
0 90 180 270 360 450 540 630 720
Days since Randomization
No. at Risk
Rivaroxaban group 826 792 759 718 636 499 356 219 92
Antiplatelet group 818 797 765 728 650 519 351 218 95


C Primary Safety Outcome
Hazard ratio for rivaroxaban group vs. antiplatelet group, 1.50 (95% CI, 0.95–2.37)
Rivaroxaban group
Antiplatelet group
Cumulative Risk
1.00
0.75
0.50
0.25
0.00
0.20
0.15
0.10
0.05
0.00
0 90 180 270 360 450 540 630 720
Days since Randomization
No. at Risk
Rivaroxaban group 826 768 730 688 606 480 341 209 89
Antiplatelet group 818 784 748 712 634 503 338 211 92

GALILEO Trial

Table 2. Efficacy and Safety Outcomes (Intention-to-Treat Analysis).*

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*	
Efficacy outcomes						
Primary efficacy outcome†	105 (12.7)	9.8	78 (9.5)	7.2	2.6 (0.1 to 5.1)	1.35 (1.01 to 1.81)
Death	64 (7.7)	5.8	38 (4.6)	3.4	2.4 (0.6 to 4.1)	1.69 (1.13 to 2.53)
From cardiovascular causes	35 (4.2)	3.2	27 (3.3)	2.4	0.7 (–0.7 to 2.1)	1.30 (0.79 to 2.14)
From noncardiovascular causes	29 (3.5)	2.6	11 (1.3)	1.0	1.6 (0.5 to 2.7)	2.67 (1.33 to 5.35)
Stroke	30 (3.6)	2.8	25 (3.1)	2.3	0.5 (–0.8 to 1.8)	1.20 (0.71 to 2.05)
Ischemic	28 (3.4)	2.6	22 (2.7)	2.0	0.6 (–0.7 to 1.8)	1.28 (0.73 to 2.23)
Hemorrhagic	2 (0.2)	0.2	3 (0.4)	0.3	–0.1 (–0.5 to 0.3)	0.67 (0.11 to 3.98)
Myocardial infarction	23 (2.8)	2.1	17 (2.1)	1.5	0.6 (–0.6 to 1.7)	1.37 (0.73 to 2.56)
Symptomatic valve thrombosis	3 (0.4)	0.3	7 (0.9)	0.6	–0.4 (–0.9 to 0.2)	0.43 (0.11 to 1.66)
Pulmonary embolism	3 (0.4)	0.3	2 (0.2)	0.2	0.1 (–0.3 to 0.5)	1.49 (0.25 to 8.93)
Deep-vein thrombosis	1 (0.1)	0.1	4 (0.5)	0.4	–0.3 (–0.7 to 0.1)	0.25 (0.03 to 2.23)
Systemic embolism	1 (0.1)	0.1	1 (0.1)	0.1	0.0 (–0.3 to 0.3)	0.98 (0.06 to 15.69)
Key secondary efficacy outcome‡	83 (10.0)	7.8	68 (8.3)	6.3	1.5 (–0.8 to 3.7)	1.22 (0.89 to 1.69)
Net clinical benefit§	137 (16.6)	13.2	100 (12.2)	9.4	3.8 (0.9 to 6.7)	1.39 (1.08 to 1.80)
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)

* The 95% confidence intervals (CIs) were not adjusted for multiple comparisons. The proportionality assumption for the primary efficacy and safety outcomes was not violated. BARC denotes Bleeding Academic Research Consortium, ISTH International Society on Thrombosis and Hemostasis, TIMI Thrombolysis in Myocardial Infarction, and VARC Valve Academic Research Consortium.

† The primary efficacy outcome was defined as the composite of death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism.

‡ The key secondary efficacy outcome was defined as the composite of death from cardiovascular causes, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism.

§ Net clinical benefit was defined as the composite of the primary efficacy and primary safety outcomes.

¶ The primary safety outcome was defined as the composite of VARC life-threatening, disabling, or major bleeding.

