Interventional pharmacology

The year in-review

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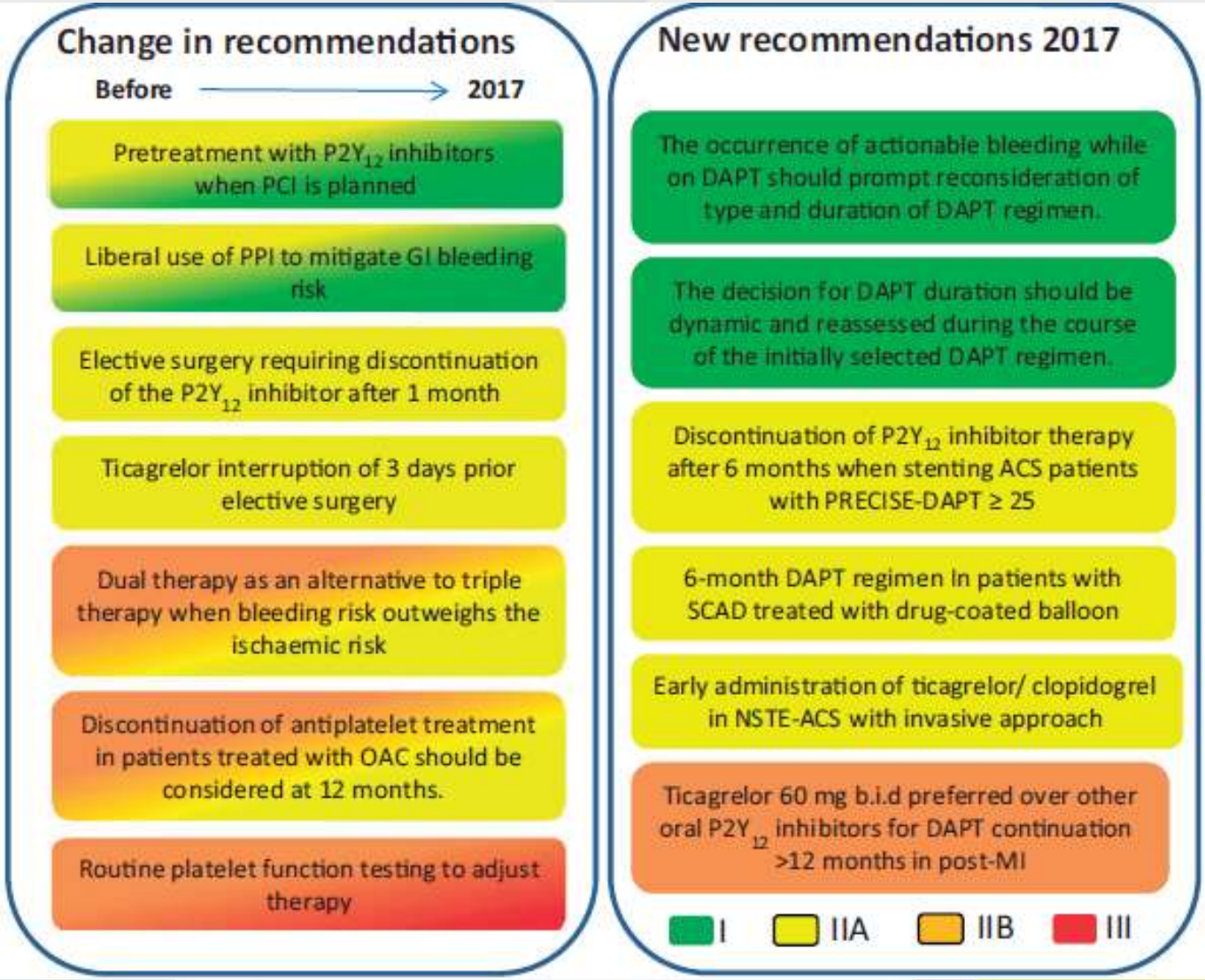
Conflict of interest

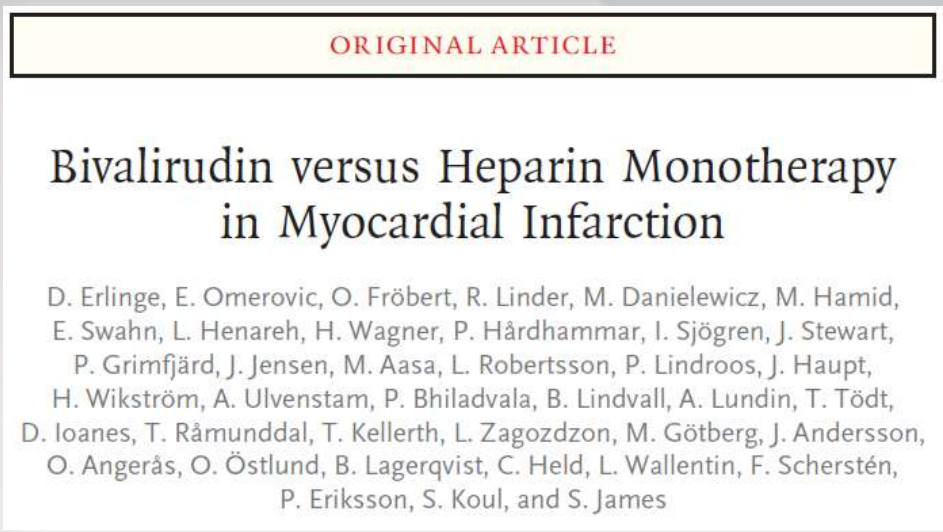
- **Consulting Fees/Honoraria**: Abbot Vascular, American College of Cardiology, AstraZeneca, Medscape, Shanghai BraccoSine, Spectranetics, Abiomed, The Medicines Company (spouse)
- **DSMB membership** paid to the institution: Watermark Research Partners
- **Executive Committee**: Janssen Pharmaceuticals
- **Grant/Reseach Support (Institutional):** AstraZeneca, Bayer, Beth Israel Deaconess, Bristol Myers-Squibb, CSL, Behring, Diachi Sankyo, Medtronick, Novartis Pharmaceuticals, OrbusNeich
- **Speaker fees:** Lifescience Conference

Percutaneous coronary intervention

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS



Valgimigli et al, Eur Heart J. 2018 Jan 14;39(3):213-260.


ORIGINAL ARTICLE

Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

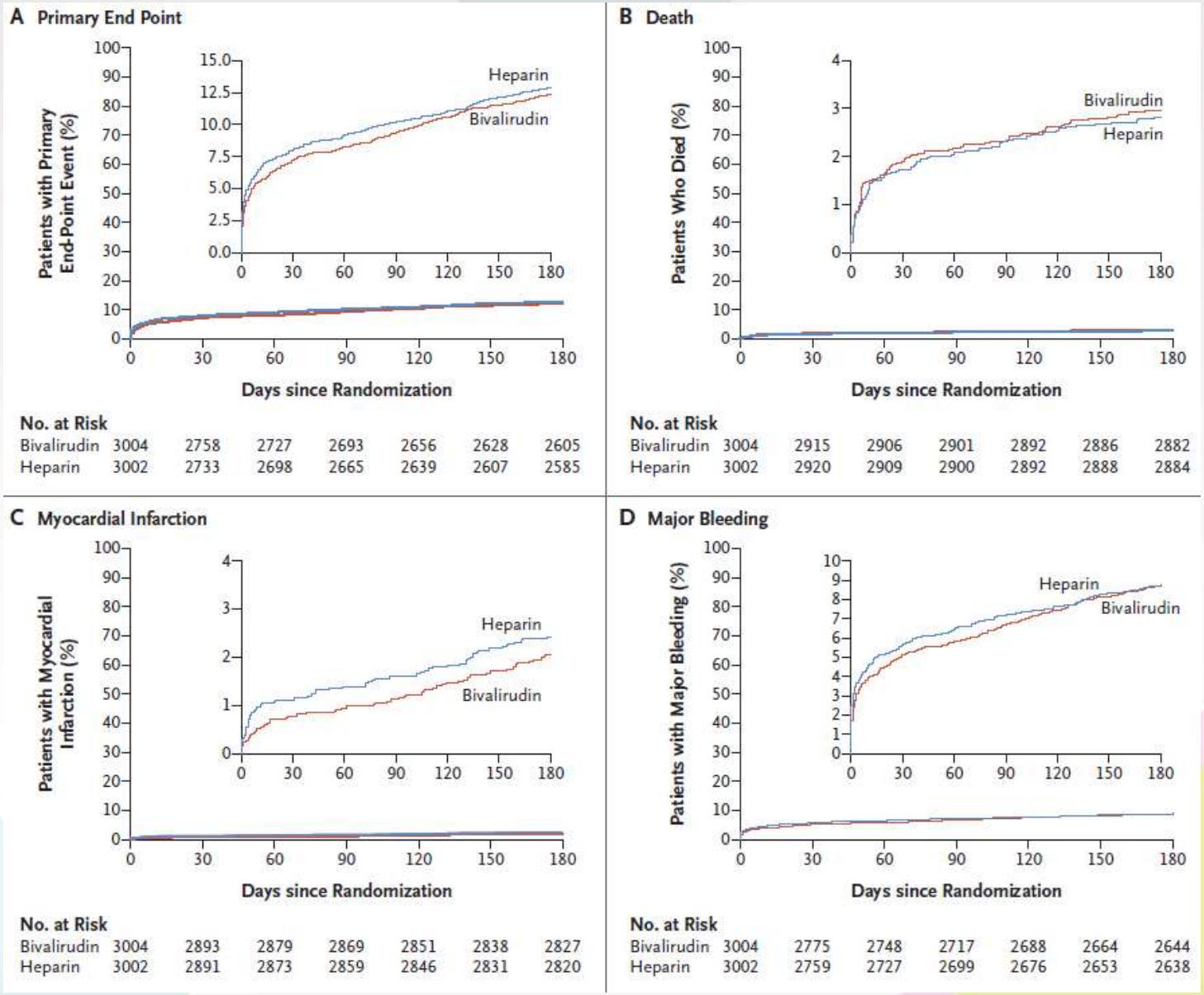
D. Erlinge, E. Omerovic, O. Fröbert, R. Linder, M. Danielewicz, M. Hamid, E. Swahn, L. Henareh, H. Wagner, P. Hårdhammar, I. Sjögren, J. Stewart, P. Grimfjärd, J. Jensen, M. Aasa, L. Robertsson, P. Lindroos, J. Haupt, H. Wikström, A. Ulvenstam, P. Bhiladvala, B. Lindvall, A. Lundin, T. Tödt, D. Ioanes, T. Råmunddal, T. Kellerth, L. Zagozdzon, M. Götberg, J. Andersson, O. Angerås, O. Östlund, B. Lagerqvist, C. Held, L. Wallentin, F. Scherstén, P. Eriksson, S. Koul, and S. James

- **Randomized**
- **Multicenter**
- **Registry-based**
  - **SWEDEHEART registry**

- **Target population: patients undergoing PCI for STEMI/NSTEMI**
  - **Co-treatment with potent P2Y12 inhibitor (ticagrelor/prasugrel/cangrelor)**
  - **Without planned used of GPIIb/IIIa inhibitor**
- **Randomized to**
  - **Bivalirudin (0.75 mg bolus followed by 1.75mg/kg/hour)**
  - **Heparin only (70-100U/kg)**
- **Primary endpoint: death, MI or major bleeding (BARC≥2) within 180 days**
- **6006 patients with STEMI/NSTEMI**
  - **97.5% statistical power to detect a hazard ratio of 0.75 in favor of bivalirudin**

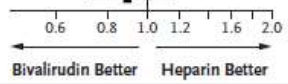
Erlinge et al, N Engl J Med. 2017 21;337(12):1132-1142.

No significant difference between bivalirudin and heparin



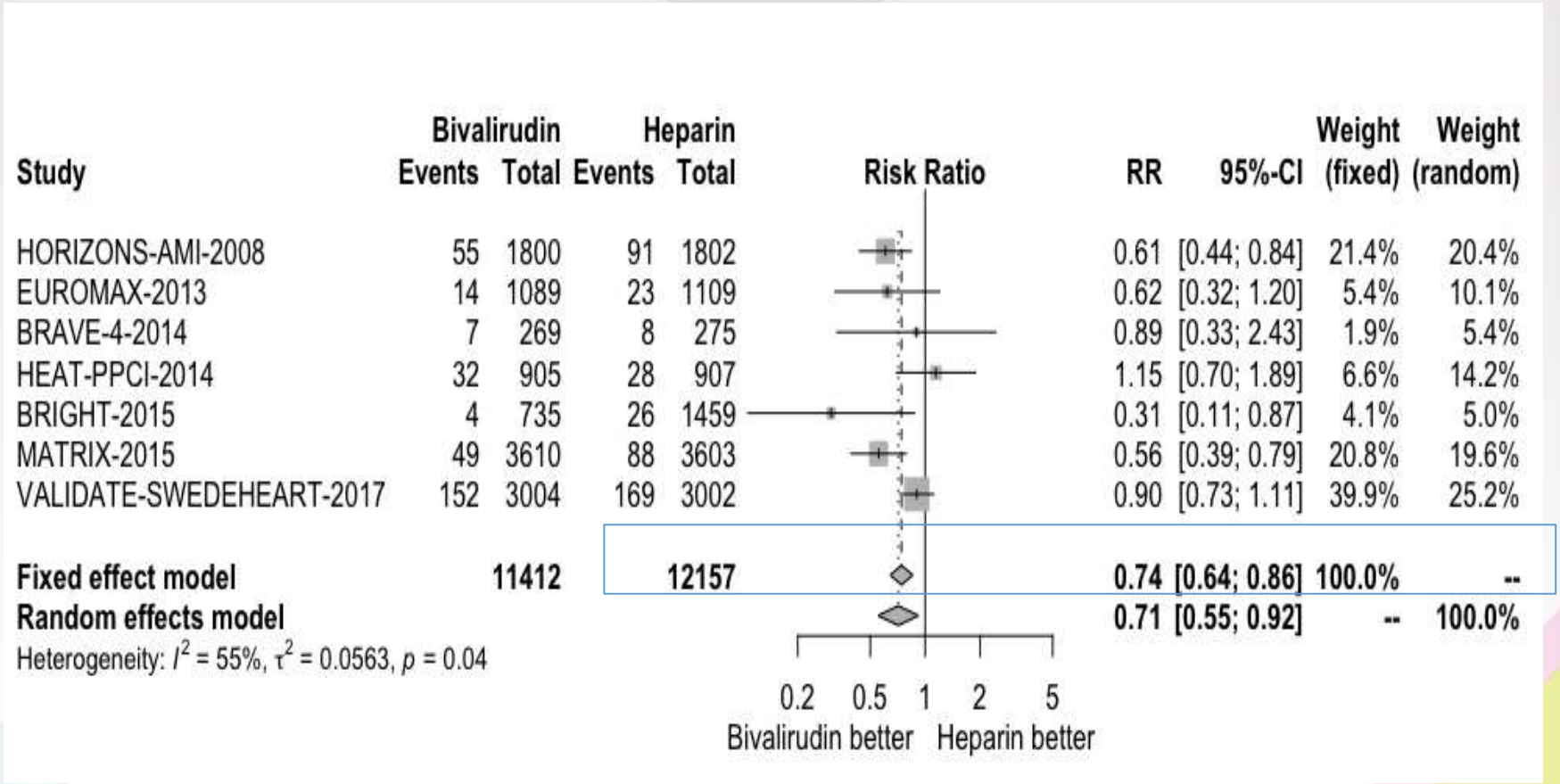
Erlinge et al, N Engl J Med. 2017 21;337(12):1132-1142.

