Antiplatelet Therapy

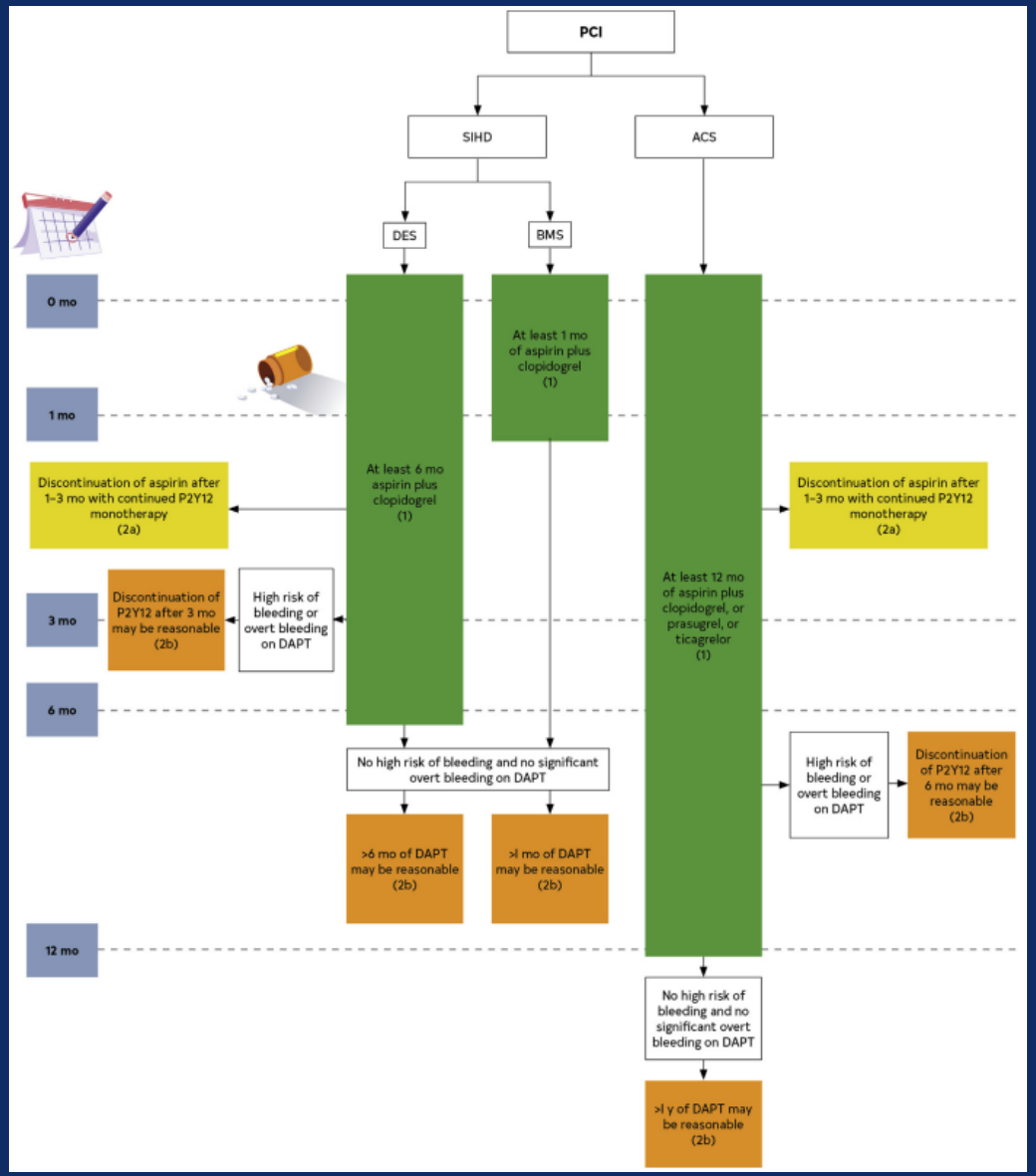
Antiplatelet therapy

Recommendations for Aspirin and Oral P2Y12 Inhibitors in Patients Undergoing PCI
Referenced studies that support the recommendations are summarized in Online Data Supplement 32.

COR	LOE	RECOMMENDATIONS
1	B-R	1. In patients undergoing PCI, a loading dose of aspirin, followed by daily dosing, is recommended to reduce ischemic events (1-4).*
1	B-R	2. In patients with ACS undergoing PCI, a loading dose of P2Y12 inhibitor, followed by daily dosing, is recommended to reduce ischemic events (5-15).
1	C-LD	3. In patients with SIHD undergoing PCI, a loading dose of clopidogrel, followed by daily dosing, is recommended to reduce ischemic events (8,12,15-19).
1	C-LD	4. In patients undergoing PCI within 24 hours after fibrinolytic therapy, a loading dose of 300 mg of clopidogrel, followed by daily dosing, is recommended to reduce ischemic events (5).
2a	B-R	5. In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis (6,14,20).
2b	B-R	6. In patients <75 years of age undergoing PCI within 24 hours after fibrinolytic therapy, ticagrelor may be a reasonable alternative to clopidogrel to reduce ischemic events (21).
3: Harm	B-R	7. In patients undergoing PCI who have a history of stroke or transient ischemic attack, prasugrel should not be administered (6).

Lawton et al. 2021 ACC/AHA/SCAI Coronary Revascularization Guideline

Antiplatelet therapy

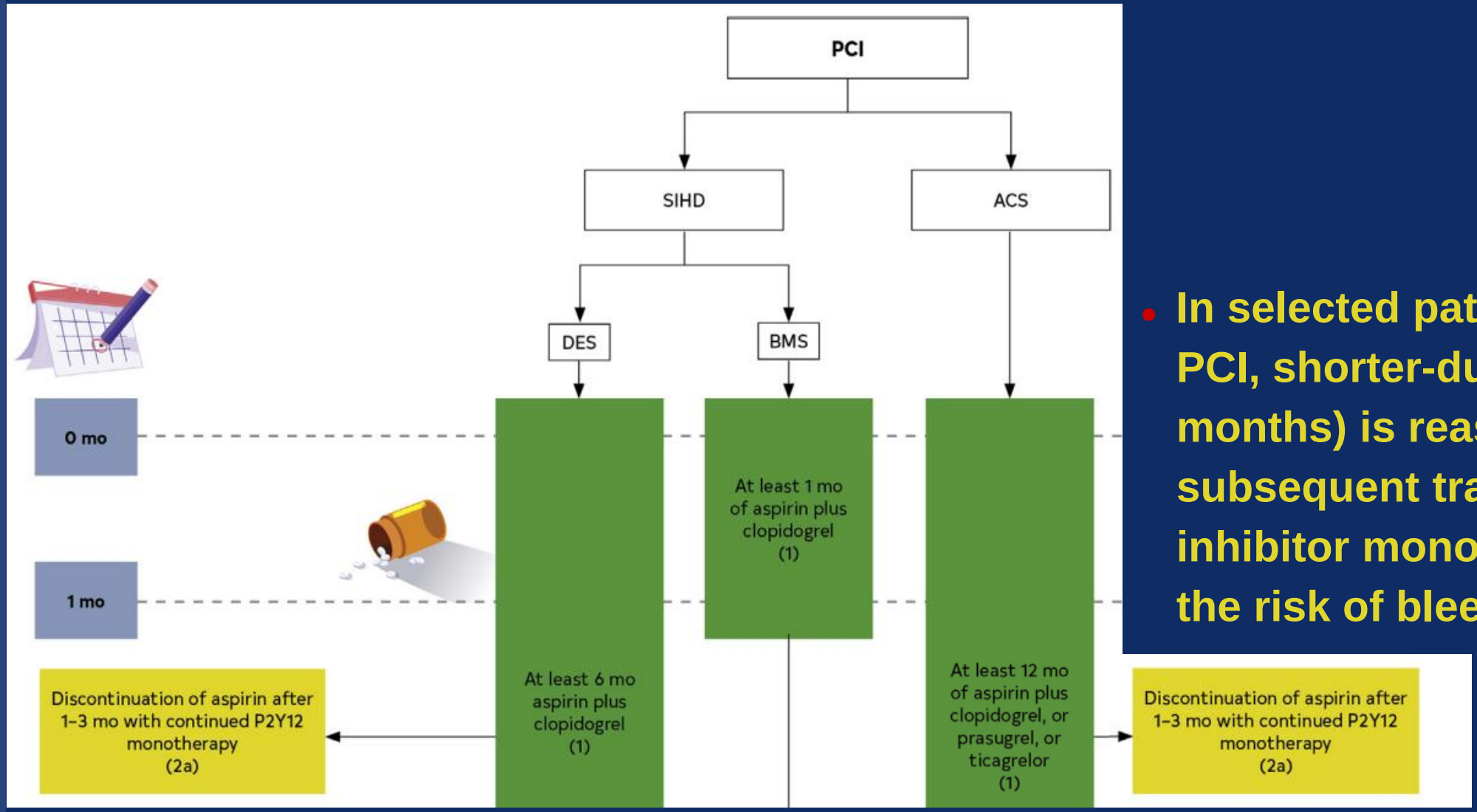


- In selected patients undergoing PCI, shorter-duration DAPT (1-3 months) is reasonable, with subsequent trasition to P2Y12 inhibitor monotherapy to reduce the risk of bleeding events (2a).