POPULAR TAVI Cohort A

POPULAR TAVI Cohort A

- Conducted in Europe (17 European sites)
- ASA Group
  - If patients were not on ASA beforehand, got 300 mg load 1 day before TAVI.
  - Had washout period of 5 days if on other antiplatelet agents
- DAPT group
  - If not on ASA before, got 300 mg load within 1 day
  - 300 mg clopidogrel load day before or day of TAVI
- Switching protocol
  - If patient had stroke during trial, those in ASA group -> DAPT group
- Anticoagulation
  - Anticoag with heparin during TAVR was allowed, standardized ACT
  - If patient developed Afib afterwards, can use VKA or DOAC and recommended to replace ASA

POPULAR TAVI Cohort A

- December 2013 - March 2019
- 690 patients -> 665 included (most excluded due to TAVI not performed, was aborted or converted to an open procedure)
- mITT
  - 16 patients (4.8%) assigned to ASA group also received clopidogrel due to medical reasons at direction of provider
  - 10 patients (3.0%) on clopidogrel prior to enrollment were assigned to DAPT and received both ASA and clopidogrel
- No patients were lost to follow up - data 100% for primary and secondary endpoints

POPular TAVI Cohort A

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Aspirin (N=331)	Aspirin plus Clopidogrel (N=334)
Age — yr	80.4±6.2	79.5±6.4
Female sex — no. (%)	164 (49.5)	160 (47.9)
NYHA class III or IV — no. (%)	212 (64.0)	220 (65.9)
Body-mass index†	27.0±4.7	27.1±4.6
Society of Thoracic Surgeons risk score — %‡		
Median	2.6	2.4
IQR	1.6–3.7	1.7–3.7
Indication for TAVI — no. (%)		
Normal flow, high-gradient aortic stenosis	253 (76.4)	251 (75.1)
Low-flow, low-gradient aortic stenosis	64 (19.3)	58 (17.4)
Pure aortic regurgitation	8 (2.4)	7 (2.1)
Combination of above	6 (1.8)	18 (5.4)
Hypertension — no. (%)	243 (73.4)	255 (76.3)
Diabetes mellitus — no. (%)	78 (23.6)	85 (25.4)
Coronary artery disease — no. (%)	134 (40.5)	138 (41.3)
Previous myocardial infarction — no. (%)	28 (8.5)	31 (9.3)
Peripheral artery disease — no. (%)	47 (14.2)	68 (20.4)
Previous stroke — no. (%)	18 (5.4)	12 (3.6)
Estimated glomerular filtration rate — ml/min/1.73 m^2§	57.5±18.1	57.9±19.7
Chronic obstructive pulmonary disease — no. (%)	52 (15.7)	74 (22.2)
Previous coronary-artery bypass grafting — no. (%)	61 (18.4)	65 (19.5)
Previous aortic-valve surgery — no. (%)	23 (6.9)	20 (6.0)
Left ventricular ejection fraction — no. (%)		
>50%	244 (73.7)	245 (73.4)
31–50%	74 (22.4)	65 (19.5)
≤30%	13 (3.9)	24 (7.2)

* Plus–minus values are means ±SD. There were no significant differences between the two groups. Percentages may not total 100 because of rounding. IQR denotes interquartile range, NYHA New York Heart Association, and TAVI transcatheter aortic-valve implantation.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Society of Thoracic Surgeons risk scores range from 0 to 100%, with higher scores indicating a higher risk of death after cardiac surgery.
§ In the calculation of the estimated glomerular filtration rate, the creatinine clearance was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

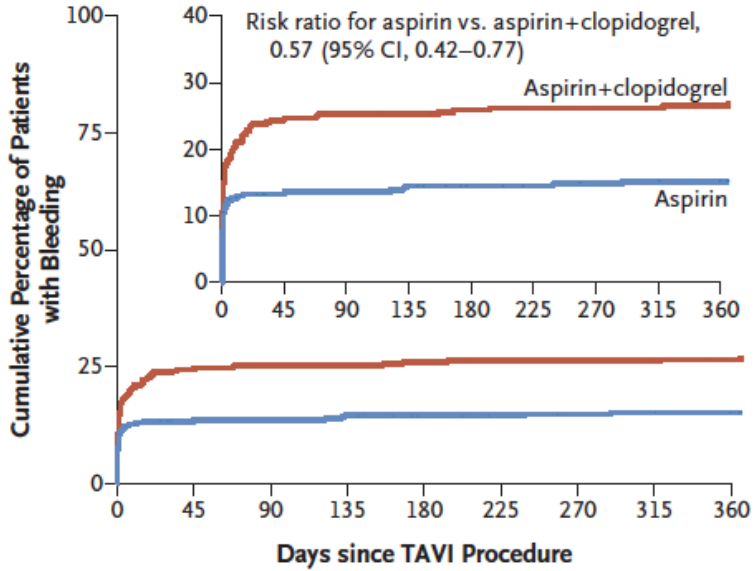
Table 2. Primary and Secondary Outcomes.*