Subgroup	Bivalirudin	Heparin	Hazard Ratio (95% CI)	P Value
	no. of events/total no. of patients (%)			
Overall	369/3004 (12.3)	383/3002 (12.8)	0.96 (0.83–1.10)	0.54
Type of myocardial infarction				0.97
NSTEMI	182/1503 (12.1)	187/1498 (12.5)	0.96 (0.78–1.18)	
STEMI	187/1501 (12.5)	196/1504 (13.0)	0.95 (0.78–1.17)	
Sex				0.05
Female	105/771 (13.6)	140/821 (17.1)	0.78 (0.60–1.00)	
Male	263/2229 (11.8)	243/2177 (11.2)	1.06 (0.89–1.26)	
Age				0.70
>65 yr	289/1819 (15.9)	299/1852 (16.1)	0.97 (0.83–1.15)	
≤65 yr	79/1181 (6.7)	84/1146 (7.3)	0.91 (0.67–1.24)	
Diabetes mellitus				0.82
Yes	74/491 (15.1)	82/508 (16.1)	0.93 (0.68–1.27)	
No	293/2502 (11.7)	299/2482 (12.0)	0.97 (0.82–1.13)	
Renal failure				0.16
Yes	101/450 (22.4)	95/477 (19.9)	1.13 (0.85–1.50)	
No	258/2511 (10.3)	283/2484 (11.4)	0.89 (0.75–1.06)	
Smoker				0.97
Yes	81/716 (11.3)	85/710 (12.0)	0.95 (0.70–1.29)	
No	277/2209 (12.5)	290/2205 (13.2)	0.94 (0.80–1.11)	
Weight				0.38
<60 kg	28/139 (20.1)	27/156 (17.3)	1.19 (0.70–2.02)	
≥60 kg	335/2847 (11.8)	355/2829 (12.5)	0.93 (0.80–1.08)	
Previous myocardial infarction				0.55
Yes	61/490 (12.4)	69/484 (14.3)	0.86 (0.61–1.22)	
No	300/2474 (12.1)	307/2467 (12.4)	0.97 (0.83–1.13)	
Previous PCI				0.39
Yes	60/456 (13.2)	66/426 (15.5)	0.83 (0.58–1.17)	
No	308/2544 (12.1)	317/2572 (12.3)	0.98 (0.84–1.14)	
Target vessel				0.50
Left coronary artery	221/1807 (12.2)	248/1848 (13.4)	0.90 (0.75–1.08)	
Right coronary artery	97/807 (12.0)	96/806 (11.9)	1.01 (0.76–1.34)	
Thrombus grade				0.91
0–3	313/2589 (12.1)	328/2587 (12.7)	0.94 (0.81–1.10)	
4 or 5	52/398 (13.1)	55/405 (13.6)	0.97 (0.66–1.41)	
Access site for PCI				0.89
Femoral	65/290 (22.4)	64/280 (22.9)	0.97 (0.69–1.37)	
Radial	303/2708 (11.2)	319/2716 (11.7)	0.95 (0.81–1.11)	
Time from administration of $P2Y_{12}$ inhibitor to PCI				0.62
<1 hr	144/1148 (12.5)	161/1129 (14.3)	0.87 (0.69–1.09)	
1–2 hr	73/588 (12.4)	75/604 (12.4)	1.00 (0.72–1.37)	
>2 hr	146/1252 (11.7)	144/1256 (11.5)	1.01 (0.80–1.27)	
TIMI flow grade before PCI				0.53
0	151/1178 (12.8)	133/1114 (11.9)	1.08 (0.86–1.37)	
1	28/222 (12.6)	33/220 (15.0)	0.81 (0.49–1.34)	
2	58/483 (12.0)	61/487 (12.5)	0.94 (0.66–1.35)	
3	130/1113 (11.7)	156/1178 (13.2)	0.87 (0.69–1.09)	
Thrombus aspiration				0.73
Yes	15/169 (8.9)	16/153 (10.5)	0.85 (0.42–1.71)	
No	353/2831 (12.5)	367/2845 (12.9)	0.96 (0.83–1.11)	
Maximum ACT <median ACT				0.84
Yes	111/926 (12.0)	158/1238 (12.8)	0.93 (0.73–1.18)	
No	139/1183 (11.7)	160/1239 (12.9)	0.90 (0.72–1.13)	



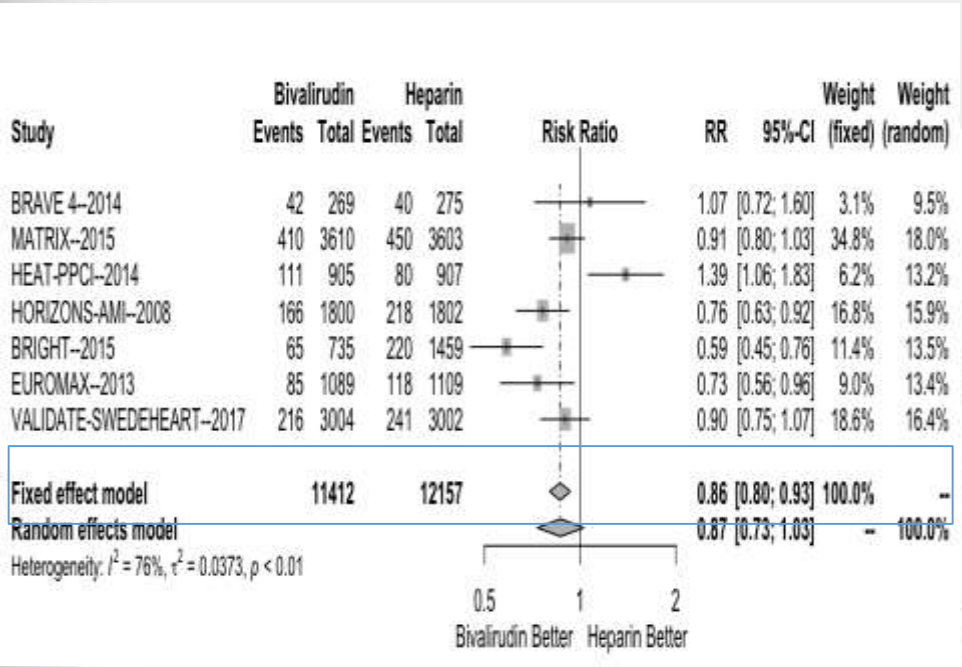
Erlinge et al, N Engl J Med. 2017 21;337(12):1132-1142.

Major bleeding-pooled analysis

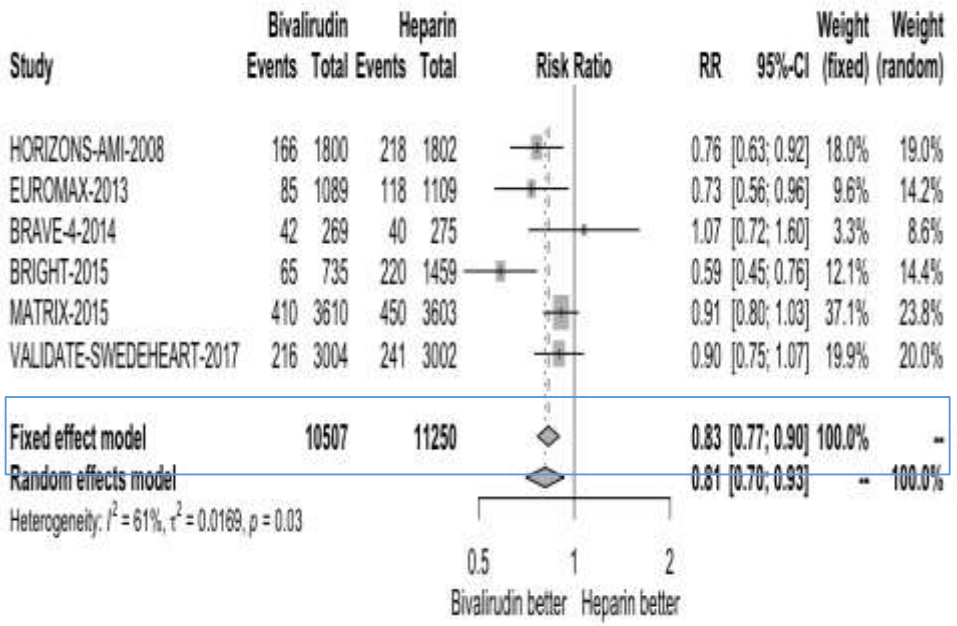


Ge Z, Chandrasekhar J, Mehran R, CVIA 2018, in press

NACE: pooled analysis from 7 AMI trials



Excluding HEAT-PPCI trial



Ge Z, Chandrasekhar J, Mehran R, CVIA 2018, in press

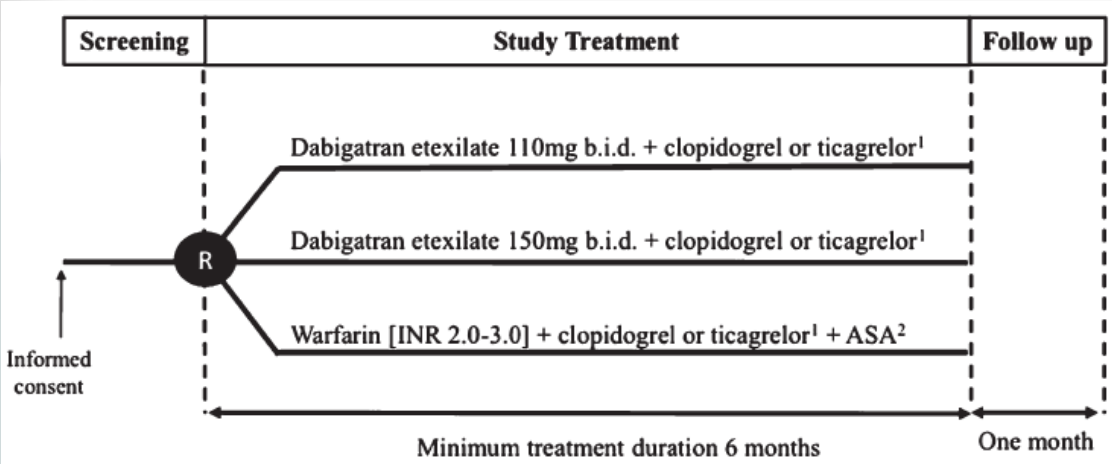
RE-DUAL PCI trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

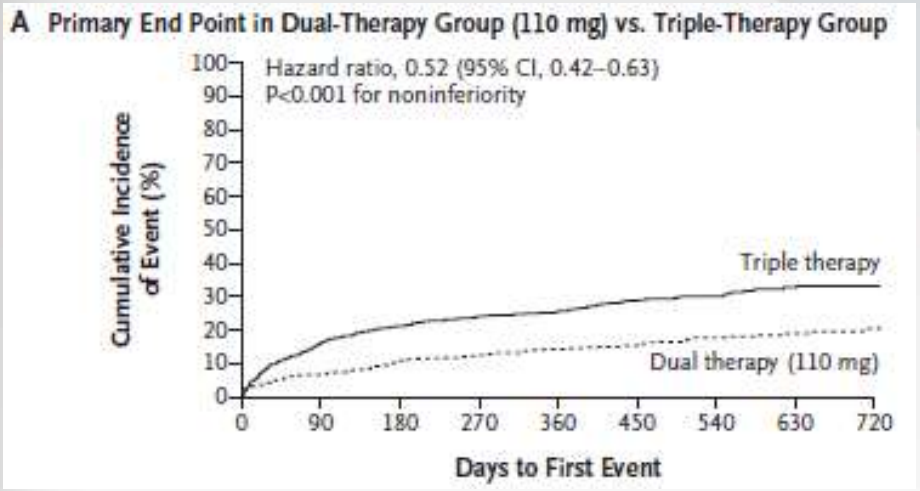
Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