- In patients undergoing PCI, discontinuation of P2Y12 after 3mo (SIHD) or 6mo (ACS) may be reasonable (2b).

Lawton et al. 2021 ACC/AHA/SCAI Coronary Revascularization Guideline

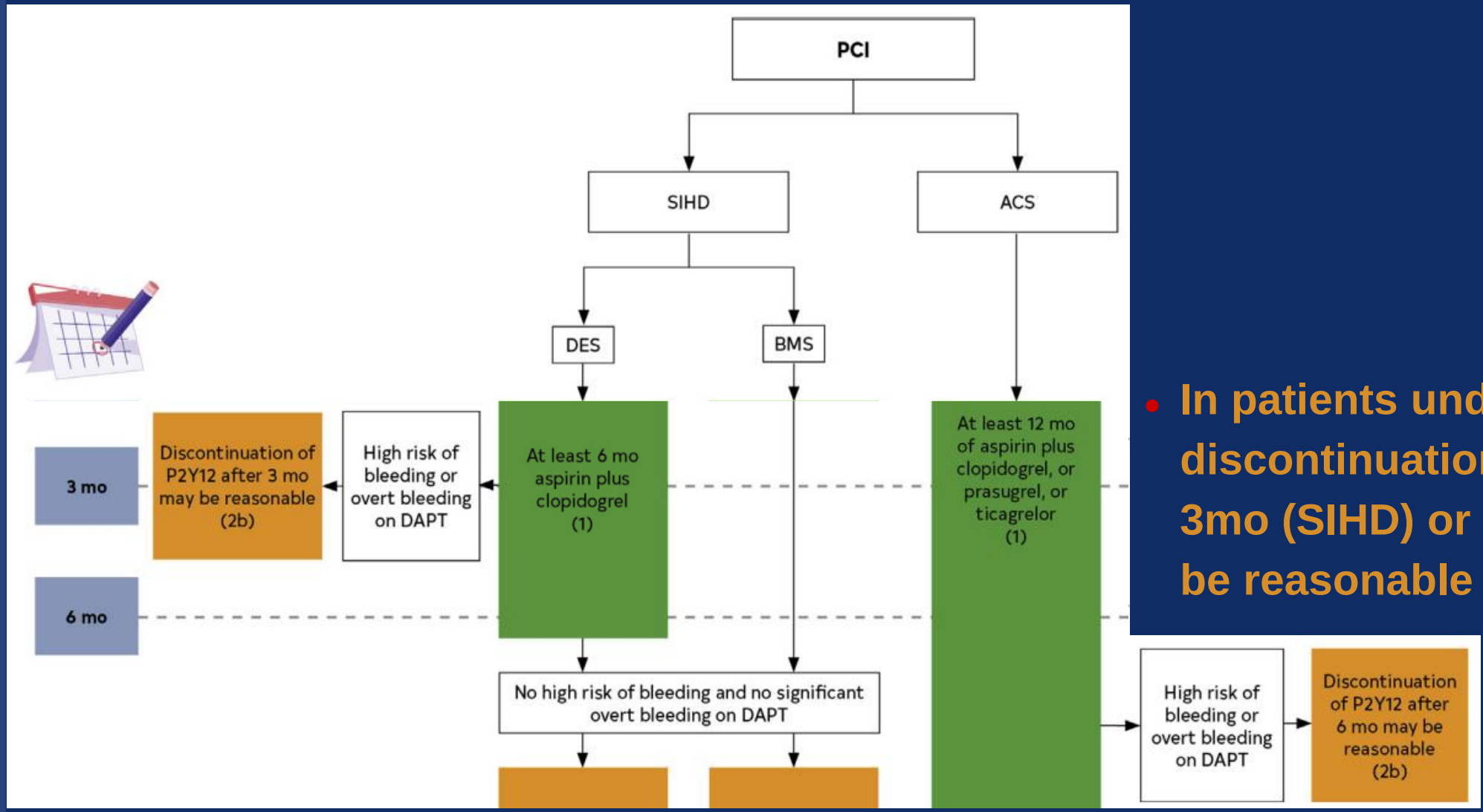
Antiplatelet therapy



- **In selected patients undergoing PCI, shorter-duration DAPT (1-3 months) is reasonable, with subsequent trasition to P2Y12 inhibitor monotherapy to reduce the risk of bleeding events (2a).**

Lawton et al. 2021 ACC/AHA/SCAI Coronary Revascularization Guideline

Antiplatelet therapy

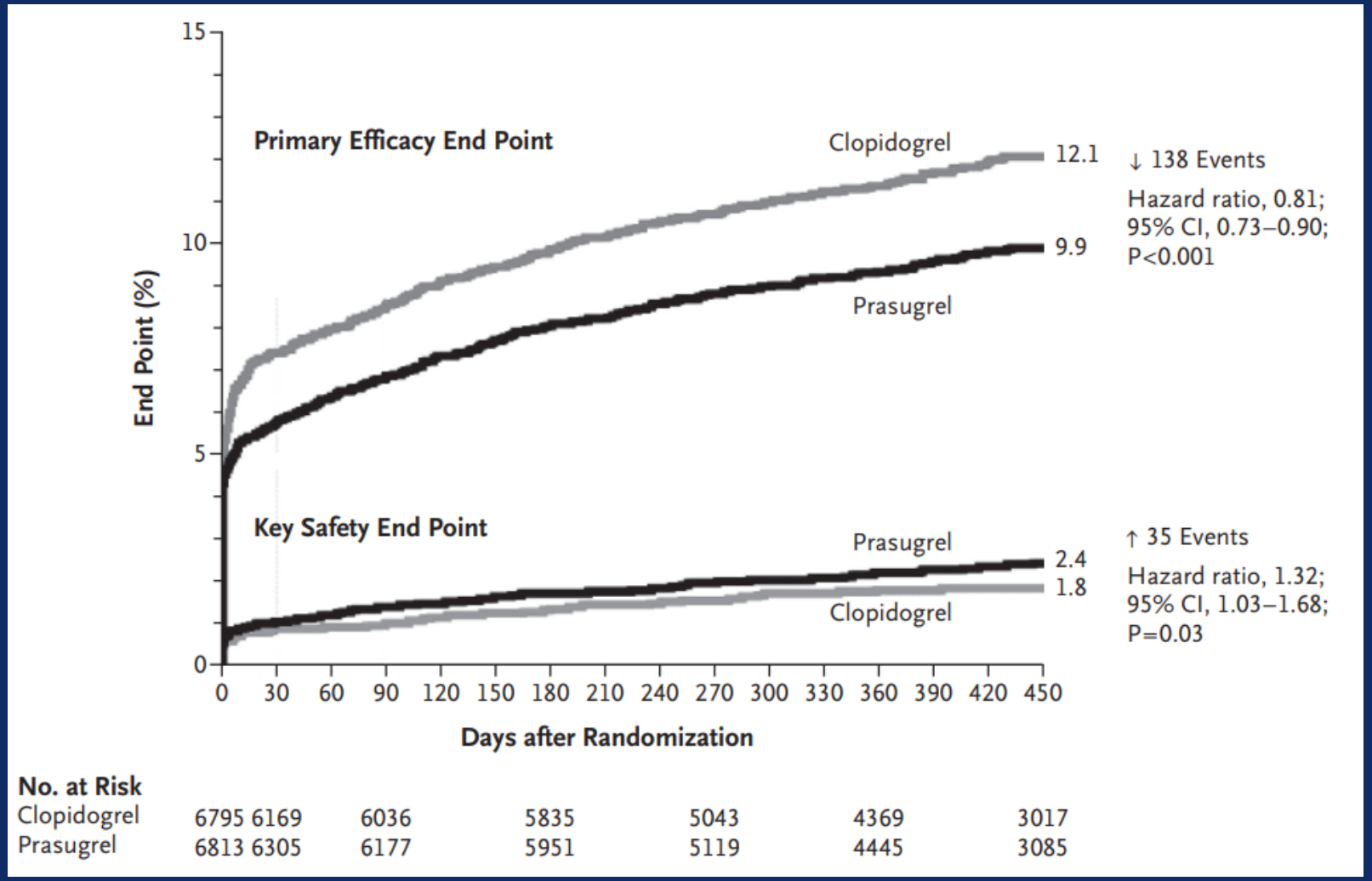


- In patients undergoing PCI, discontinuation of P2Y12 after 3mo (SIHD) or 6mo (ACS) may be reasonable (2b).