Outcome	Aspirin (N=331)	Aspirin plus Clopidogrel (N=334)	Risk Ratio (95% CI)	Absolute Difference (95% CI)	P Value
	number (percent)			*percentage points*	
Primary outcomes					
All bleeding	50 (15.1)	89 (26.6)	0.57 (0.42 to 0.77)		0.001
Non–procedure-related bleeding	50 (15.1)	83 (24.9)	0.61 (0.44 to 0.83)		0.005
Secondary outcomes					
First composite secondary outcome†					
Noninferiority analysis	76 (23.0)	104 (31.1)		−8.2 (−14.9 to −1.5)	<0.001
Superiority analysis	76 (23.0)	104 (31.1)	0.74 (0.57 to 0.95)		0.04
Second composite secondary outcome‡					
Noninferiority analysis	32 (9.7)	33 (9.9)		−0.2 (−4.7 to 4.3)	0.004
Superiority analysis	32 (9.7)	33 (9.9)	0.98 (0.62 to 1.55)		0.93
Death					
From any cause	21 (6.3)	19 (5.7)	1.12 (0.61 to 2.04)		
From cardiovascular cause	14 (4.2)	13 (3.9)	1.09 (0.52 to 2.28)		
Stroke	17 (5.1)	19 (5.7)	0.90 (0.48 to 1.71)		
Ischemic	17 (5.1)	18 (5.4)	0.95 (0.50 to 1.82)		
Hemorrhagic	0	1 (0.3)			
Nondisabling stroke	11 (3.3)	14 (4.2)	0.79 (0.37 to 1.72)		
Disabling stroke	6 (1.8)	5 (1.5)	1.21 (0.37 to 3.93)		
Myocardial infarction	4 (1.2)	6 (1.8)	0.67 (0.19 to 2.36)		
VARC bleeding					
Life-threatening or disabling bleeding	9 (2.7)	11 (3.3)	0.83 (0.35 to 1.97)		
Major bleeding	8 (2.4)	25 (7.5)	0.32 (0.15 to 0.71)		
Major, life-threatening, or disabling bleeding	17 (5.1)	36 (10.8)	0.48 (0.27 to 0.83)		
Minor bleeding	33 (10.0)	53 (15.9)	0.63 (0.42 to 0.94)		

* All outcomes were confirmed by an independent adjudication committee. The P values for the primary and secondary outcomes were adjusted for multiple comparisons with the use of the Hochberg method. The individual components of the secondary outcomes were analyzed post hoc, the 95% confidence intervals were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses. VARC denotes Valve Academic Research Consortium.

† A first composite secondary outcome was defined as a nonhierarchical composite of death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or myocardial infarction.

‡ A second composite secondary outcome was defined as the nonhierarchical composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction.

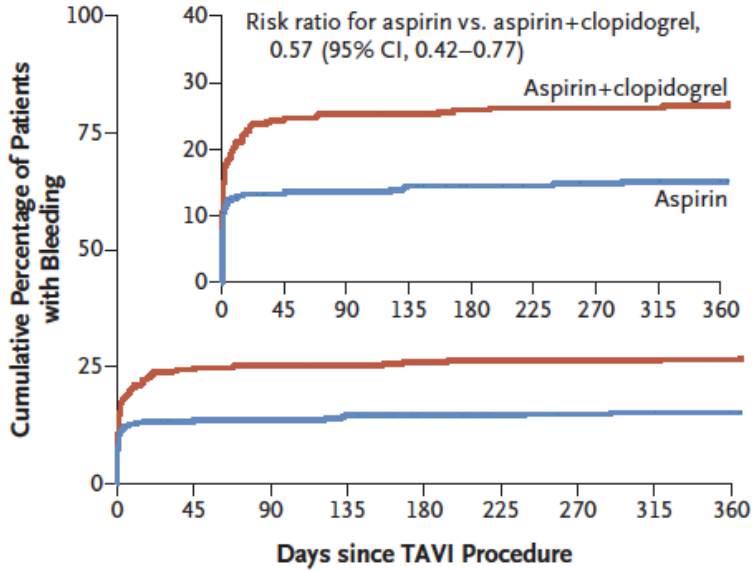


No. at Risk

Aspirin+clopidogrel	334	248	244	243	239	238	237	237	234
Aspirin	331	280	279	276	271	269	267	266	264

Figure 2. Primary Outcome of All Bleeding.