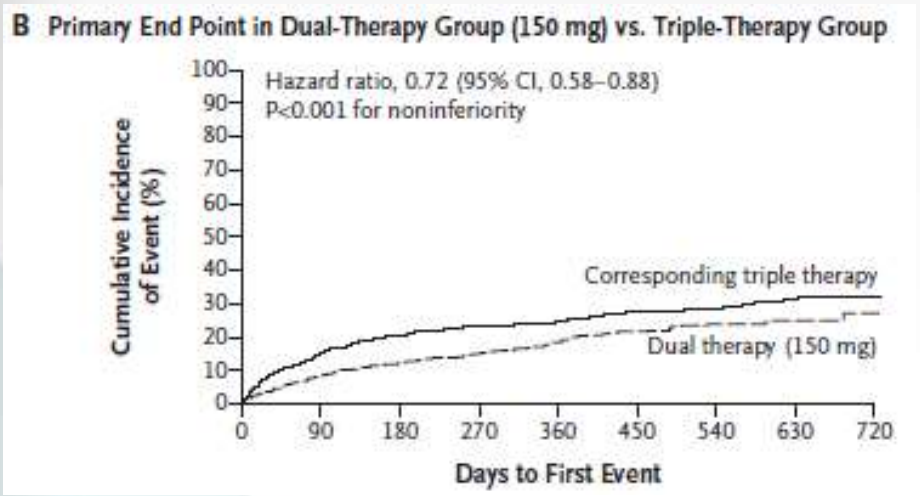


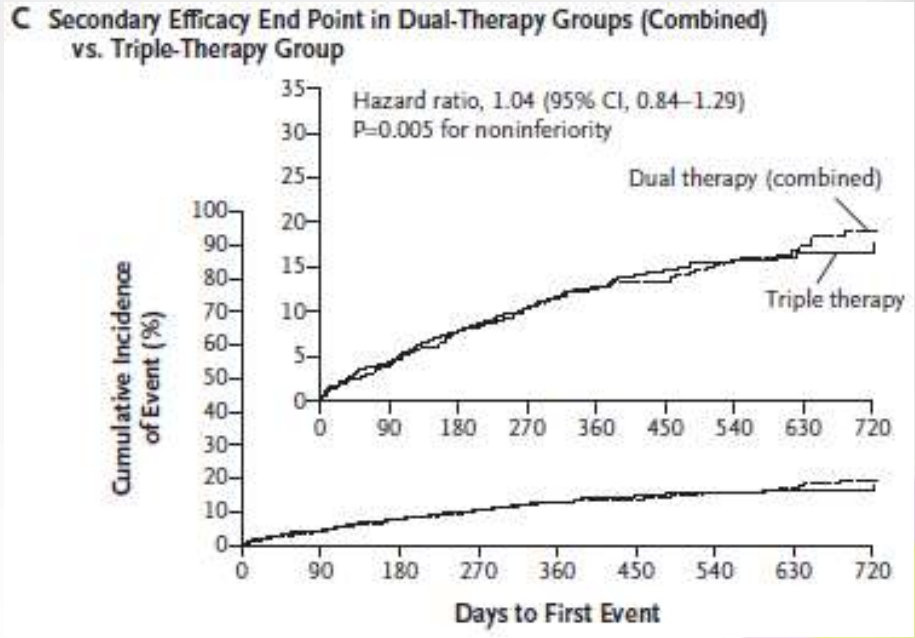
- Primary composite endpoint:
  - major bleeding (ISTH)
  - clinically relevant non-major bleeding
- Secondary composite endpoint
  - Thromboembolic events
  - Death

Cannon et al, N Engl J Med. 2017 19;377(16):1513-1524

Mean follow-up : 14 months







Dual antiplatelet therapy with dabigatran is associated with less bleeding than triple therapy with VKA

Cannon et al, N Engl J Med. 2017 19;377(16):1513-1524.

Table 2. Safety End Points.*

End Point	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Hazard Ratio (95% CI)	P Value†	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*			
Primary end point: ISTH major or clinically relevant nonmajor bleeding	151 (15.4)	264 (26.9)	0.52 (0.42–0.63)	<0.001 (<0.001 for noninferiority)	154 (20.2)	196 (25.7)	0.72 (0.58–0.88)	0.002 (<0.001 for noninferiority)
ISTH major bleeding	49 (5.0)	90 (9.2)	0.52 (0.37–0.74)	<0.001	43 (5.6)	64 (8.4)	0.64 (0.43–0.94)	0.02
Total bleeding	266 (27.1)	421 (42.9)	0.54 (0.46–0.63)	<0.001	254 (33.3)	316 (41.4)	0.72 (0.61–0.84)	<0.001
Intracranial hemorrhage	3 (0.3)	10 (1.0)	0.30 (0.08–1.07)	0.06	1 (0.1)	8 (1.0)	0.12 (0.02–0.98)	0.047
TIMI major bleeding	14 (1.4)	37 (3.8)	0.37 (0.20–0.68)	0.002	16 (2.1)	30 (3.9)	0.51 (0.28–0.93)	0.03
TIMI major or minor bleeding	29 (3.0)	69 (7.0)	0.41 (0.26–0.63)	<0.001	27 (3.5)	48 (6.3)	0.53 (0.33–0.85)	0.009

Table 3. Efficacy End Points.*

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*				*no. (%)*			
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
Death					55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Myocardial infarction					44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stroke					17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Definite stent thrombosis					15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

Cannon et al, N Engl J Med. 2017 19;377(16):1513-1524.

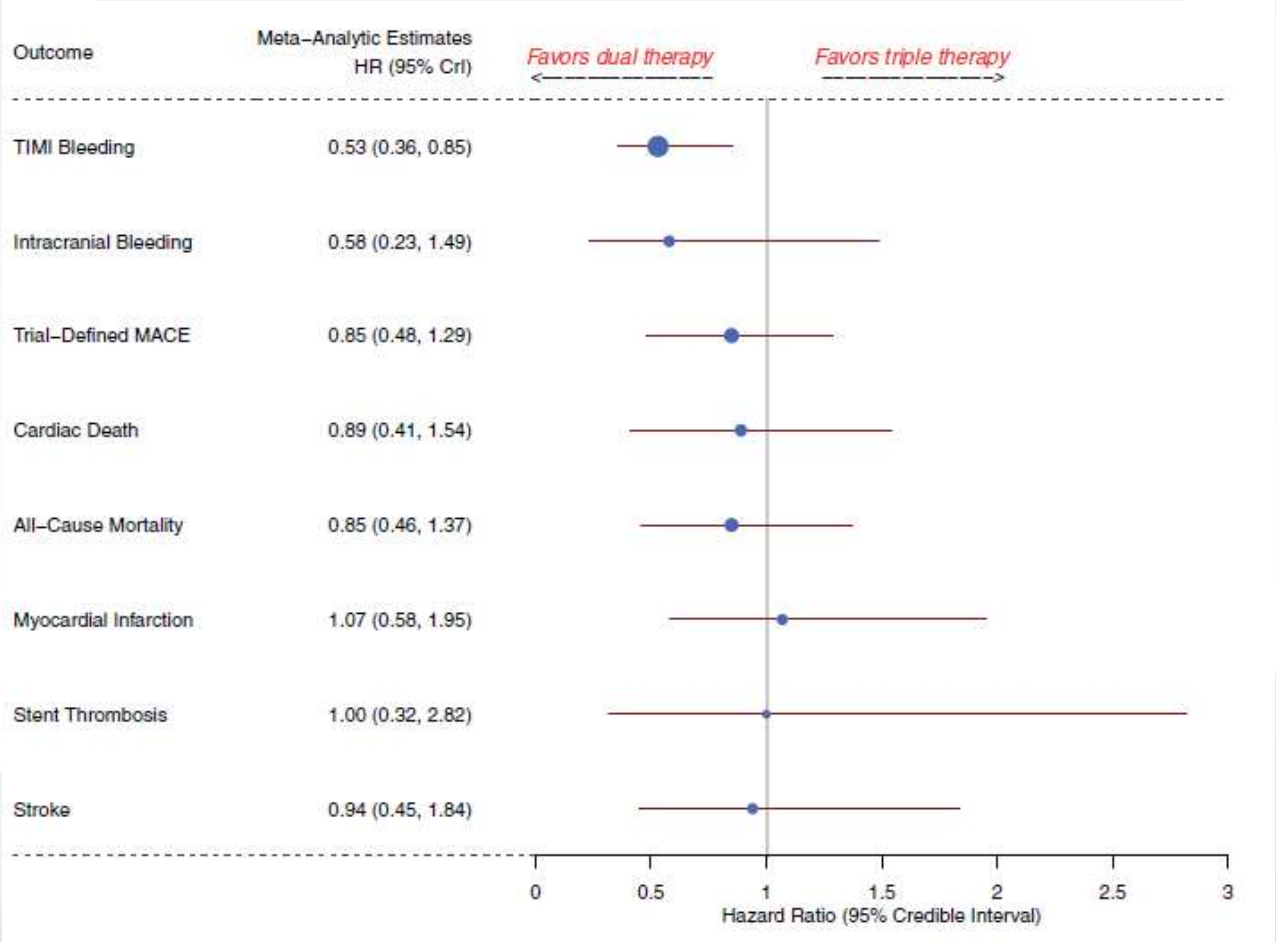
Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials

Harsh B. Golwala[1], Christopher P. Cannon[1,2], Ph. Gabriel Steg[3], Gheorghe Doros[2,4], Arman Qamar[1], Stephen G. Ellis[5], Jonas Oldgren[6], Jurrien M. ten Berg[7], Takeshi Kimura[8], Stefan H. Hohnloser[9], Gregory Y. H. Lip[10], and Deepak L. Bhatt[1]*

ESC European Society of Cardiology
European Heart Journal (2018) 00, 1–11
doi:10.1093/eurheartj/ehy162

WOEST[12]		ISAR-TRIPLE[13]		PIONEER AF-PCI[14]		RE-DUAL PCI[15]			Combined	
DAT (n = 279)	TAT (n = 284)	DAT (n = 307)	TAT (n = 307)	DAT (n = 709)	TAT (n = 706)	DAT (n = 981) Dabigatran 110 mg	DAT (n = 763) Dabigatran 150 mg	TAT (n = 981)	DAT (n = 3039)	TAT (n = 2278)

Summary of bleeding and ischaemic risks for dual versus triple antithrombotic therapy.



Golwala et al Eur Heart J. 2018 Apr 13.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 11, 2017 VOL. 376 NO. 19

Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI

M. Götberg, E.H. Christiansen, I.J. Gudmundsdottir, L. Sandhall, M. Danielewicz, L. Jakobsen, S.-E. Olsson, P. Öhagen, H. Olsson, E. Omerovic, F. Calais, P. Lindroos, M. Maeng, T. Tödt, D. Venetsanos, S.K. James, A. Kåregren, M. Nilsson, J. Carlsson, D. Hauer, J. Jensen, A.-C. Karlsson, G. Panayi, D. Erlinge, and O. Fröbert, for the iFR-SWEDEHEART Investigators*

Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI

J.E. Davies, S. Sen, H.-M. Dehbi, R. Al-Lamee, R. Petraco, S.S. Nijjer, R. Bhindi, S.J. Lehman, D. Walters, J. Sapontis, L. Janssens, C.J. Vrints, A. Khashaba, M. Laine, E. Van Belle, F. Krackhardt, W. Bojara, O. Going, T. Härle, C. Indolfi, G. Niccoli, F. Ribichini, N. Tanaka, H. Yokoi, H. Takashima, Y. Kikuta, A. Erglis, H. Vinhas, P. Canas Silva, S.B. Baptista, A. Alghamdi, F. Hellig, B.-K. Koo, C.-W. Nam, E.-S. Shin, J.-H. Doh, S. Brugaletta, E. Alegria-Barrero, M. Meuwissen, J.J. Piek, N. van Royen, M. Sezer, C. Di Mario, R.T. Gerber, I.S. Malik, A.S.P. Sharp, S. Talwar, K. Tang, H. Samady, J. Altman, A.H. Seto, J. Singh, A. Jeremias, H. Matsuo, R.K. Kharbanda, M.R. Patel, P. Serruys, and J. Escaned

In both trials

All-comers undergoing PCI with at least on native artery with 40-70% stenosis

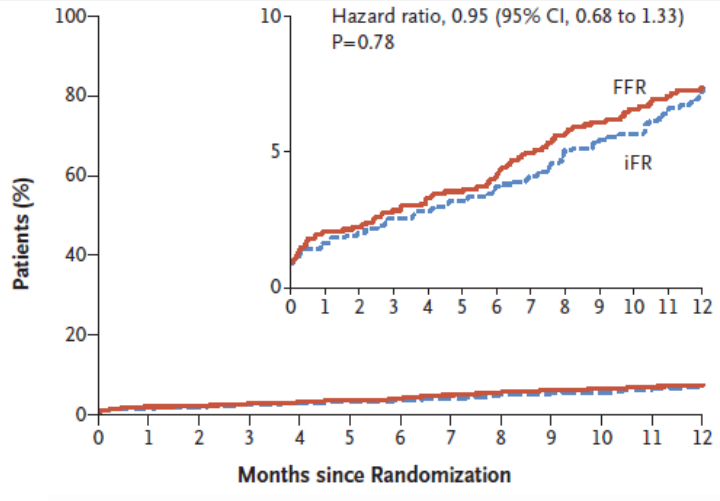
iFR threshold : 0.89 vs. **FFR (adenosine) threshold 0.8**

One-year follow-up for the composite of death, MI or unplanned revascularization.

Goteborg et al, N Engl J Med. 2017 May 11;376(19):1813-1823.
Davies et al, N Engl J Med. 2017 May 11;376(19):1824-1834.

Götberg et al

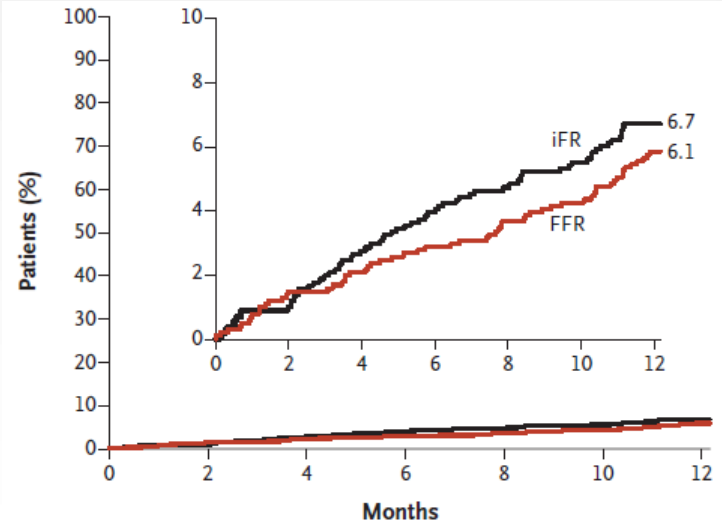
- 2037 patients, 62% stable angina
- No difference for the primary endpoint
  p < 0.001 for non-inferiority



- More frequent periprocedural chest discomfort with FFR

Davies et al

- 2492 patients, 80.2% stable angina
- No difference for the primary endpoint
  p =0.007 for non-inferiority



- More frequent heart-rhythm disturbance With FFR

iFR (threshold at 0.89) is non inferior to FFR

Goteborg et al, N Engl J Med. 2017 May 11;376(19):1813-1823.
Davies et al, N Engl J Med. 2017 May 11;376(19):1824-1834.