Lawton et al. 2021 ACC/AHA/SCAI Coronary Revascularization Guideline

TRITON-TIMI 38 Trial

Prasugrel vs. Clopidogrel in patients with ACS



- The primary efficacy end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
- The key safety end point was major bleeding.

Stephen D. Wiviott et al. N Engl J Med. 2007;357:2001-15.

TRITON-TIMI 38 Trial

Prasugrel vs. Clopidogrel in patients with ACS

Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

Stephen D. Wiviott et al. N Engl J Med. 2007;357:2001-15.

TRITON-TIMI 38 Trial

Prasugrel vs. Clopidogrel in patients with ACS

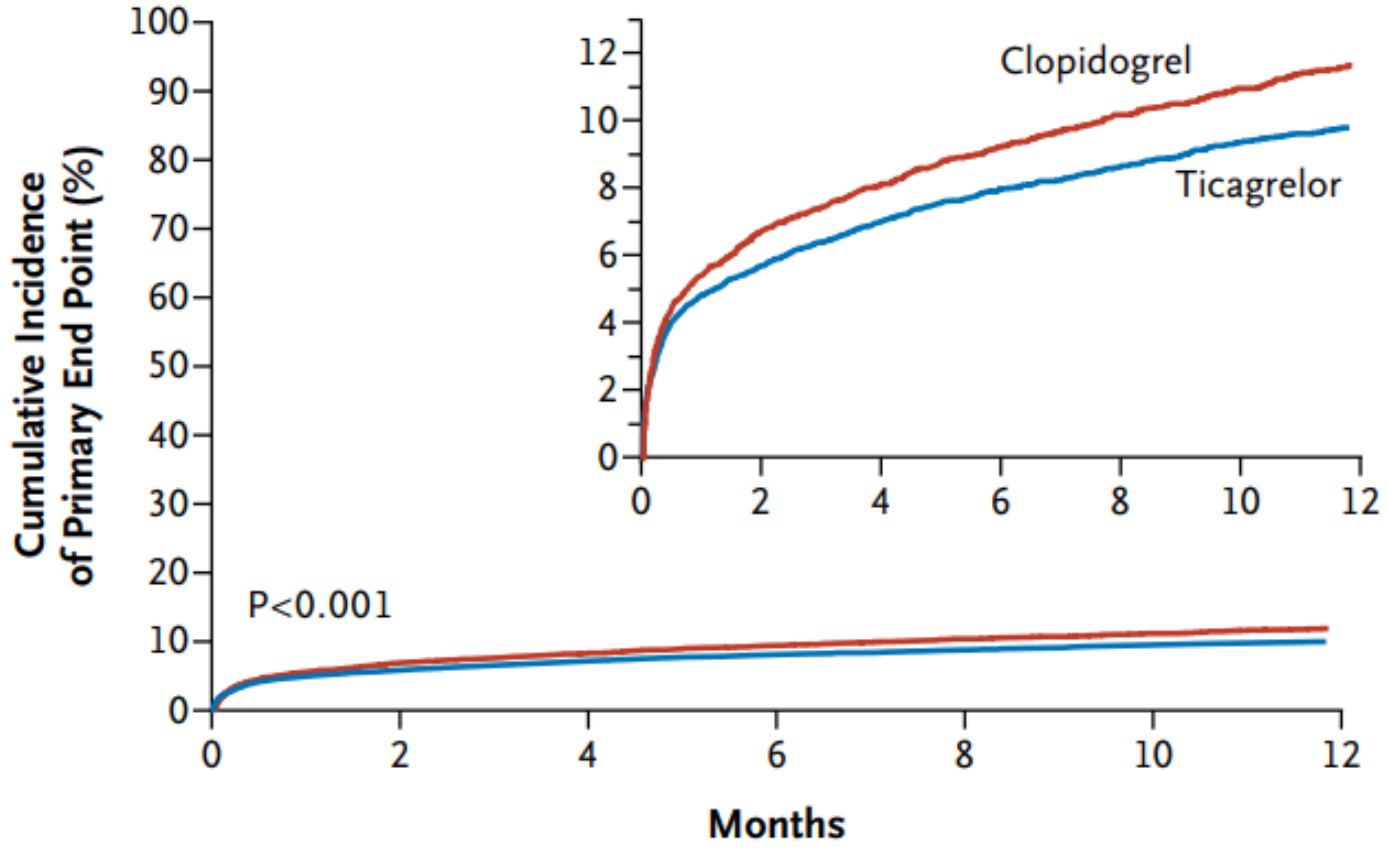
Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

Stephen D. Wiviott et al. N Engl J Med. 2007;357:2001-15.

PLATO Trial

Ticagrelor vs. Clopidogrel in patients with ACS



No. at Risk

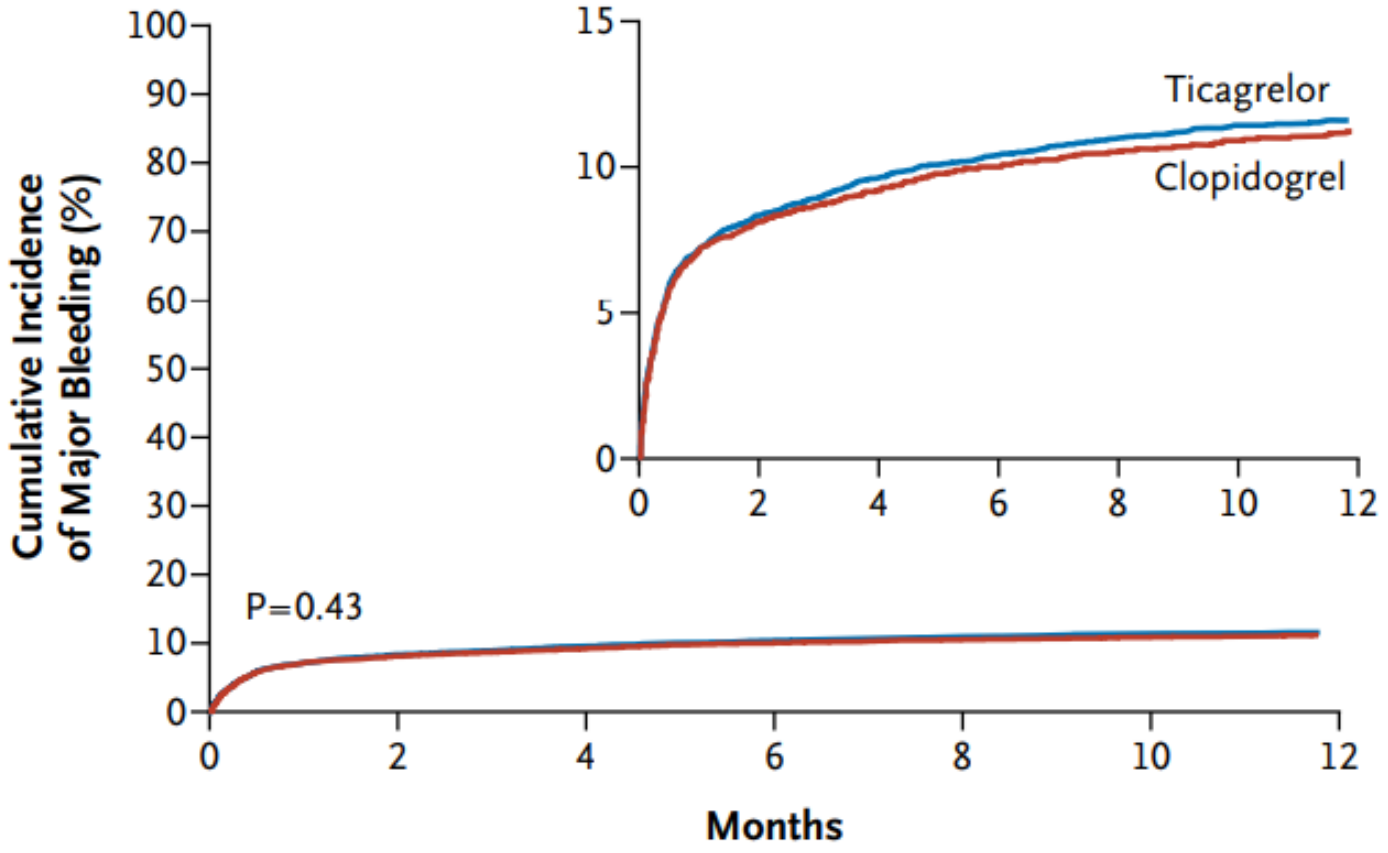
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