Shown are time-to-event Kaplan–Meier curves of one of the two primary outcomes (all bleeding, including minor, major, and life-threatening or disabling bleeding). The inset shows the same data on an enlarged y axis. Given the nonproportionality of the hazards during the follow-up period, a risk-ratio analysis with 95% confidence intervals was performed.



No. at Risk

Aspirin+clopidogrel	334	248	244	243	239	238	237	237	234
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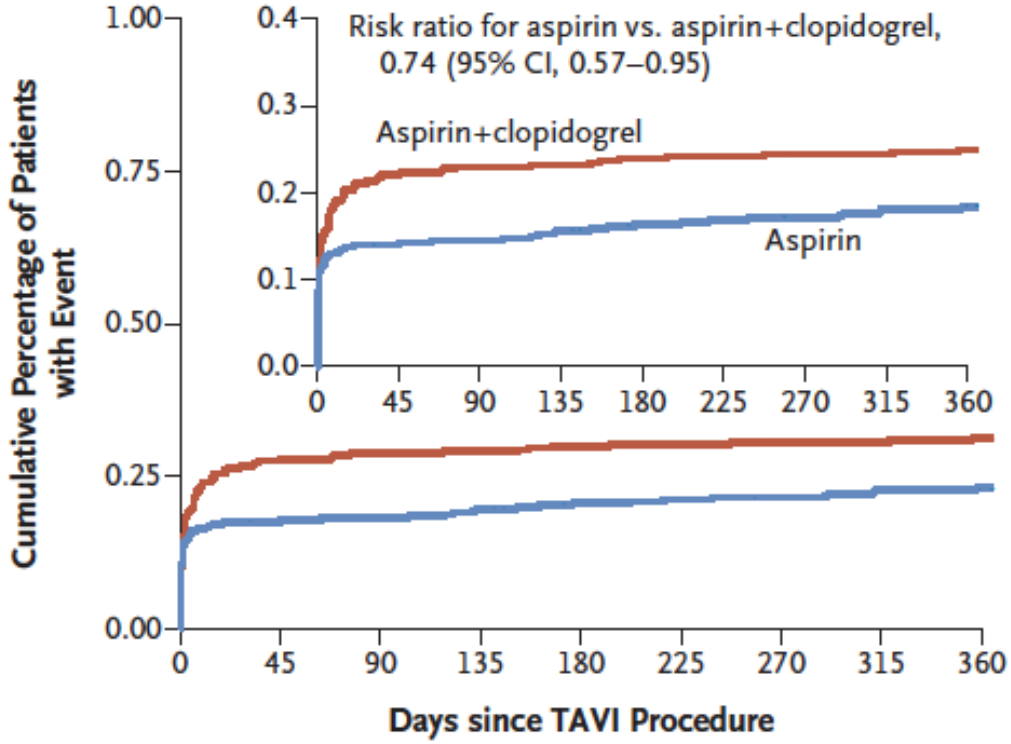
Figure 2. Primary Outcome of All Bleeding.

Shown are time-to-event Kaplan–Meier curves of one of the two primary outcomes (all bleeding, including minor, major, and life-threatening or disabling bleeding). The inset shows the same data on an enlarged y axis. Given the nonproportionality of the hazards during the follow-up period, a risk-ratio analysis with 95% confidence intervals was performed.

POPular TAVI Cohort A

A Death from Cardiovascular Causes, Non–Procedure-Related Bleeding, Stroke from Any Cause, or MI