Lancet 2018; 391: 41-50

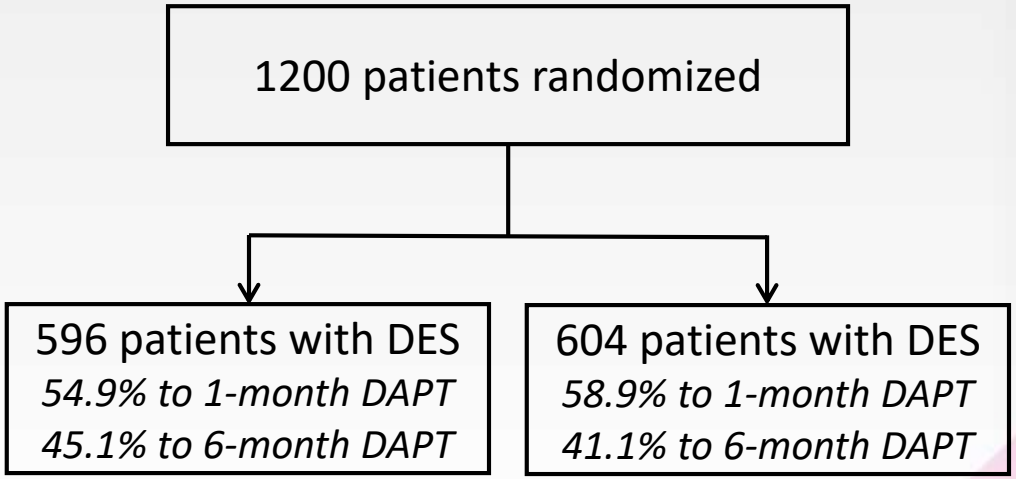
SENIOR trial

Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial

Olivier Varenne, Stéphane Cook, Georgios Sideris, Sasko Kedev, Thomas Cuisset, Didier Carrié, Thomas Hovasse, Philippe Garot, Rami El Mahmoud, Christian Spaulding, Gérard Helft, José F Diaz Fernandez, Salvatore Brugaletta, Eduardo Pinar-Bermudez, Josepa Mauri Ferre, Philippe Commeau, Emmanuel Teiger, Kris Bogaerts, Manel Sabate, Marie-Claude Morice, Peter R Sinnaeve, for the SENIOR investigators

Inclusion criteria

- Age ≥ 75 year, undergoing PCI
  - Randomized to DES or BMS
- Pre-specified DAPT duration
  - On-month if stable CAD
  - 6-month if ACS



Primary endpoint

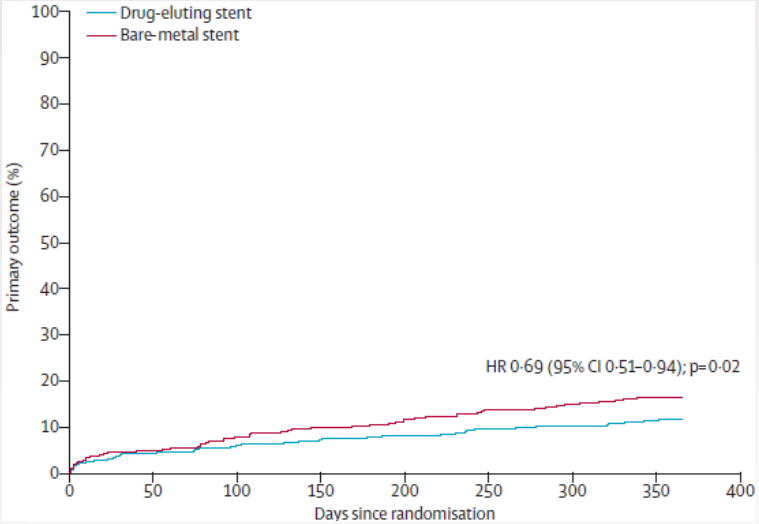
- MACCE: Death, MI, stroke or ischemia-driven target lesion revascularization
- Within on-year of index PCI

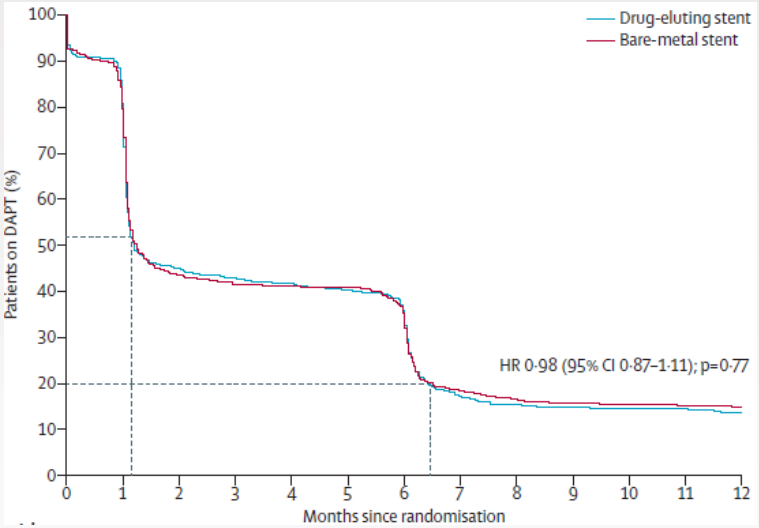
Varenne et al, Lancet 2018 Jan 6;391(10115):41-50

Lancet 2018; 391: 41-50

SENIOR trial

- Mean age 8.4 ± 4.3 years
- Clinical indication for PCI: ACS in 45.3% of the patients





Secondary endpoints				
All-cause mortality				
30 days	9 (2%)	15 (2%)	0·61 (0·20–1·42)	0·23
180 days	24 (4%)	30 (5%)	0·81 (0·46–1·39)	0·44
1 year	36 (6%)	48 (8%)	0·76 (0·49–1·16)	0·20
Cardiovascular death				
30 days	7 (1%)	14 (2%)	0·51 (0·13–0·26)	0·13
180 days	15 (3%)	25 (4%)	0·61 (0·29–1·14)	0·12
1 year	22 (4%)	36 (6%)	0·62 (0·34–1·04)	0·07
Myocardial infarction				
30 days	12 (2%)	11 (2%)	1·11 (0·44–2·93)	0·81
180 days	13 (2%)	17 (3%)	0·77 (0·33–1·65)	0·48
1 year	21 (4%)	22 (4%)	0·97 (0·51–1·82)	0·92
Stroke				
30 days	2 (<1%)	1 (<1%)	2·03 (0·18–22·37)	0·56
180 days	8 (1%)	1 (<1%)	8·15 (1·02–64·85)	0·02
1 year	12 (2%)	5 (1%)	2·43 (0·88–7·04)	0·08
Ischaemia-driven target lesion revascularisation				
30 days	2 (<1%)	3 (<1%)	0·67 (0·00–1·88)	0·66
180 days	7 (1%)	23 (4%)	0·31 (0·08–0·66)	0·003
1 year	10 (2%)	35 (6%)	0·29 (0·11–0·54)	0·0002

Secondary endpoints				
Bleeding complications*				
BARC 2–5				
30 days	11 (2%)	13 (2%)	0·85 (0·32–2·07)	0·69
180 days	20 (3%)	20 (3%)	1·01 (0·52–1·96)	0·97
1 year	26 (5%)	29 (5%)	0·90 (0·51–1·54)	0·68
BARC 3–5				
30 days	10 (2%)	8 (1%)	1·26 (0·43–4·37)	0·62
180 days	15 (3%)	14 (2%)	1·08 (0·48–2·47)	0·83
1 year	20 (3%)	21 (4%)	0·95 (0·49–1·81)	0·86

In the elderly, with short DAPT duration, DES > BMS

CVRF

Varenne et al, Lancet 2018 Jan 6;391(10115):41-50

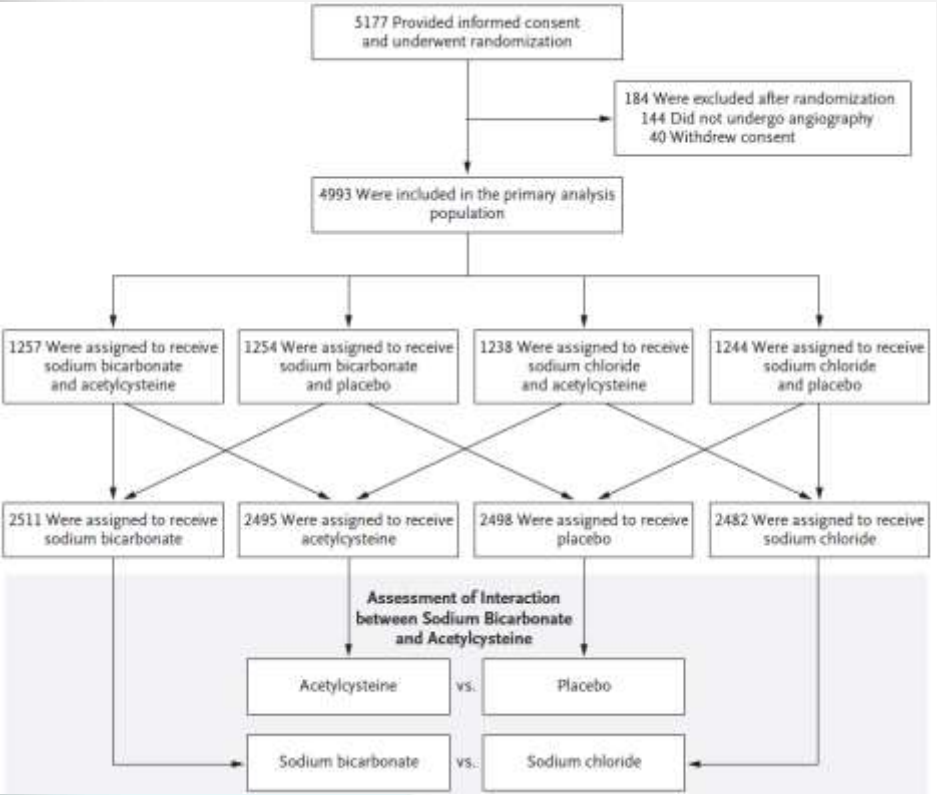
PRESERVE trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 15, 2018 VOL. 378 NO. 7

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

S.D. Weisbord, M. Gallagher, H. Jneid, S. Garcia, A. Cass, S.-S. Thwin, T.A. Conner, G.M. Chertow, D.L. Bhatt, K. Shunk, C.R. Parikh, E.O. McFalls, M. Brophy, R. Ferguson, H. Wu, M. Androsenko, J. Myles, J. Kaufman, and P.M. Palevsky, for the PRESERVE Trial Group*



Target population:

- eGFR between 15 to 44.9ml/min/1.73m²
- eGFR between 45 to 59.9ml/min/1.73m²

AND diabetes

Primary endpoint: death, need for dialysis or >50% increase of creatinine from baseline

Characteristic	Sodium Bicarbonate (N=2511)	Sodium Chloride (N=2482)	Acetylcysteine (N=2495)	Placebo (N=2498)
Procedural				
Procedure type — no./total no. (%)				
Coronary	2238/2480 (90.2)	2228/2457 (90.7)	2237/2469 (90.6)	2229/2468 (90.3)
Noncoronary	242/2480 (9.8)	229/2457 (9.3)	232/2469 (9.4)	239/2468 (9.7)
Percutaneous intervention — no./total no. (%)	705/2480 (28.4)	701/2457 (28.5)	719/2469 (29.1)	687/2468 (27.9)
Contrast type — no./total no. (%)				
Iodixanol	1404/2480 (56.6)	1388/2457 (56.5)	1405/2469 (56.9)	1387/2468 (56.2)
Low-osmolal agent	1076 /2480 (43.4)	1069/2457 (43.5)	1064/2469 (43.1)	1081/2468 (43.8)
Median volume of contrast material (IQR) — ml	85 (56–135)	85 (55–138)	85 (55–140)	85 (55–135)
Left ventricular end-diastolic pressure — mm Hg	17.9±8.1	18.3±8.2	18.1±8.0	18.1±8.3

Weisbord et al, N Engl J Med. 2018 Feb 15;378(7):603-614.

PRESERVE trial

No difference between Sodium chloride and Sodium bicarbonate
No impact of Acetylsteine

Outcome	Sodium Bicarbonate (N=2511)	Sodium Chloride (N=2482)	Odds Ratio (95% CI)	P Value	Acetylcysteine (N=2495)	Placebo (N=2498)	Odds Ratio (95% CI)	P Value
	no. of patients (%)				*no. of patients (%)*			
Primary end point*	110 (4.4)	116 (4.7)	0.93 (0.72–1.22)	0.62	114 (4.6)	112 (4.5)	1.02 (0.78–1.33)	0.88
Secondary end points								
Contrast-associated acute kidney injury†	239 (9.5)	206 (8.3)	1.16 (0.96–1.41)	0.13	228 (9.1)	217 (8.7)	1.06 (0.87–1.28)	0.58
Death by 90 days	60 (2.4)	68 (2.7)	0.87 (0.61–1.24)	0.43	67 (2.7)	61 (2.4)	1.10 (0.78–1.57)	0.59
Need for dialysis by 90 days	32 (1.3)	29 (1.2)	1.09 (0.65–1.81)	0.73	30 (1.2)	31 (1.2)	0.97 (0.58–1.60)	0.90
Persistent kidney impairment by 90 days	28 (1.1)	25 (1.0)	1.10 (0.64–1.91)	0.71	26 (1.0)	27 (1.1)	0.96 (0.56–1.66)	0.89
Hospitalization with acute coronary syndrome, heart failure, or stroke by 90 days	272 (10.8)	251 (10.1)	1.08 (0.90–1.29)	0.40	244 (9.8)	279 (11.2)	0.86 (0.71–1.04)	0.11
All-cause hospitalization by 90 days	1071 (42.7)	1052 (42.4)	1.01 (0.90–1.13)	0.85	1069 (42.8)	1054 (42.2)	1.03 (0.91–1.15)	0.64

Weisbord et al, N Engl J Med. 2018 Feb 15;378(7):603-614. doi:10.1059/NEJMoa1710933.