- **The primary end point - a composite of death from vascular causes, myocardial infarction, or stroke – occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7% at 12months; hazard ratio, 0.84; 95% confidence interval, 0.77 to 0.92; P<0.001).**

Lars Wallentin et al. N Engl J Med. 2009;361:1045-57.

PLATO Trial

Ticagrelor vs. Clopidogrel in patients with ACS



No. at Risk

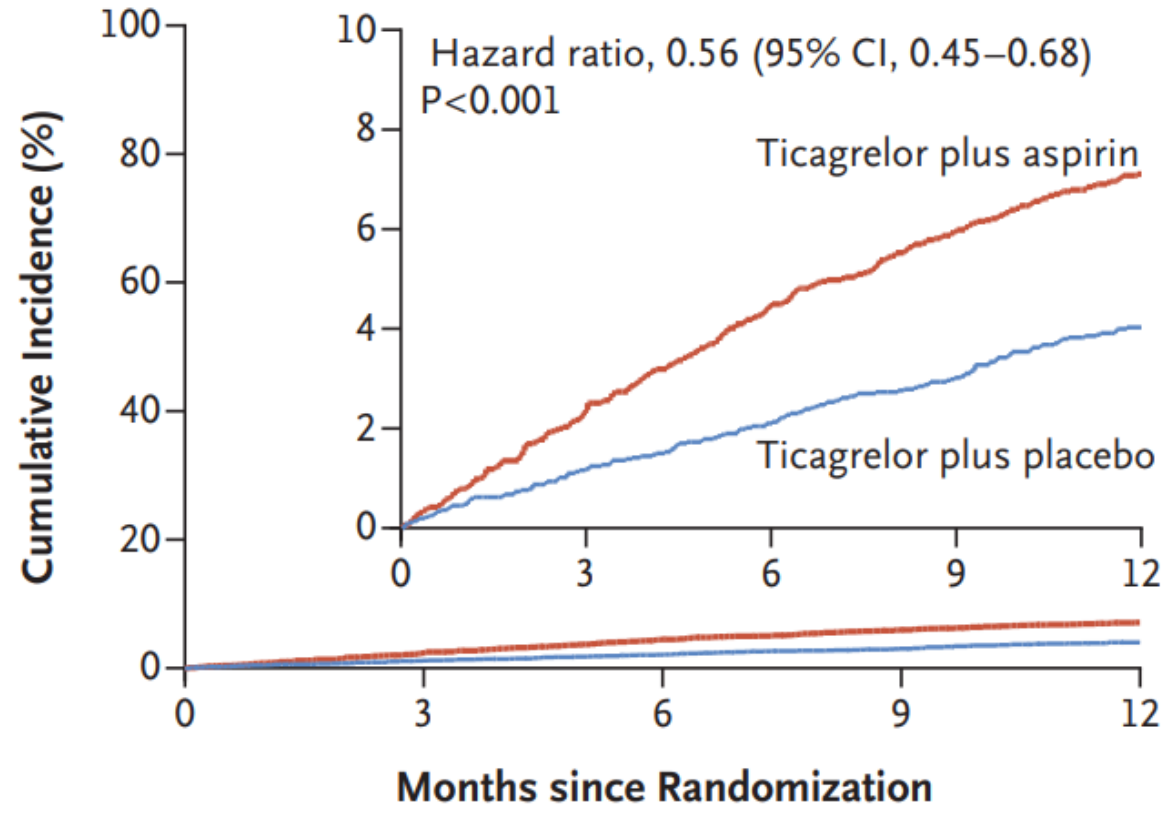
Ticagrelor	9235	7246	6826	6545	5129	3783	3433
Clopidogrel	9186	7305	6930	6670	5209	3841	3479

- The time was estimated from the first dose of the study drug in the safety population. The hazard ratio for major bleeding, defined according to the study criteria, for the ticagrelor group as compared with the clopidogrel group was 1.04 (95% confidence interval, 0.95 to 1.13).

Lars Wallentin et al. N Engl J Med. 2009;361:1045-57.

TWILIGHT Trial

Ticagrelor with or without Aspirin in High-Risk patients after PCI



No. at Risk

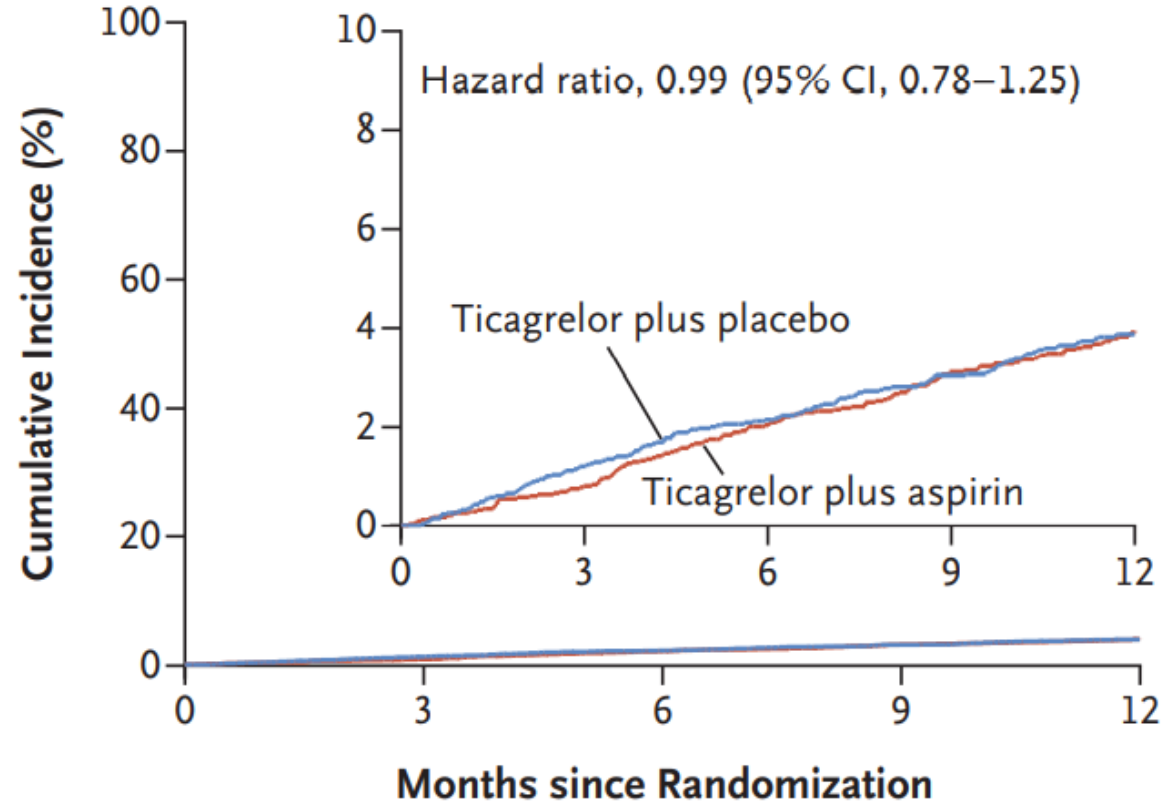
Ticagrelor plus aspirin	3564	3454	3357	3277	3213
Ticagrelor plus placebo	3555	3474	3424	3366	3321