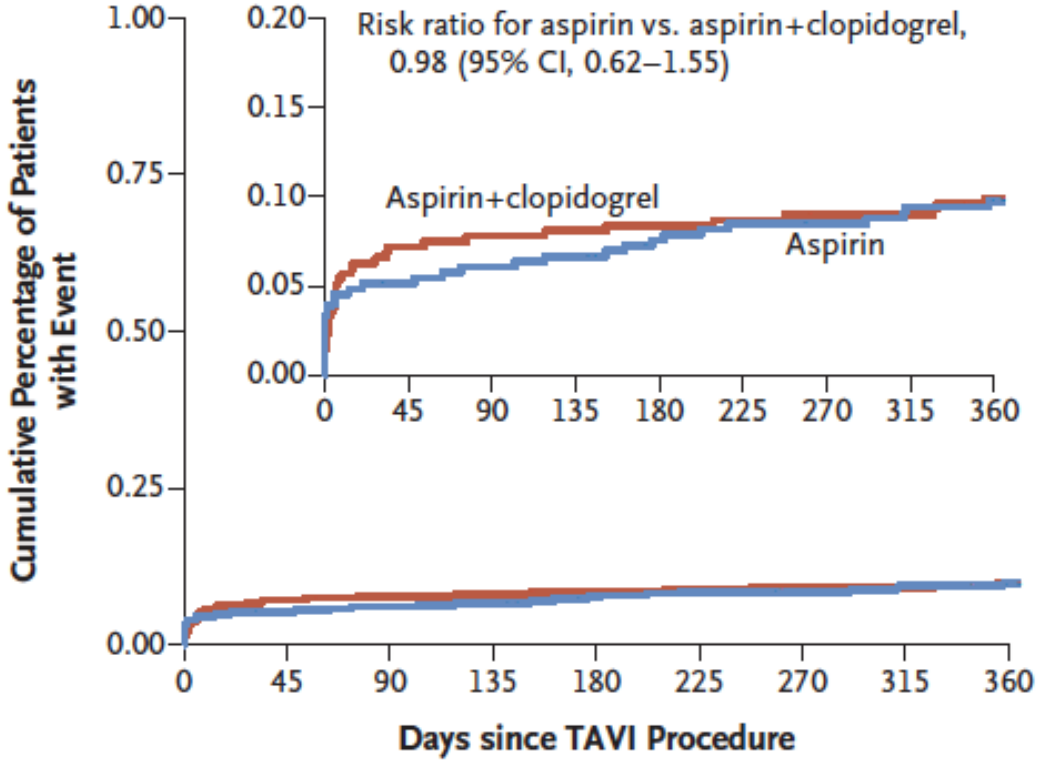


No. at Risk

Aspirin+clopidogrel	334	242	238	237	232	231	229	229	226
Aspirin	331	272	270	265	259	257	255	251	249

POPular TAVI Cohort A

B Death from Cardiovascular Causes, Ischemic Stroke, or MI



No. at Risk

Aspirin+clopidogrel	334	310	307	306	303	302	300	300	296
Aspirin	331	313	310	308	302	299	298	295	293

POPULAR TAVI Cohort B

POPULAR TAVI Cohort B

- Conducted in Europe (17 European sites)
- Anticoagulation:
  - Decision to interrupt or continue anticoagulation periprocedurally at physician discretion
  - For procedure itself, UFH was recommended with ACT goal >250 seconds in those who interrupted oral anticoagulation or >200 in those who did not interrupt anticoagulation
- December 2013-August 2018
- n= 326 -> 313 (mostly due to TAVR not performed, did not meet inclusion, TAVR aborted or converted to open chest)
- Data on primary and secondary outcomes: 100% complete
- Adherence to clopidogrel: 95.5%
- Discontinuation of anticoagulation:
  - Anticoagulation group alone: n=2
  - Anticoagulation + clopidogrel: n=0