Percutaneous structural intervention

ARTE trial

JACC: CARDIOVASCULAR INTERVENTIONS

PUBLISHED BY ELSEVIER

Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve

The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) Randomized Clinical Trial

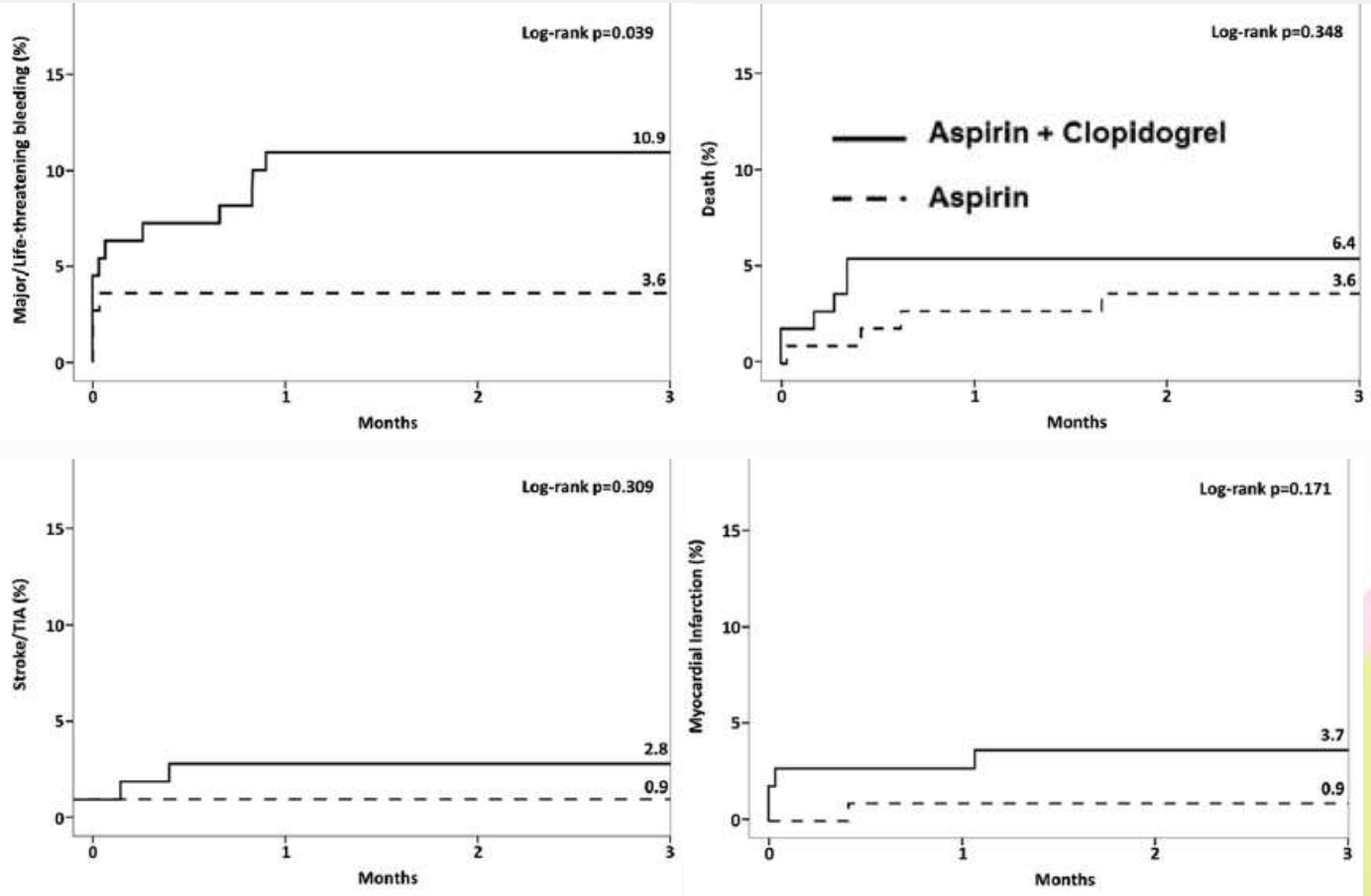
Josep Rodés-Cabau, MD,[a] Jean-Bernard Masson, MD,[b] Robert C. Welsh, MD,[c] Bruno Garcia del Blanco, MD,[d] Marc Pelletier, MD,[e] John G. Webb, MD,[f] Faisal Al-Qoofi, MD,[g] Philippe Généreux, MD,[h] Gabriel Maluenda, MD,[i] Martin Thoenes, MD, PhD,[j] Jean-Michel Paradis, MD,[a] Chekrallah Chamandi, MD,[a] Vicenç Serra, MD,[d] Eric Dumont, MD,[a] Mélanie Côté, MSc[a]

222 patients randomized after successful TAVI to

- 3 months SAPT

or

- 3 months DAPT



Rodes-cabau JACC cardiovasc Interv 2017 10;10(13):1357-1365

Antithrombotic Therapy for Prevention of Cerebral Thromboembolic Events After Transcatheter Aortic Valve Replacement

Evolving Paradigms and Ongoing Directions*

Davide Capodanno, MD, PhD,[a] Dominick J. Angiolillo, MD, PhD[b]

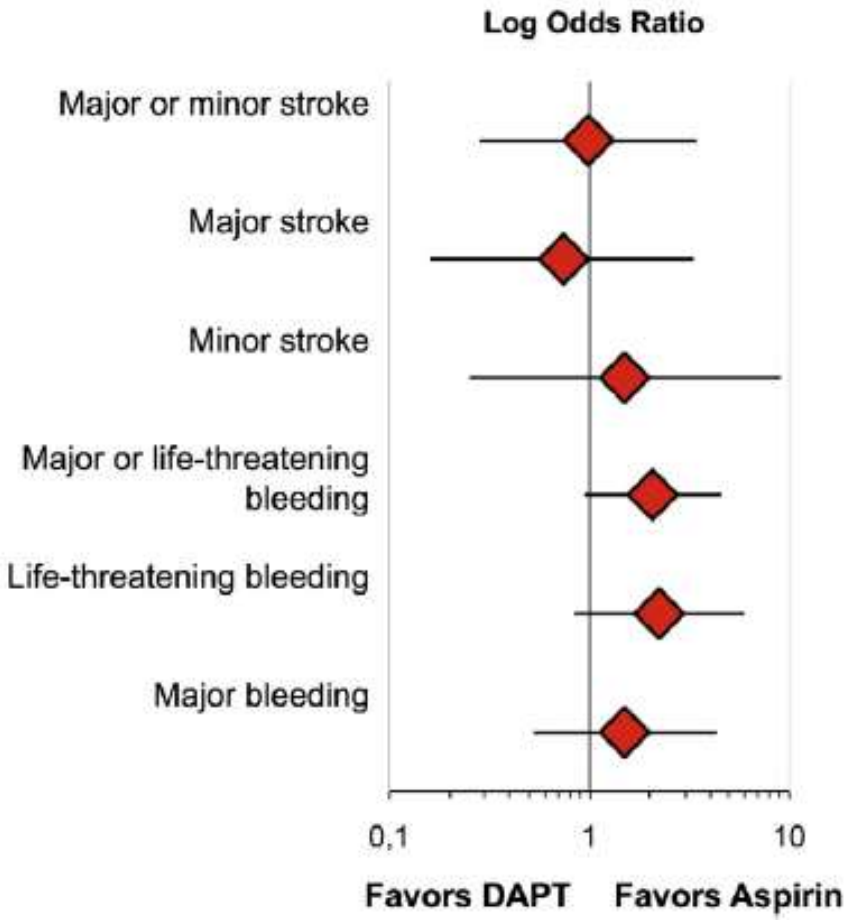
EDITORIAL COMMENT

JACC: CARDIOVASCULAR INTERVENTIONS

PUBLISHED BY ELSEVIER

Thirty-day outcomes of DAPT vs. Aspirin after TAVR

Meta-analysis of 421 patients from 3 RCTs



Capodanno JACC cardiovasc Interv 2017 10;10(13):1366-1369

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

Recommendations for Antithrombotic Therapy for Patients with Prosthetic Heart Valves

IIb	B-NR	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 (203,210,211).	NEW: Studies have shown that valve thrombosis may develop in patients after TAVR, as assessed by multidetector computerized tomographic scanning. This valve thrombosis occurs in patients who received antiplatelet therapy alone but not in patients who were treated with VKA.

See Online Data Supplement 6.

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

Indications for antithrombotic therapy in patients with a prosthetic heart valve or valve repair

Bioprostheses

Single antiplatelet therapy may be considered after TAVI in the case of high bleeding risk.	IIb	C

Baumgartner et al Eur. Heart J.2017 Sep 21;38(36):2739-279
Nishimura et al J Am Coll Cardiol. 2017 Jul 11;70(2):252-289

CLOSE trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Merveveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*

- 663 patients with cryptogenic stroke and PFO with atrial septal aneurysm or large interatrial shunt

- Randomized to
  - Antiplatelet therapy (Aspirin / Clopidogrel / Aspirin and dypiridamol)
  - Oral anticoagulant: VKA (INR:2-3) or NOACs
  - PFO percutaneous closure and antiplatelet

- Primary : fatal or non-fatal stroke recurrence

Mas et al, N Engl J Med. 2017 14;337(11):1011-1021

Mean follow-up 5.3 ± 2.0 years

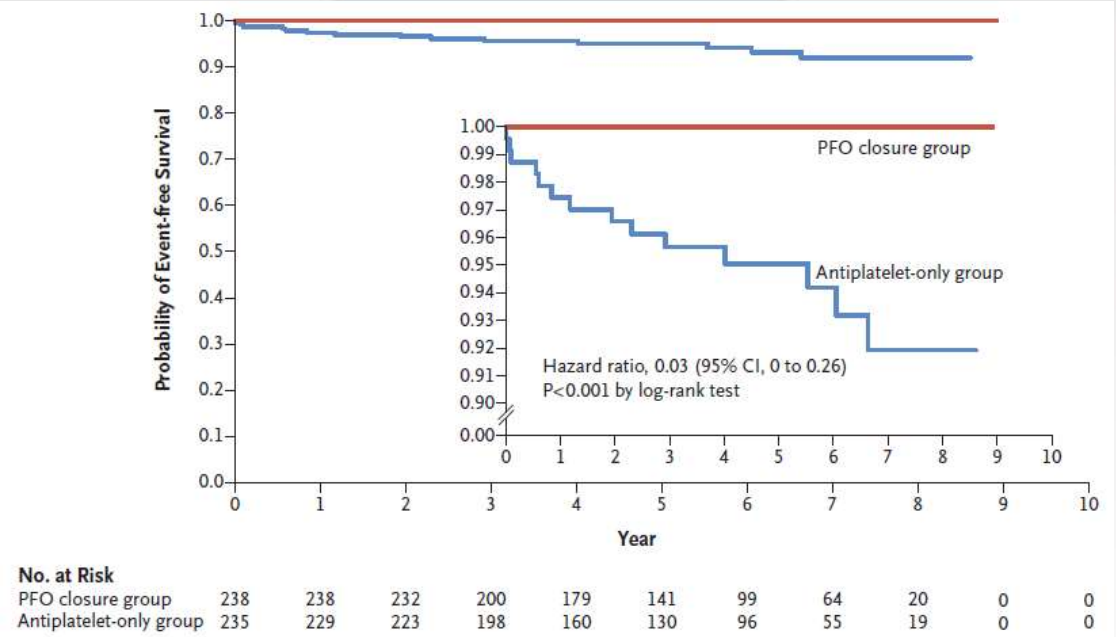


Figure 2. Kaplan–Meier Cumulative Estimates of Probability of Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.