- **Kaplan-Meier Estimates of the Incidence of BARC Type 2, 3, or 5 Bleeding 1 Year**
- **The hazard ratio shown is for ticagrelor plus placebo versus ticagrelor plus aspirin. Bleeding Academic Research Consortium (BARC) types range from 0 (no bleeding) to 5 (fatal bleeding).**

R. Mehran, U. Baber et al. N Engl J Med. 2019;381:2032-42.

TWILIGHT Trial

Ticagrelor with or without Aspirin in High-Risk patients after PCI



No. at Risk

Ticagrelor plus aspirin	3515	3466	3415	3361	3320
Ticagrelor plus placebo	3524	3457	3412	3365	3330

- **Kaplan-Meier Estimates of the Incidence of Death from Any Cause, Nonfatal MI, or Nonfatal Stroke 1 Year**
- **The per-protocol population included patients who underwent randomization and had no major deviations from the protocol. The hazard ratio shown is for ticarelor plus placebo versus ticarelor plus aspirin.**

R. Mehran, U. Baber et al. N Engl J Med. 2019;381:2032-42.

TWILIGHT Trial

Ticagrelor with or without Aspirin in High-Risk patients after PCI

Table 2. Bleeding and Ischemic Events 1 Year after Randomization.*

Variable	Ticagrelor plus Placebo (N=3555)	Ticagrelor plus Aspirin (N=3564)	Hazard Ratio (95% CI)†	P Value
	no. of patients (%)‡			
Bleeding end points				
Primary end point: BARC type 2, 3, or 5§	141 (4.0)	250 (7.1)	0.56 (0.45–0.68)	<0.001¶
BARC type 3 or 5§	34 (1.0)	69 (2.0)	0.49 (0.33–0.74)	
TIMI minor or major	141 (4.0)	250 (7.1)	0.56 (0.45–0.68)	
GUSTO moderate or severe	26 (0.7)	49 (1.4)	0.53 (0.33–0.85)	
ISTH major	39 (1.1)	72 (2.1)	0.54 (0.37–0.80)	
Ischemic end points				
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	135 (3.9)	137 (3.9)	0.99 (0.78–1.25)	<0.001‖
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal ischemic stroke	126 (3.6)	130 (3.7)	0.97 (0.76–1.24)	
Death from any cause	34 (1.0)	45 (1.3)	0.75 (0.48–1.18)	
Death from cardiovascular causes	26 (0.8)	37 (1.1)	0.70 (0.43–1.16)	
Myocardial infarction	95 (2.7)	95 (2.7)	1.00 (0.75–1.33)	
Ischemic stroke	16 (0.5)	8 (0.2)	2.00 (0.86–4.67)	
Stent thrombosis, definite or probable	14 (0.4)	19 (0.6)	0.74 (0.37–1.47)	

- **Among high-risk patients who underwent PCI and completed 3 months of dual antiplatelet therapy, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, with no higher risk of death, myocardial infarction, or stroke.**