POPular TAVI Cohort B

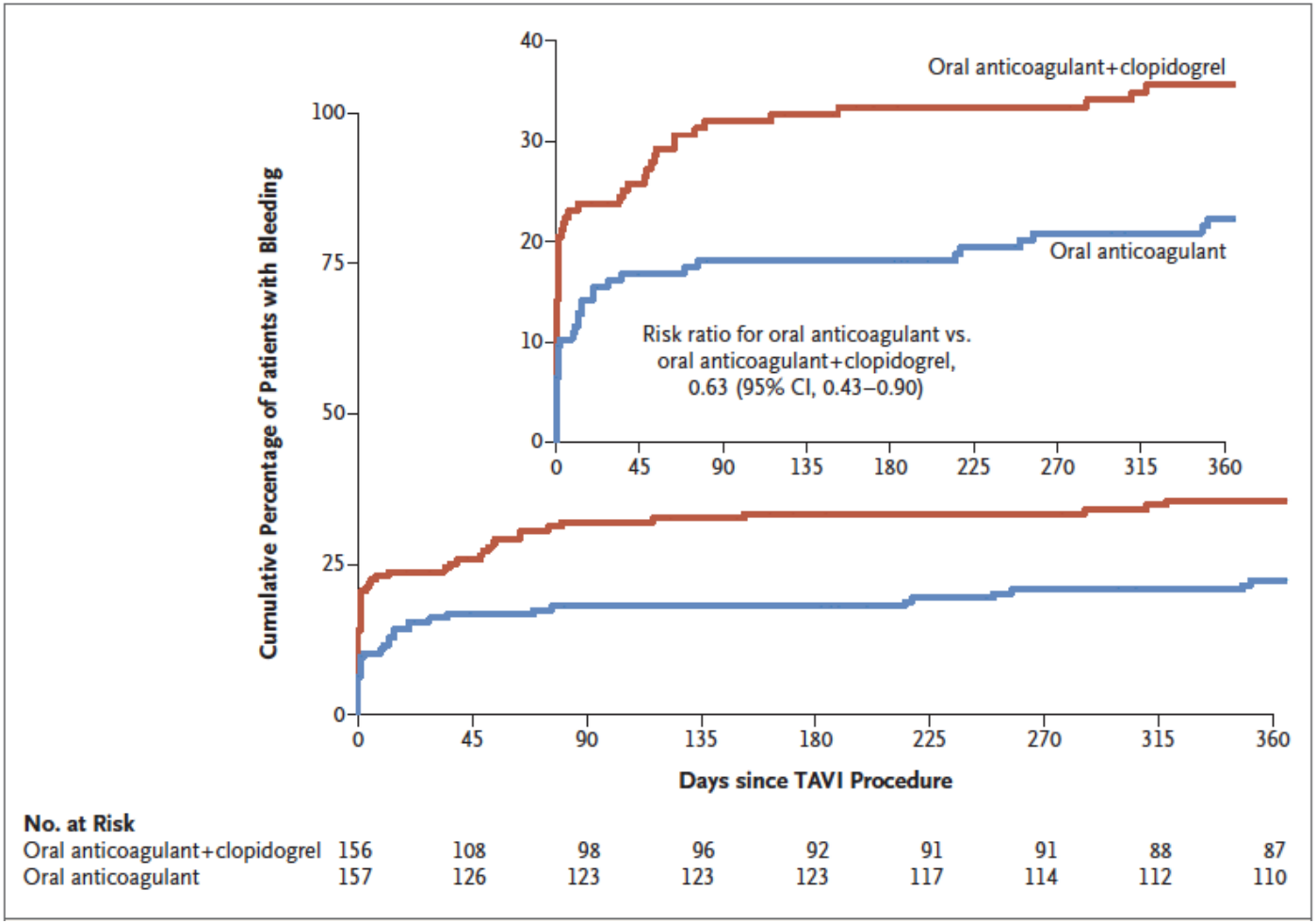
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Oral Anticoagulation (N=157)	Oral Anticoagulation plus Clopidogrel (N=156)
Age — yr	80.9±6.2	81.0±5.5
Female sex — no. (%)	69 (43.9)	73 (46.8)
NYHA class III or IV — no. (%)	119 (75.8)	110 (70.5)
Body-mass index†	27.4±5.3	27.5±5.1
Logistic EuroSCORE — %‡		
Median	15.6	14.1
IQR	9.2–23.8	10.6–22.8
Society of Thoracic Surgeons risk score — %§		
Median	3.2	3.1
IQR	2.2–4.8	2.3–4.5
Indication for TAVI — no. (%)		
Normal-flow, high-gradient aortic stenosis	98 (62.4)	98 (62.8)
Low-flow, low-gradient aortic stenosis	51 (32.5)	50 (32.1)
Pure aortic regurgitation	6 (3.8)	4 (2.6)
Combination of above	2 (1.3)	4 (2.6)
Atrial fibrillation — no. (%)¶	150 (95.5)	147 (94.2)
Hypertension — no. (%)	115 (73.2)	105 (67.3)
Diabetes mellitus — no. (%)	43 (27.4)	46 (29.5)
Coronary artery disease — no. (%)	65 (41.4)	69 (44.2)
Previous myocardial infarction — no. (%)	14 (8.9)	20 (12.8)
Peripheral artery disease — no. (%)	30 (19.1)	28 (17.9)
Previous stroke — no. (%)	15 (9.6)	15 (9.6)
Estimated glomerular filtration rate — ml/min/1.73 m^2‖	53.4±17.7	55.6±17.1
Chronic obstructive pulmonary disease — no. (%)	33 (21.0)	30 (19.2)
Previous coronary-artery bypass grafting — no. (%)	30 (19.1)	30 (19.2)
Previous aortic-valve surgery — no. (%)	7 (4.5)	9 (5.8)
Left ventricular ejection fraction — no. (%)		
>50%	91 (58.0)	97 (62.2)
31–50%	54 (34.4)	46 (29.5)
≤30%	12 (7.6)	13 (8.3)