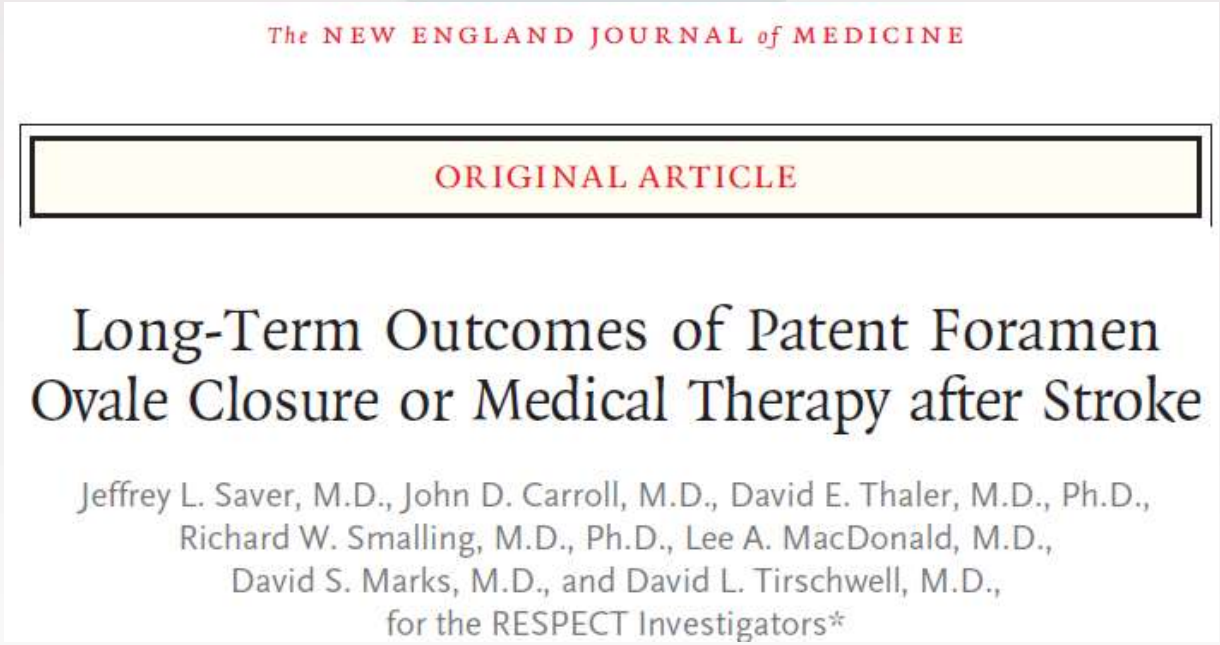
PFO + antiplatelet > antiplatelet therapy only for the primary endpoint

No significant difference between PFO + antiplatelet vs. oral anticoagulant

Table 2. Efficacy Outcomes.*

Outcome	Randomization Groups 1 and 2				Randomization Groups 1 and 3		
	PFO Closure Group (N–238)	Antiplatelet-Only Group (N–235)	Hazard Ratio (95% CI)†	P Value	Anticoagulant Group (N–187)	Antiplatelet-Only Group (N–174)	Hazard Ratio (95% CI)‡
Primary efficacy outcome							
Stroke in the intention-to-treat population — no. of patients	0	14§	0.03 (0.00–0.26)	<0.001	3¶	7§	0.44 (0.11–1.48)
Stroke in the per-protocol population — no./total no. of patients	0/217	14/223§	0.04 (0.00–0.27)	<0.001	2/143¶	7/164§	0.37 (0.07–1.38)

RESPECT trial



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

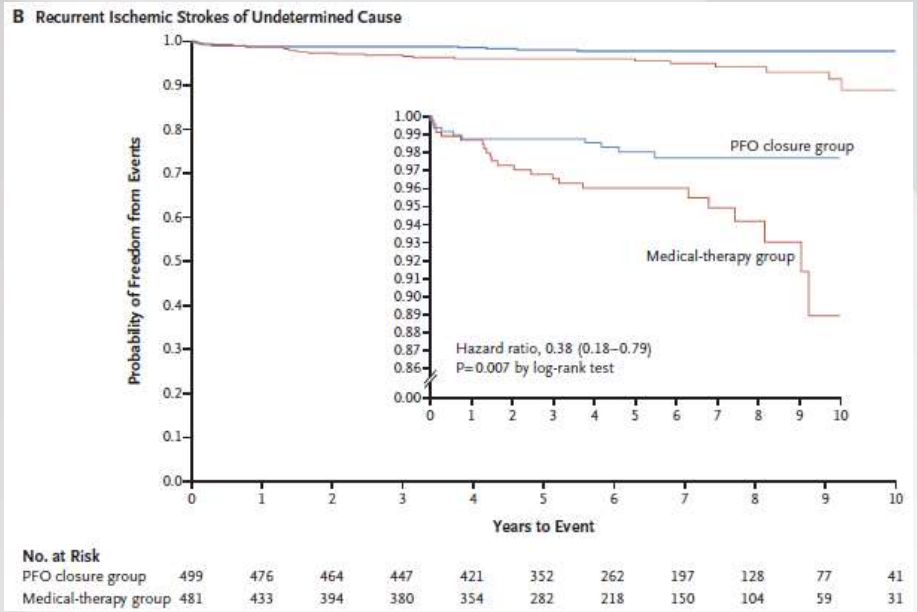
Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

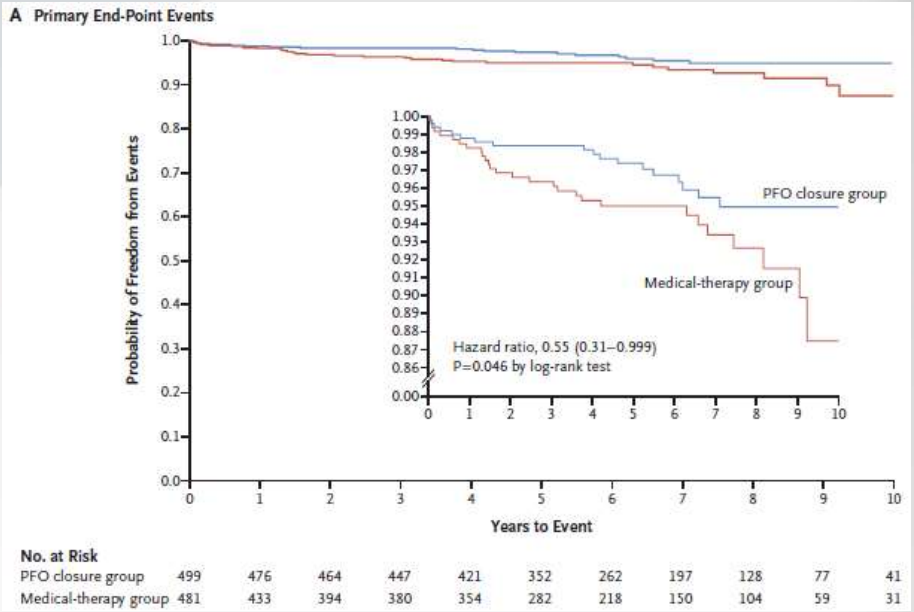
Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

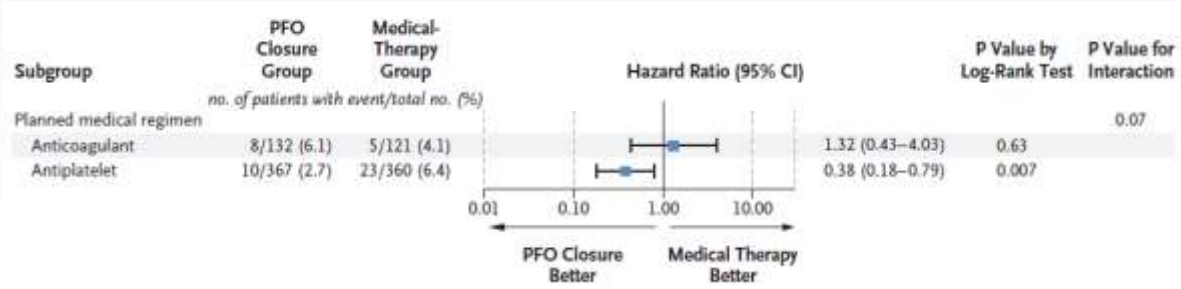
- 980 patients with cryptogenic stroke and PFO
- Randomized to
  - PFO percutaneous closure and antiplatelet
  - Medical therapy only (Aspirin or Clopidogrel or Warfarin or Aspirin + Dypiridamol)
- Primary endpoint: fatal or non-fatal stroke recurrence or early death

Saver et al, N Engl J Med. 2017 14;337(11):1022-1032

Median follow-up 5.9 years (IQR 4.2 to 8.0) years



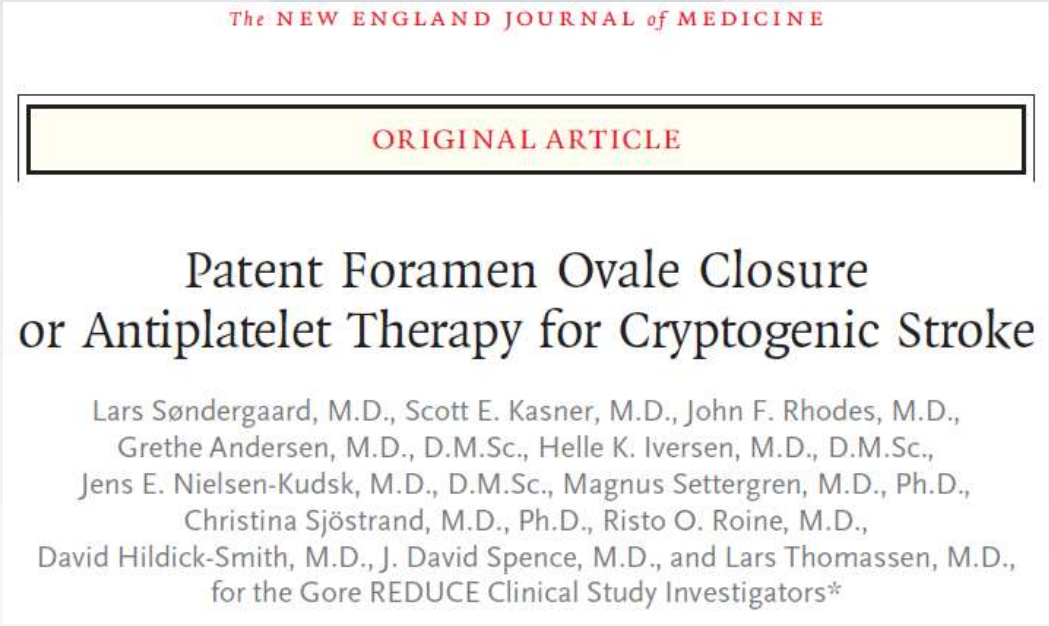




PFO closure > medical therapy overall

- PFO closure > antiplatelet only
- No difference between PFO closure and anticoagulant

Gore REDUCE trial



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

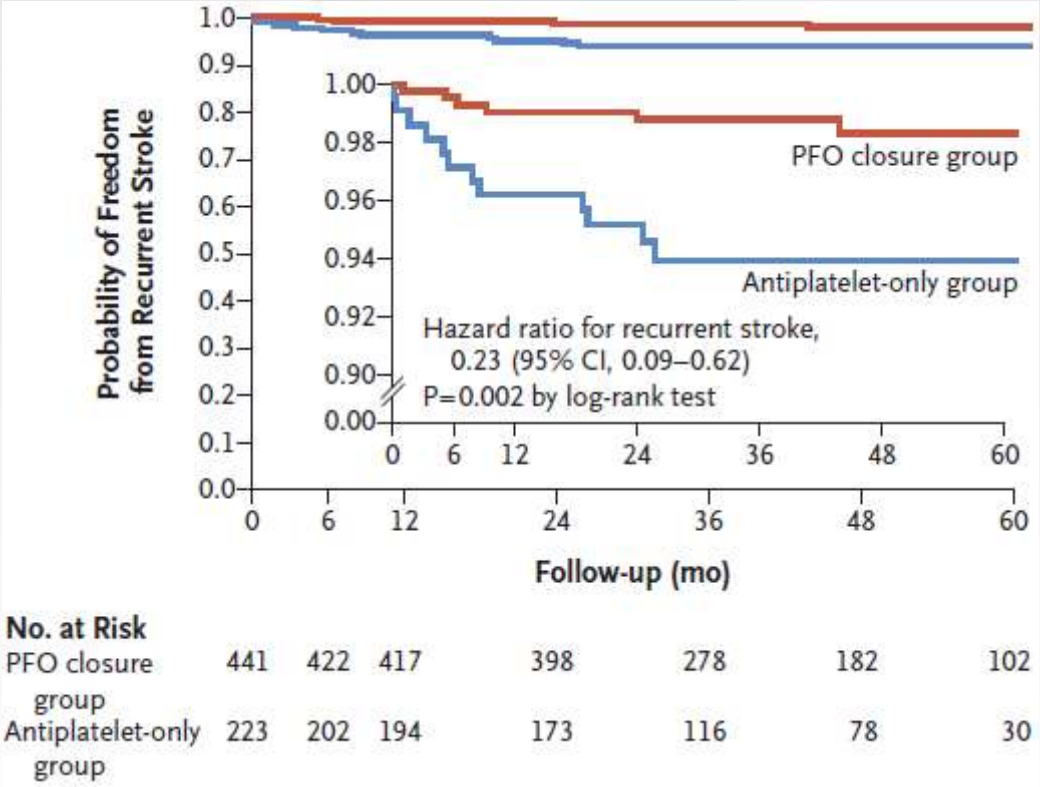
Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

- 664 patients with cryptogenic stroke and PFO
- Randomized to
  - Antiplatelet therapy (Aspirin / Clopidogrel / Aspirin and dypiridamol)
  - PFO percutaneous closure and antiplatelet
- Systematic MRI evaluation at baseline and 24 month
- Co-Primary endpoints:
  - Freedom from ischemic stroke during follow-up
  - 24-month incidence of new brain infarction (including silent infarction)

Søndergaard et al, N Engl J Med. 2017 14;337(11):1033-1042

Median follow-up: 3.2 years (IQR 2.2 to 4.8)



PFO closure and antiplatelet > Antiplatelet only

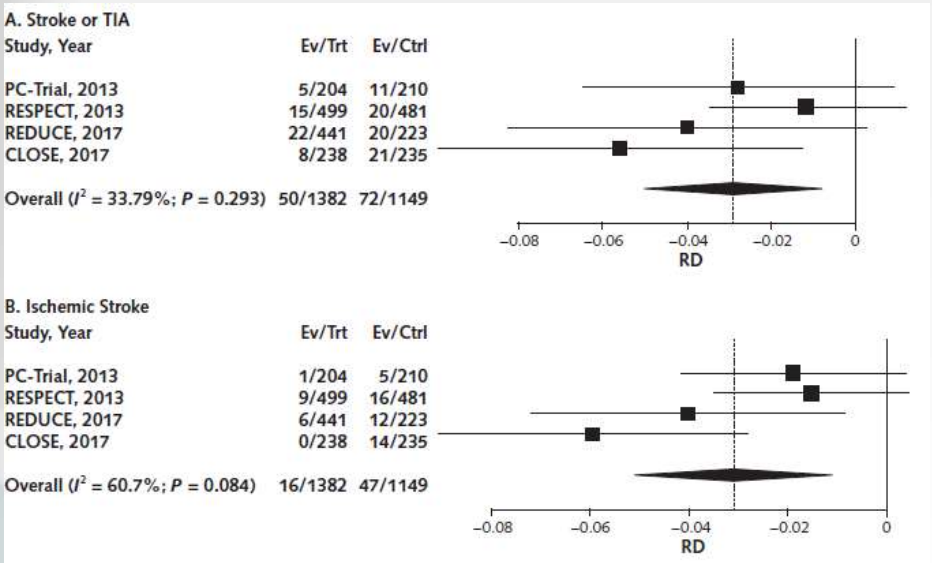
End Point	PFO Closure Group	Antiplatelet-Only Group	Effect Size	P Value
	no. of patients/total no. (%)			
Clinical ischemic stroke†	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)‡	0.002§
New brain infarction¶	22/383 (5.7)	20/177 (11.3)	0.51 (0.29–0.91)	0.04**
Recurrent clinical ischemic stroke	5/383 (1.3)	12/177 (6.8)	0.19 (0.07–0.54)	0.005**
Silent brain infarction only	17/383 (4.4)	8/177 (4.5)	0.98 (0.43–2.23)	0.97**