R. Mehran, U. Baber et al. N Engl J Med. 2019;381:2032-42.

DAPT Duration After Implantation of DES

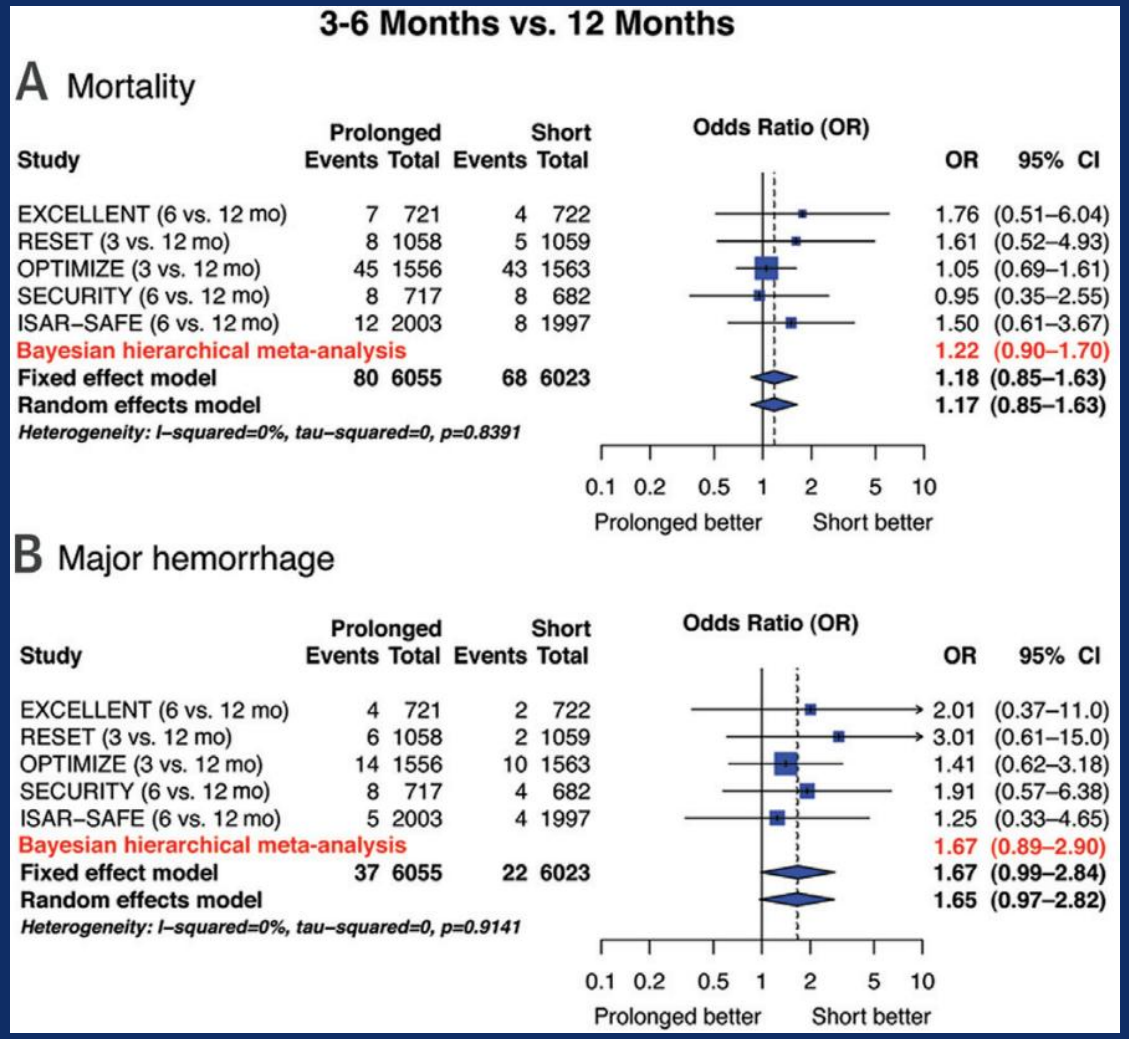
DAPT Duration After Implantation of DES

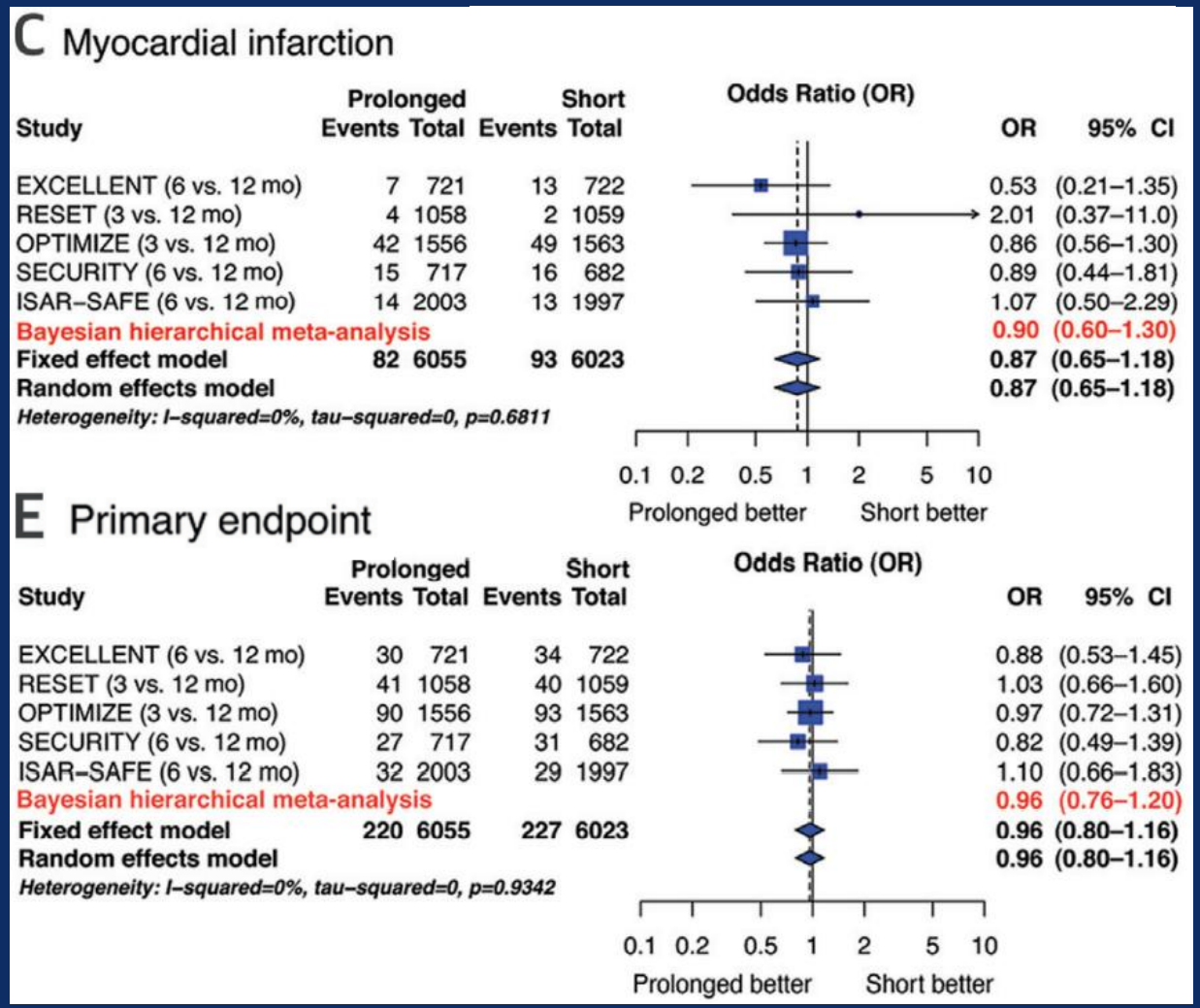
Study	Year*	Trial Completion	Primary Study Endpoint	Trial Design and Outcome	Expected Event Rate in Control Group (%)	Observed Event Rate in Control Group (%)	Proportion With Newer-Generation DES (%)
DES LATE (12 vs. 36 mo) (13)	2010	Extension of ZEST-LATE and REAL-LATE (12)	Cardiac death, MI, or stroke <24 h	Superiority not shown	2.7	2.6	30
PRODIGY (6 vs. 24 mo) (14,15)	2012	Enrollment completed	Death, MI, or stroke	Superiority not shown	8.0	10.1	67
EXCELLENT (6 vs. 12 mo) (16)	2012	Enrollment completed	Cardiac death, MI, or ischemia-driven TVR	Noninferiority confirmed	10.0	4.5	75
RESET (3 vs. 12 mo) (17)	2012	Enrollment completed	Cardiac death, MI, ST, revasc, or bleeding	Noninferiority confirmed	10.5	4.7	85
OPTIMIZE (3 vs. 12 mo) (18)	2013	Enrollment completed	NACCE-death, MI, stroke, or bleed	Noninferiority confirmed	9.0	6.0	100
ARCTIC Interruption (12 vs. 18 mo) (19)	2014	Extension of ARCTIC (39)	Death, MI, ST, stroke, or urgent TVR	Superiority not shown	6.0	4.0	63
SECURITY (6 vs. 12 mo) (20)	2014	Stopped after 1,399 enrolled of 2,740 planned	Cardiac death, MI, ST, or stroke	Noninferiority confirmed	4.5	4.5	100
ITALIC (6 vs. 24 mo) (21)	2015	Stopped after 2,031 enrolled of 2,475 planned	Death, MI, urgent TVR, stroke, or major bleeding	Noninferiority confirmed	3.0	1.5	100
ISAR-SAFE (6 vs. 12 mo) (22)	2015	Stopped after 4,005 enrolled of 6,000 planned	Death, MI, ST, stroke, or TIMI major bleed	Noninferiority confirmed	10.0	1.5	72
DAPT (12 vs. 30 mo) (23)	2015	Enrollment completed	Coprimary: ST and MACCE	Superiority shown	0.5/2.9	0.5/2.4	59
OPTIDUAL (12 vs. 48 mo) (24)	2015	Stopped after 1,385 enrolled of 1,966 planned	Death, MI, stroke, or major bleed	Superiority not shown	7.0	7.5	59

Bittl et al. J Am Coll Cardiol. 2016 Sep 6;68(10):1116-39.

DAPT Duration After Implantation of DES

Forest Plot of Endpoints After 12 Months Versus Shorter Courses





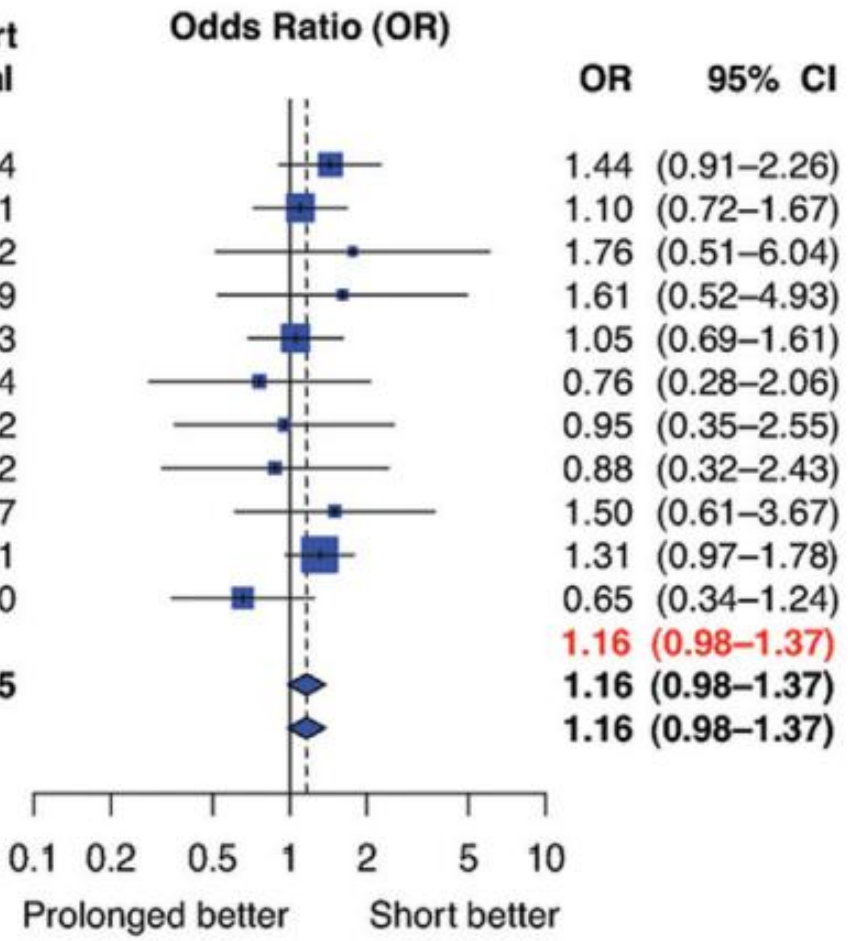
Bittl et al. J Am Coll Cardiol. 2016 Sep 6;68(10):1116-39.