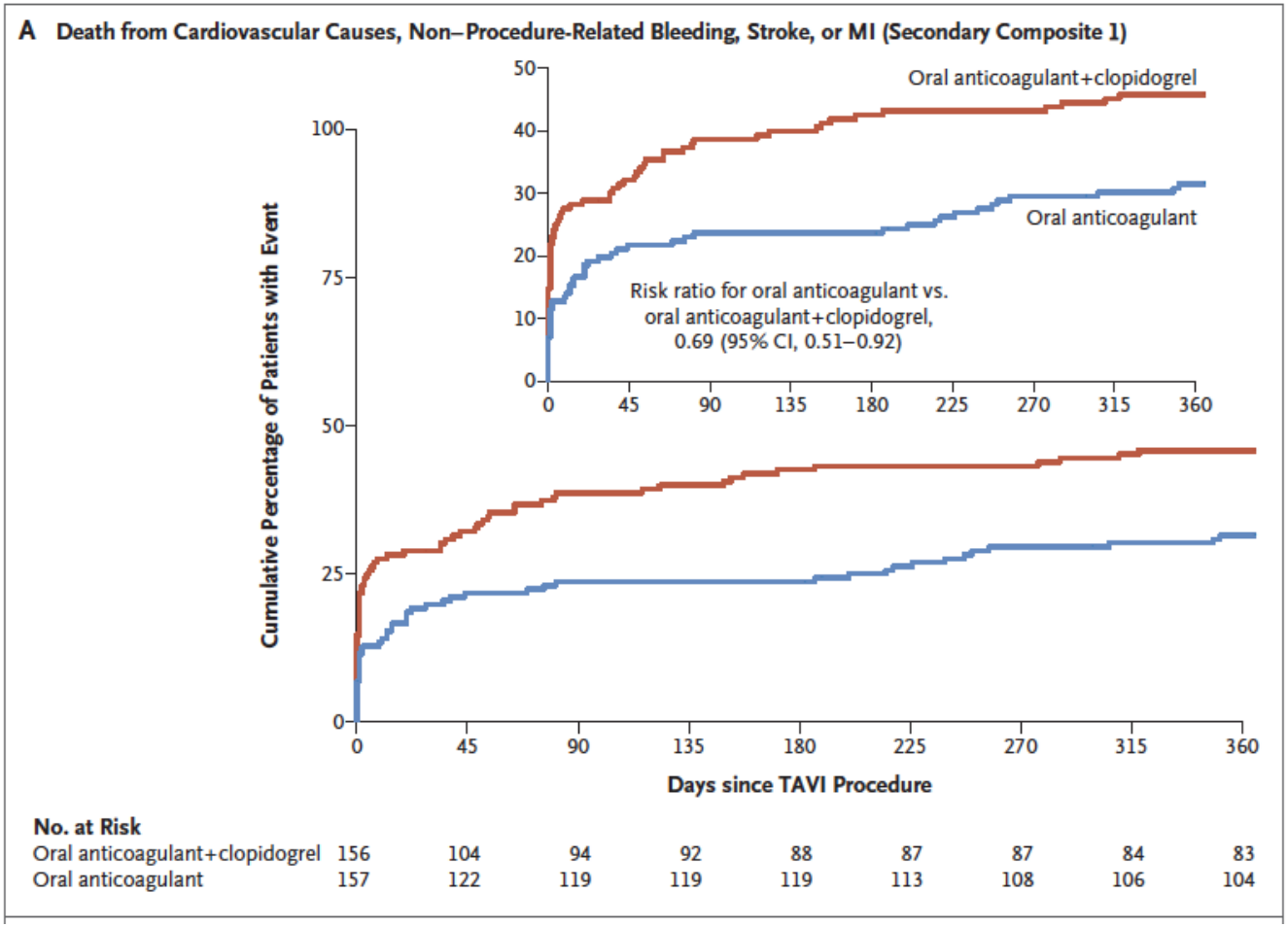
POPular TAVI Cohort B

Table 2. Primary and Secondary Outcomes.*

Outcome	Oral Anticoagulation (N=157)	Oral Anticoagulation plus Clopidogrel (N=156)	Risk Ratio (95% CI)	Absolute Difference (95% CI)	P Value
	number (percent)			*percentage points*	
Primary outcomes					
All bleeding	34 (21.7)	54 (34.6)	0.63 (0.43 to 0.90)		0.01
Non–procedure-related bleeding	34 (21.7)	53 (34.0)	0.64 (0.44 to 0.92)		0.02
Secondary outcomes					
Secondary composite 1†					
Noninferiority analysis	49 (31.2)	71 (45.5)		−14.3 (−25.0 to −3.6)	
Superiority analysis	49 (31.2)	71 (45.5)	0.69 (0.51 to 0.92)		
Secondary composite 2‡					
Noninferiority analysis	21 (13.4)	27 (17.3)		−3.9 (−11.9 to 4.0)	
Superiority analysis	21 (13.4)	27 (17.3)	0.77 (0.46 to 1.31)		
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	9 (5.7)	9 (5.8)	0.99 (0.41 to 2.44)		
Ischemic	8 (5.1)	9 (5.8)	0.88 (0.35 to 2.23)		
Hemorrhagic	1 (0.6)	0			