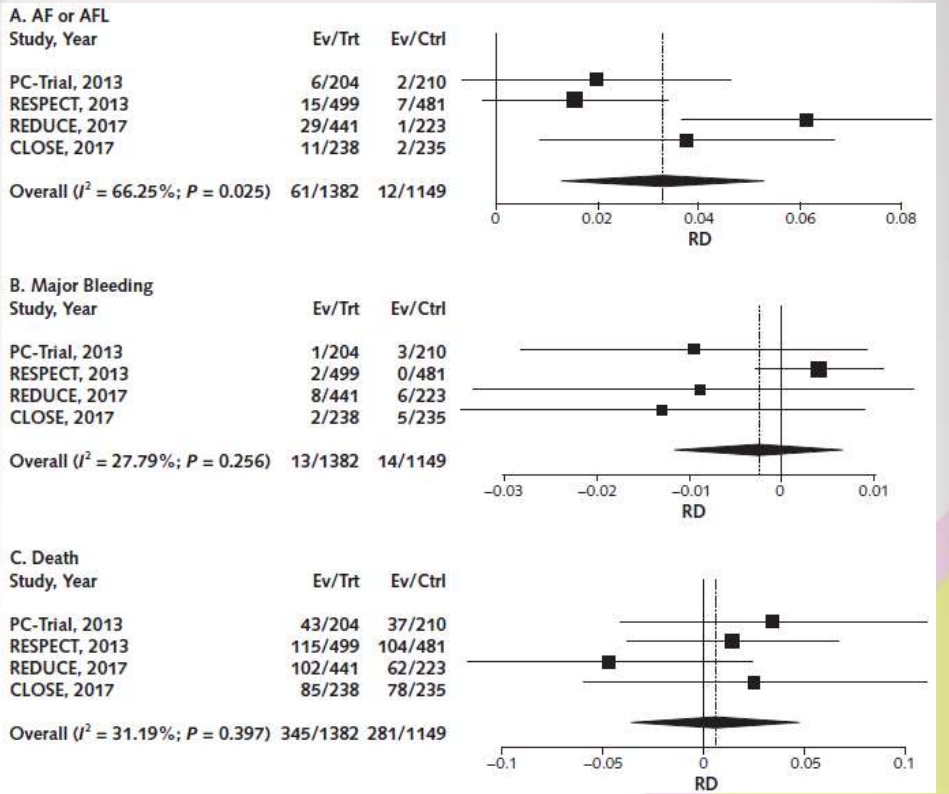
Annals of Internal Medicine REVIEW

Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale

A Systematic Review and Meta-analysis

Salvatore De Rosa, MD, PhD; Horst Sievert, MD; Jolanda Sabatino, MD; Alberto Polimeni, MD; Sabato Sorrentino, MD, PhD; and Ciro Indolfi, MD





De Rosa et al, Ann Inter Med. 2018 6;168(5):343-350

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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Device-Related Thrombosis After Percutaneous Left Atrial Appendage Occlusion for Atrial Fibrillation

Laurent Fauchier, MD,[a] Alexandre Cinaud, MD,[a] François Brigadeau, MD,[b] Antoine Lepillier, MD,[c] Bertrand Pierre, MD,[a] Selim Abbey, MD,[d] Marjaneh Fatemi, MD,[e] Frederic Franceschi, MD,[f] Paul Guedeney, MD,[g] Peggy Jacon, MD,[h] Olivier Paziaud, MD,[c] Sandrine Venier, MD,[h] Jean Claude Deharo, MD,[f] Daniel Gras, MD,[d] Didier Klug, MD,[b] Jacques Mansourati, MD,[e] Gilles Montalescot, MD,[g] Olivier Piot, MD,[c] Pascal Defaye, MD[h]

Real-world data

- Mean Follow-up 13 ± 13 months
- Thrombus on device was diagnosed with **8.3%** of the patients (TEE or CT scan)
- Mean time to thrombus detection was 3.1 ± 2.6 months

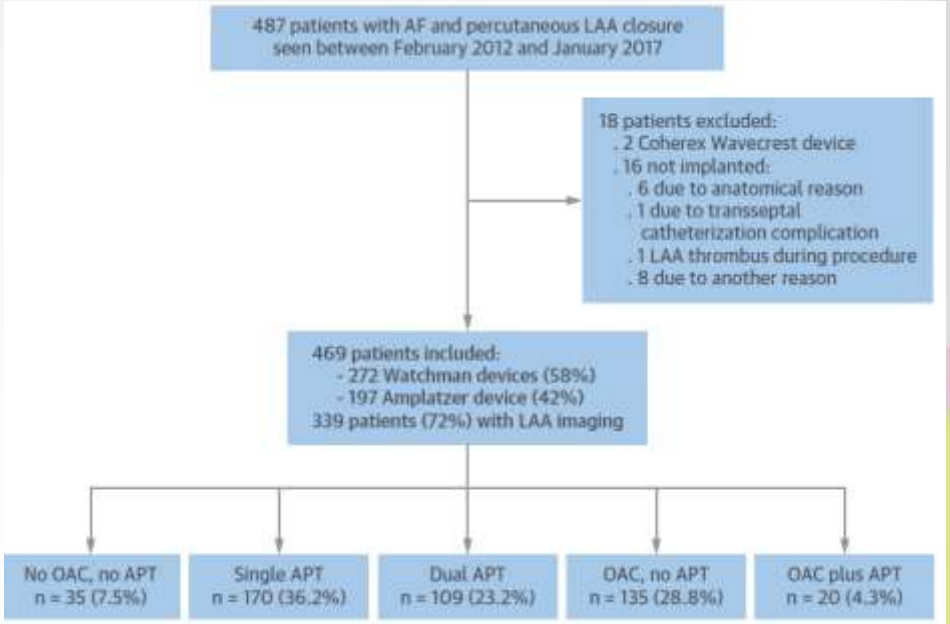


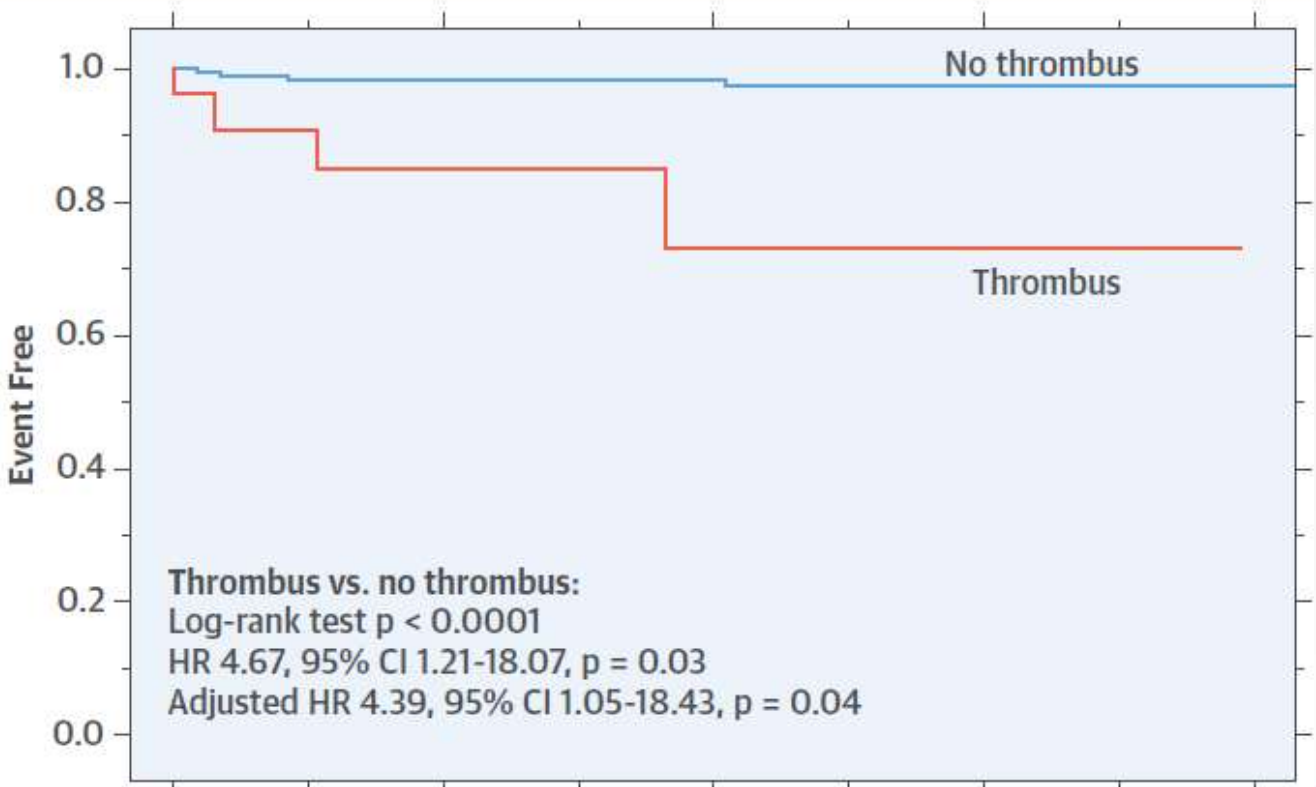
TABLE 4 Multivariable Analysis (Cox Regression Model) for Predictors of Thrombus Formation on the Device and Predictors of Stroke and TIA*

	HR (95% CI)	p Value
Thrombus formation on the device		
Age (per 1-yr increase)	1.07 (1.01–1.14)	0.02
Previous ischemic stroke	3.68 (1.17–11.62)	0.03
CHA_2DS_2-VASc score	0.69 (0.44–1.06)	0.09
APT at discharge	0.35 (0.12–1.04)	0.06
Dual APT at discharge	0.10 (0.01–0.76)	0.03
OAC at discharge	0.26 (0.09–0.77)	0.02
Strokes or TIAs		
Vascular disease	5.03 (1.39–18.23)	0.01
Thrombus on the device	4.39 (1.05–18.43)	0.04
CHA_2DS_2-VASc score	0.71 (0.47–1.06)	0.09
APT at discharge	1.35 (0.20–9.06)	0.75
Dual APT at discharge	0.64 (0.15–2.69)	0.54
OAC at discharge	0.39 (0.06–2.61)	0.33

CVRF

Fauchier et al, J Am Coll Cardiol. 2018 Apr 10;71(14):1528-1536

Ischemic Stroke / Transient Ischemic Attack



N at risk					
No thrombus	300	100	72	62	39
Thrombus	25	12	6	2	0

Fauchier et al, J Am Coll Cardiol. 2018 Apr 10;71(14):1528-1536

WIN-TAVI Registry

JACC: CARDIOVASCULAR INTERVENTIONS

1-Year Clinical Outcomes in Women After Transcatheter Aortic Valve Replacement

Results From the First WIN-TAVI Registry

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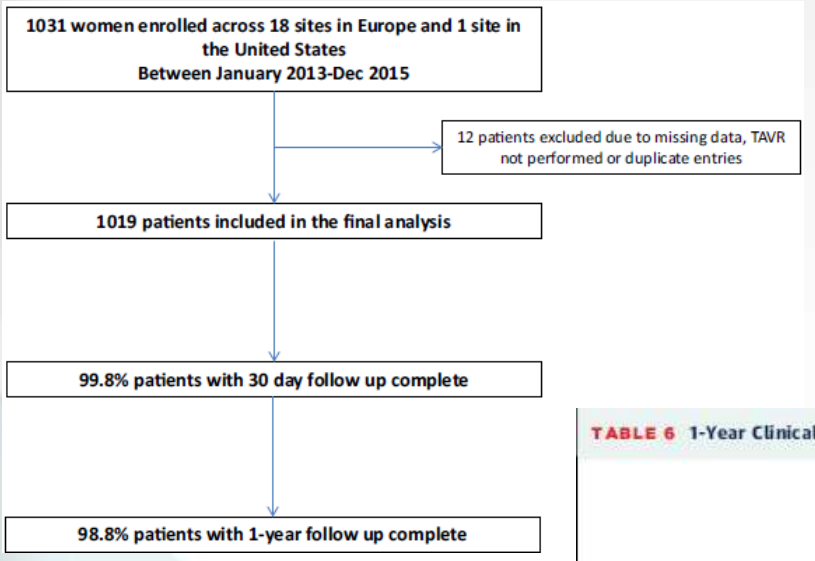


TABLE 3 Predictors of 1-Year Death or Stroke

	Univariate Associations		Multivariate Associations	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.03 (1.00-1.06)	0.031	1.03 (0.99-1.06)	0.126
BMI, kg/m^2	0.97 (0.94-1.00)	0.11		
Prior stroke	1.54 (0.90-2.64)	0.11		
Prior PCI or CABG	1.38 (0.96-1.99)	0.082	1.50 (1.03-2.19)	0.035
Prior MI	1.41 (0.86-2.31)	0.17		
Baseline PAD	1.56 (0.96-2.52)	0.073		
Baseline atrial fibrillation	1.64 (1.13-2.37)	0.10	1.58 (1.07-2.33)	0.022
LVEF <30%	1.02 (0.42-2.49)	0.97		
EuroSCORE I	1.03 (1.01-1.05)	<0.001	1.02 (1.00-1.04)	0.013
Baseline renal dysfunction	1.30 (0.92-1.83)	0.14		
Diabetes	0.88 (0.60-1.30)	0.53		
Frailty	0.88 (0.62-1.23)	0.44		
Discharge DAPT	0.77 (0.52-1.13)	0.18		
Discharge anticoagulant	1.54 (1.03-2.29)	0.034		
Procedure-related variables				
TAVR device generation (new vs. old)	0.88 (0.62-1.24)	0.46		
Access (transfemoral vs. nontransfemoral)	1.06 (0.61-1.83)	0.85		
Device size (>26 mm vs. ≤26 mm)	1.32 (0.88-1.96)	0.18		
Moderate or severe post-TAVR AI	1.09 (0.68-1.75)	0.73		
Female-specific characteristics				
History of pregnancy	0.71 (0.50-1.00)	0.050	0.73 (0.50-1.06)	0.097
Age of menopause	1.02 (0.98-1.06)	0.32		
History of osteoporosis	0.91 (0.58-1.43)	0.69		

TABLE 6 1-Year Clinical Outcomes in Patients With and Without History of Pregnancy

	0-30 Days			0-1 Years		
	History of Pregnancy (n = 738)	No History of Pregnancy (n = 281)	p Value	History of Pregnancy (n = 738)	No History of Pregnancy (n = 281)	p Value
VARC-2 efficacy endpoint*	35 (4.7)	21 (7.5)	0.10	116 (15.8)	51 (18.4)	0.28
Secondary endpoints						
All-cause death	25 (3.4)	15 (5.3)	0.08	84 (11.4)	43 (15.5)	0.075
Stroke	5 (0.7)	7 (2.5)	0.79	12 (1.8)	10 (3.6)	0.054
Composite of death or stroke	29 (3.9)	20 (7.1)	0.14	94 (12.6)	48 (17.3)	0.049
Composite of death, MI, or stroke	30 (4.1)	20 (7.1)	0.12	102 (13.9)	48 (17.3)	0.13
Death, MI, stroke, or VARC life-threatening bleeding	49 (6.6)	26 (9.3)	0.13	119 (16.2)	53 (19.1)	0.25

Chieffo et al, JACC Cardiovasc Inter. 2018 Jan 8;11(1):1-12

Ongoing trials

TWILIGHT trial met its milestones!