DAPT Duration After Implantation of DES

FIGURE 3 Forest Plot of Mortality Rates in 11 RCTs After Stent Implantation

Study	Prolonged Events	Prolonged Total	Short Events	Short Total	OR	95% CI
DES–LATE (12 vs. 36 mo)	46	2531	32	2514	1.44	(0.91–2.26)
PRODIGY (6 vs. 24 mo)	49	750	45	751	1.10	(0.72–1.67)
EXCELLENT (6 vs. 12 mo)	7	721	4	722	1.76	(0.51–6.04)
RESET (3 vs. 12 mo)	8	1058	5	1059	1.61	(0.52–4.93)
OPTIMIZE (3 vs. 12 mo)	45	1556	43	1563	1.05	(0.69–1.61)
ARCTIC (12 vs. 18 mo)	7	635	9	624	0.76	(0.28–2.06)
SECURITY (6 vs. 12 mo)	8	717	8	682	0.95	(0.35–2.55)
ITALIC (6 vs. 24 mo)	7	910	8	912	0.88	(0.32–2.43)
ISAR–SAFE (6 vs. 12 mo)	12	2003	8	1997	1.50	(0.61–3.67)
DAPT (12 vs. 30 mo)	98	5020	74	4941	1.31	(0.97–1.78)
OPTIDUAL (12 vs. 48 mo)	16	695	24	690	0.65	(0.34–1.24)
Bayesian hierarchical meta-analysis					1.16	(0.98–1.37)
Fixed effect model	**303**	**16596**	**260**	**16455**	**1.16**	**(0.98–1.37)**
Random effects model					**1.16**	**(0.98–1.37)**

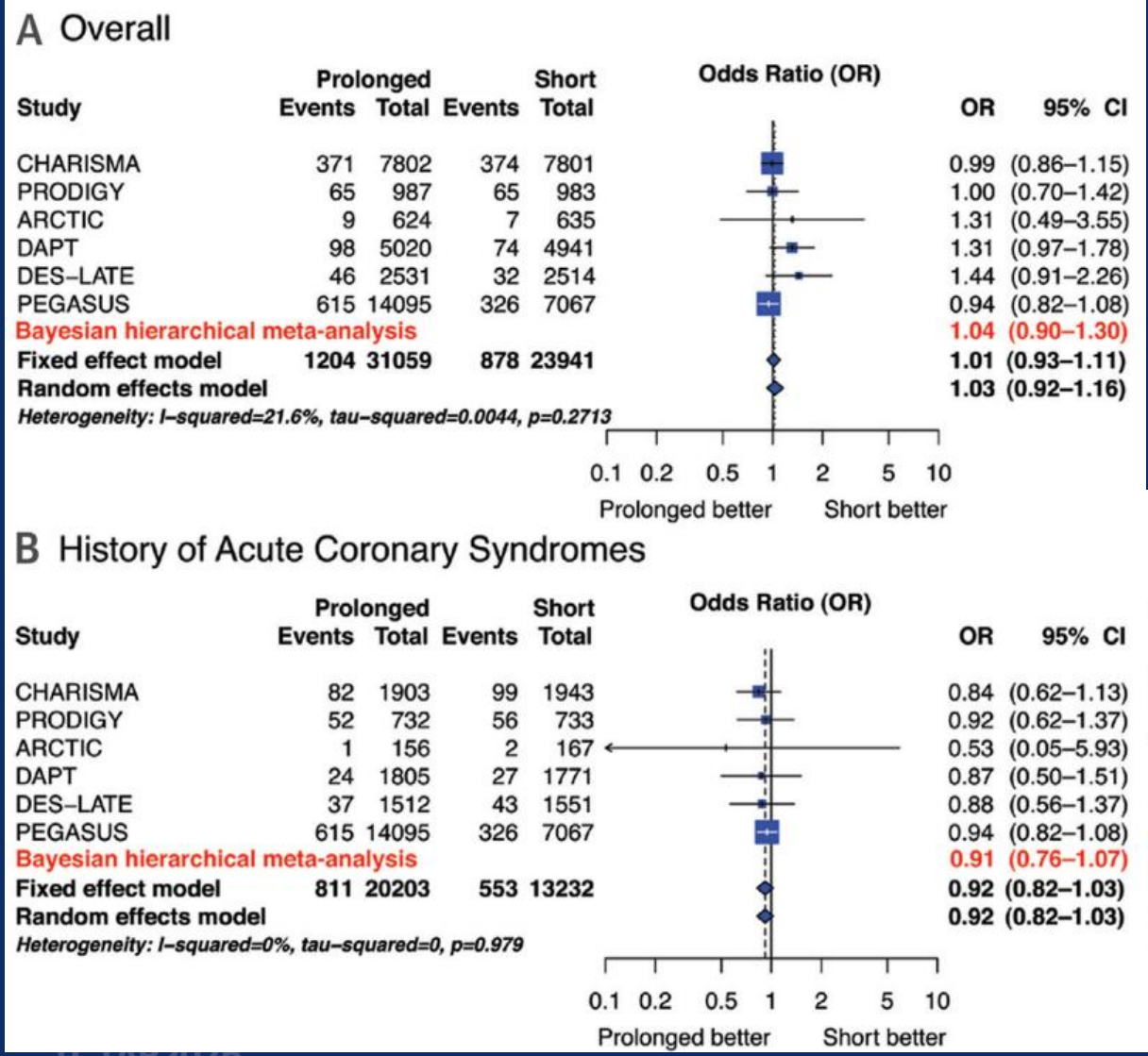
Heterogeneity: I–squared=0%, tau–squared=0, p=0.725

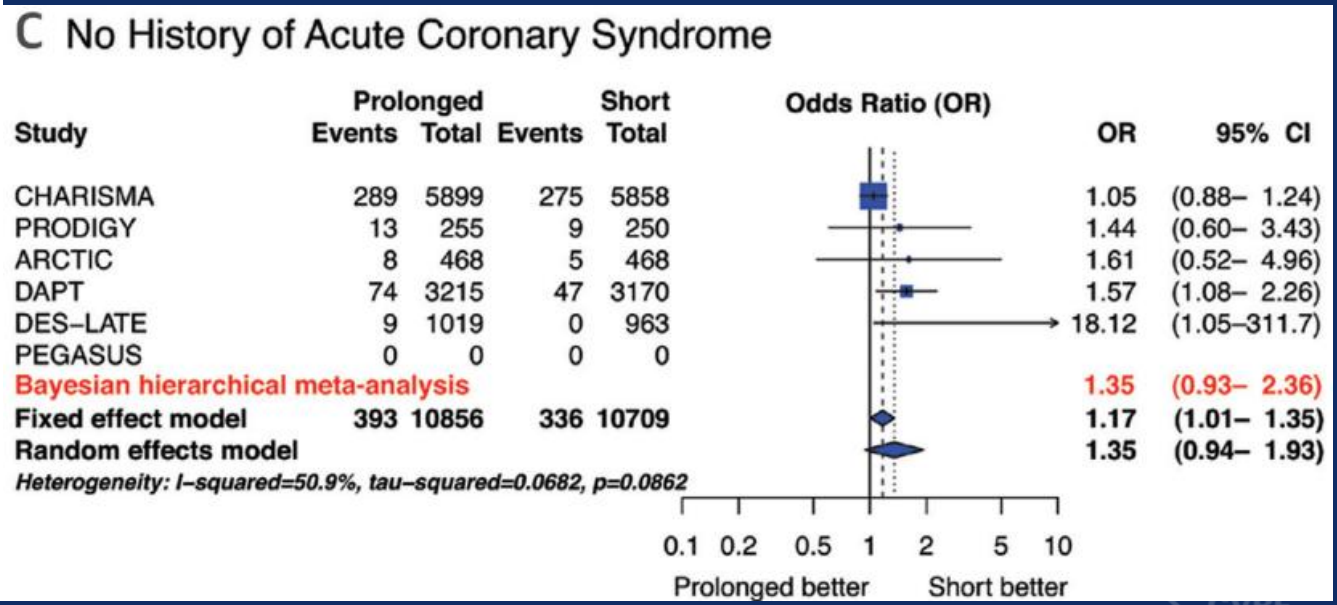


Bittl et al. J Am Coll Cardiol. 2016 Sep 6;68(10):1116-39.