Myocardial infarction	1 (0.6)	1 (0.6)	0.99 (0.06 to 15.75)		
VARC-2 bleeding					
Life-threatening or disabling bleeding	6 (3.8)	13 (8.3)	0.46 (0.18 to 1.18)		
Major bleeding	8 (5.1)	13 (8.3)	0.61 (0.26 to 1.43)		
Major, life-threatening, or disabling bleeding	14 (8.9)	26 (16.7)	0.54 (0.29 to 0.99)		
Minor bleeding	20 (12.7)	28 (17.9)	0.71 (0.42 to 1.21)		

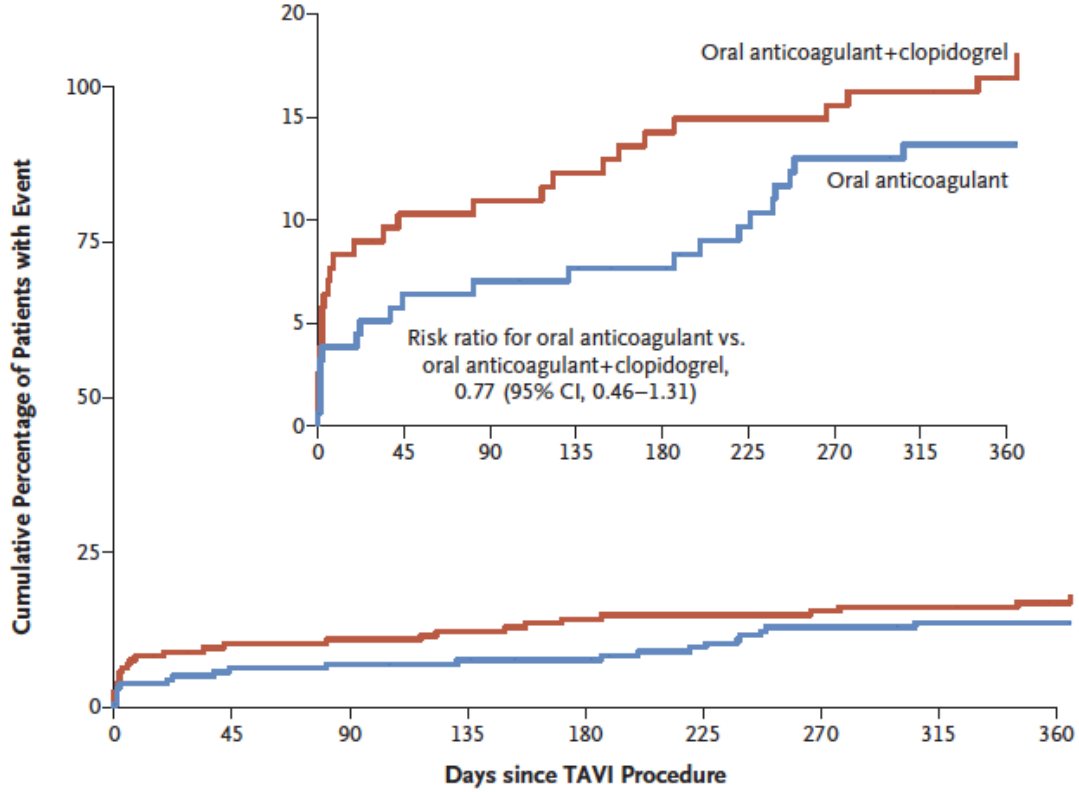

Oral anticoagulant+clopidogrel
Oral anticoagulant
Risk ratio for oral anticoagulant vs. oral anticoagulant+clopidogrel, 0.63 (95% CI, 0.43–0.90)
Cumulative Percentage of Patients with Bleeding
Days since TAVI Procedure
No. at Risk
Oral anticoagulant+clopidogrel 156 108 98 96 92 91 91 88 87
Oral anticoagulant 157 126 123 123 123 117 114 112 110

POPular TAVI Cohort B



POPular TAVI Cohort B

B **Death from Cardiovascular Causes, Ischemic Stroke, or MI (Secondary Composite 2)**



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