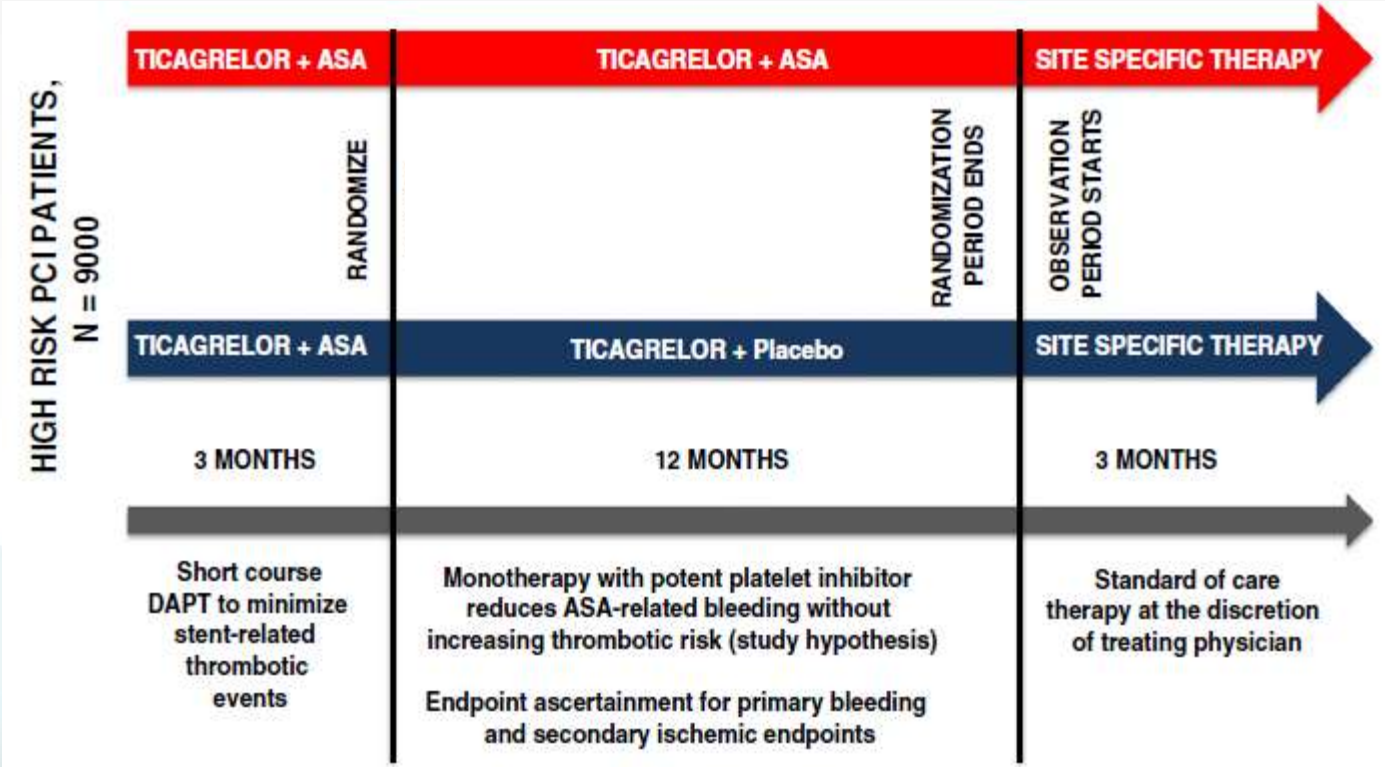
Inclusion criteria

Clinical criteria (Must meet at least one)
- Adult patients ≥65 years of age
- Female gender
- Troponin positive acute coronary syndrome
- Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization
- Diabetes mellitus treated with medications (oral hypoglycemic therapy or subcutaneous insulin)
- Chronic kidney disease defined as an estimated glomerular filtration rate< 60 mL/min per 1.73m^2 or creatinine clearance <60 mL/min

Angiographic criteria (Must meet at least one)
- Multivessel coronary artery disease
- Target lesion requiring total stent length> 30 mm
- Thrombotic target lesion
- Bifurcation lesions with Medina X,1,1 classification requiring at least 2 stents
- Left main (≥50%) or proximal LAD (≥70%) lesion
- Calcified target lesion(s) requiring atherectomy

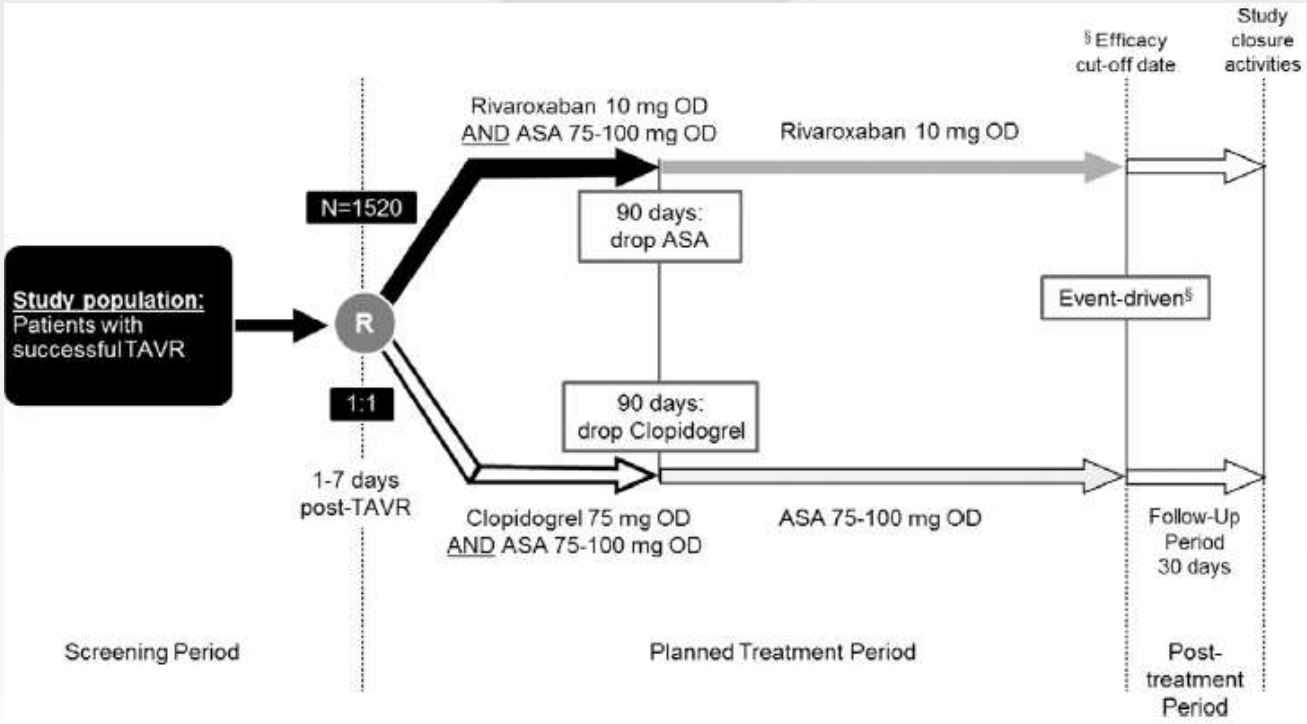
Primary endpoint:
- Clinically relevant bleeding (≥BARC 2)

Key secondary endpoint:
- Composite of death, MI or stroke



Baber et al, Am Heart J. 2016 Dec; 182:125-134

NOAC after successful TAVR in patients without AF



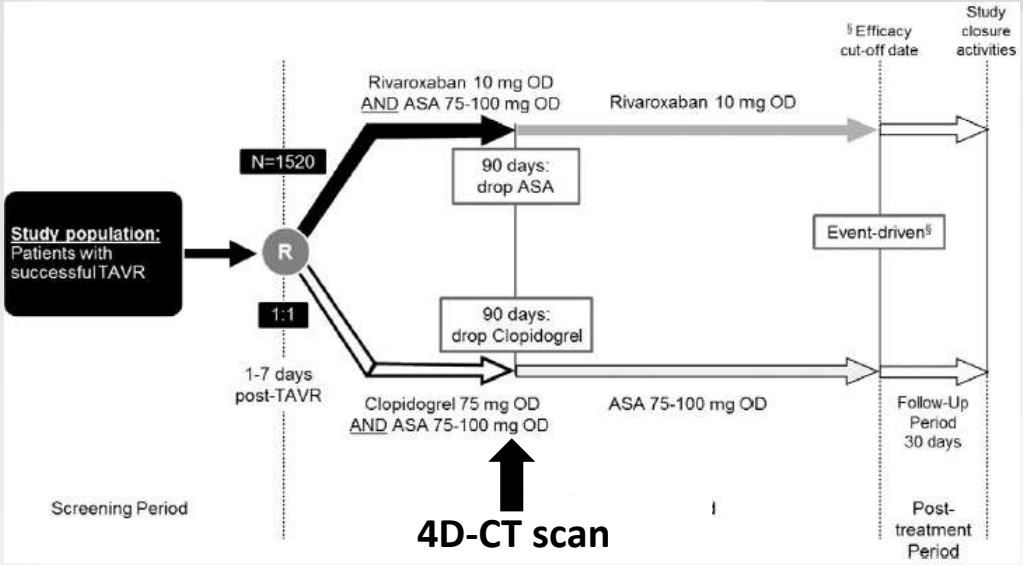
Primary efficacy endpoint

Composite of death, stroke, MI, symptomatic valve thrombosis, PE, DVT and non-central nervous system embolism

Primary safety endpoint: Bleeding events

- TIMI major and minor bleeding
- ISTH major bleeding
- BARC 2 or more

NOAC after successful TAVR in patients without AF



GALILEO 4D

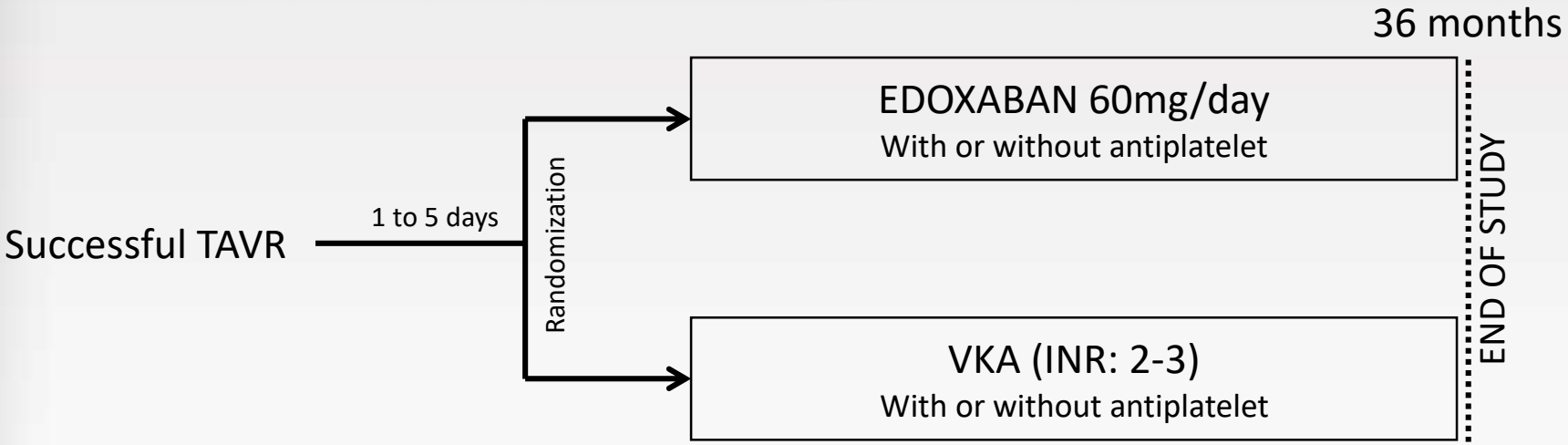
— Substudy of the GALILEO trial —

4D computed tomography scanner 3 months after TAVR with 300 patients

- Detection of prosthetic leaflet thrombosis
  - >50% motion reduction (primary endpoint)
  - Hypoattenuated leaflet thickening (secondary endpoint)

NOAC after successful TAVR in patients with AF

ENVISAGE-TAVI AF



Primary efficacy endpoint

- Composite of death, stroke, MI, ischemic stroke, systemic embolism event, valve thrombosis and ISTH major bleeding

Primary safety endpoint

- ISTH major bleeding