DAPT Duration After Implantation of DES

All-Cause Mortality Rate in All Patients (A) and in Those With (B) and Without (C) A Prior History of ACS

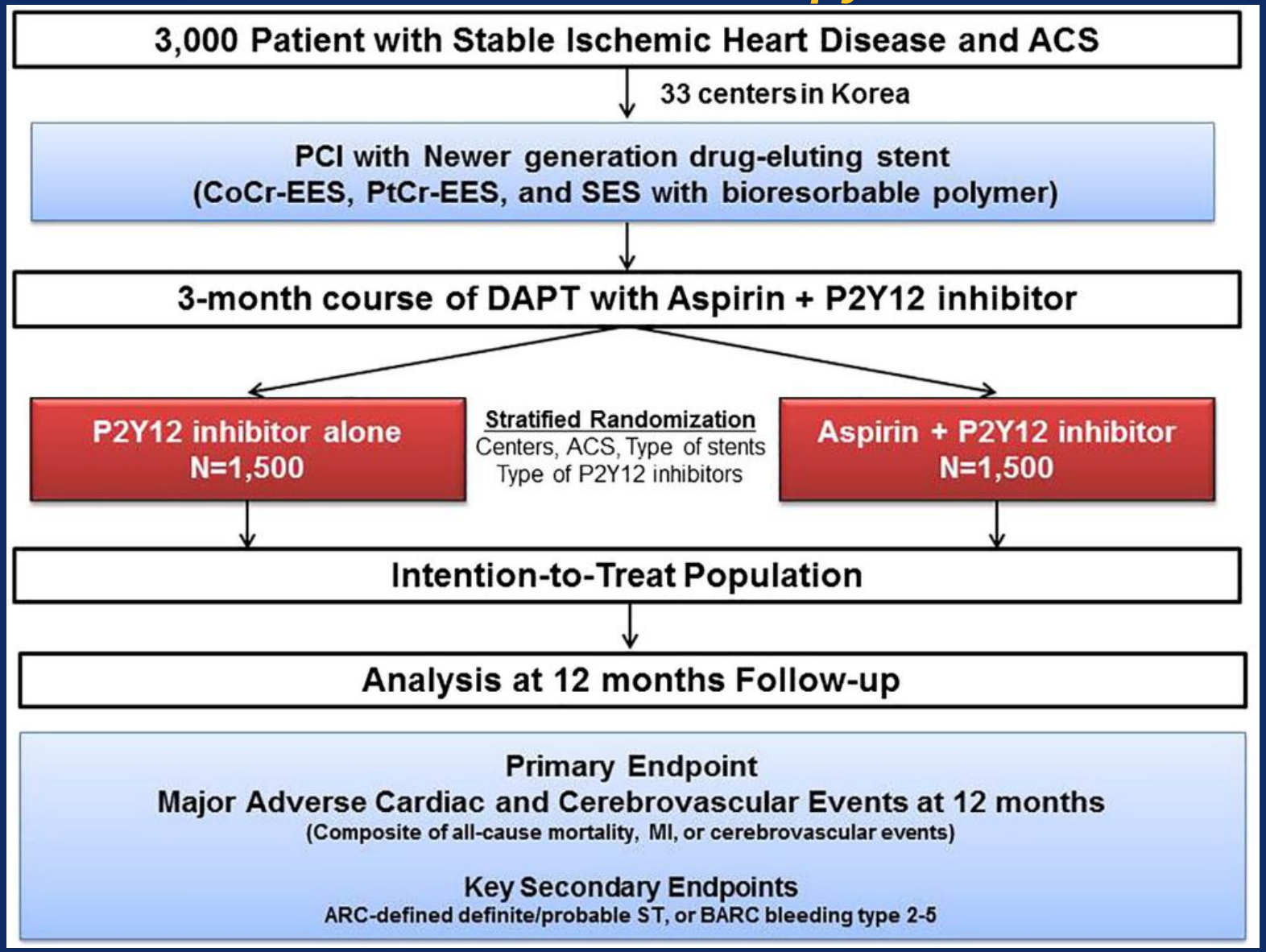




Bittl et al. J Am Coll Cardiol. 2016 Sep 6;68(10):1116-39.

SMART-CHOICE Trial

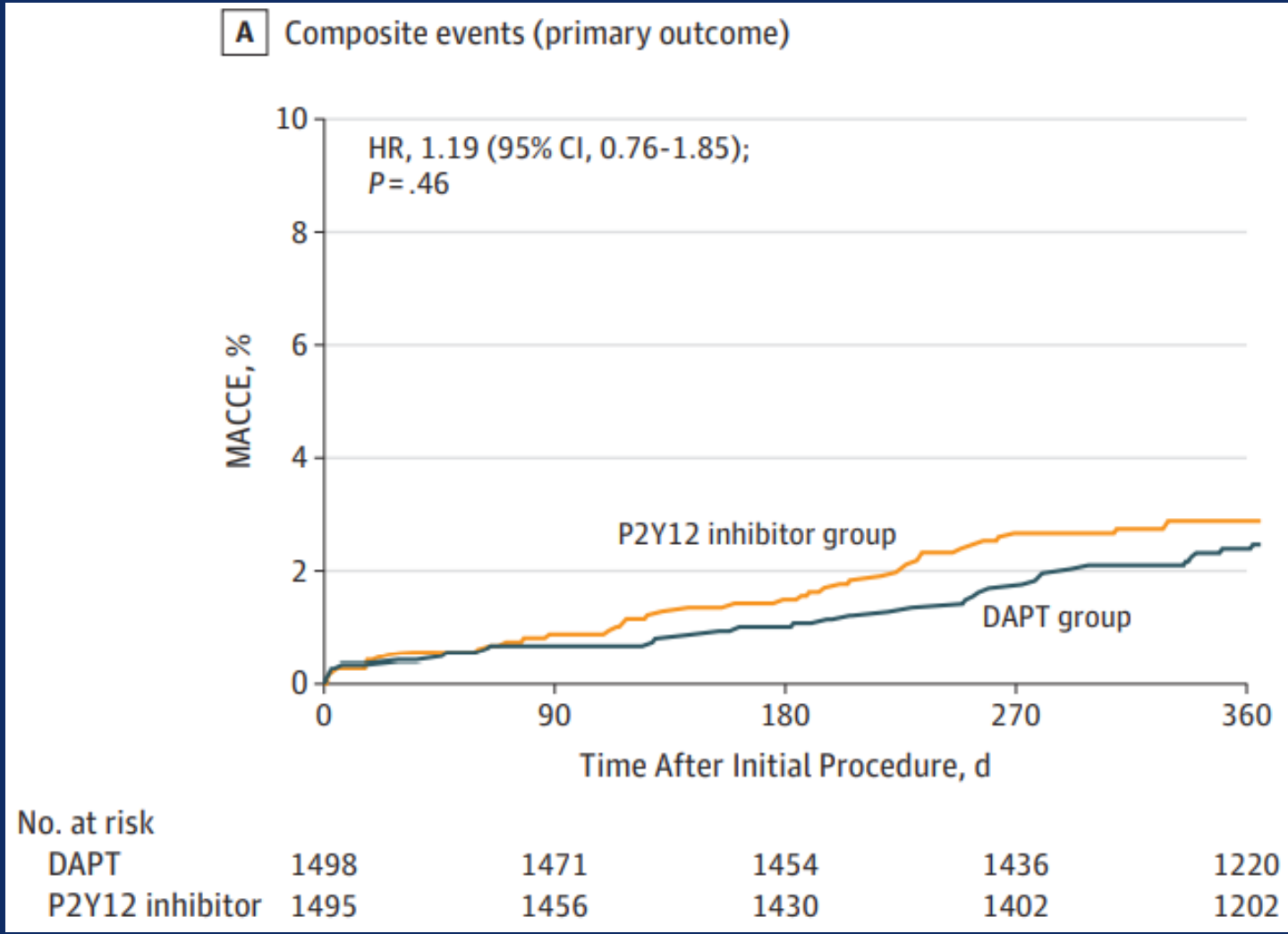
Effect of P2Y12 Inhibitor Monotherapy vs DAPT after PCI



Young Bin Song et al. Am Heart J. 2018;197:77-84.

SMART-CHOICE Trial

Effect of P2Y12 Inhibitor Monotherapy vs DAPT after PCI

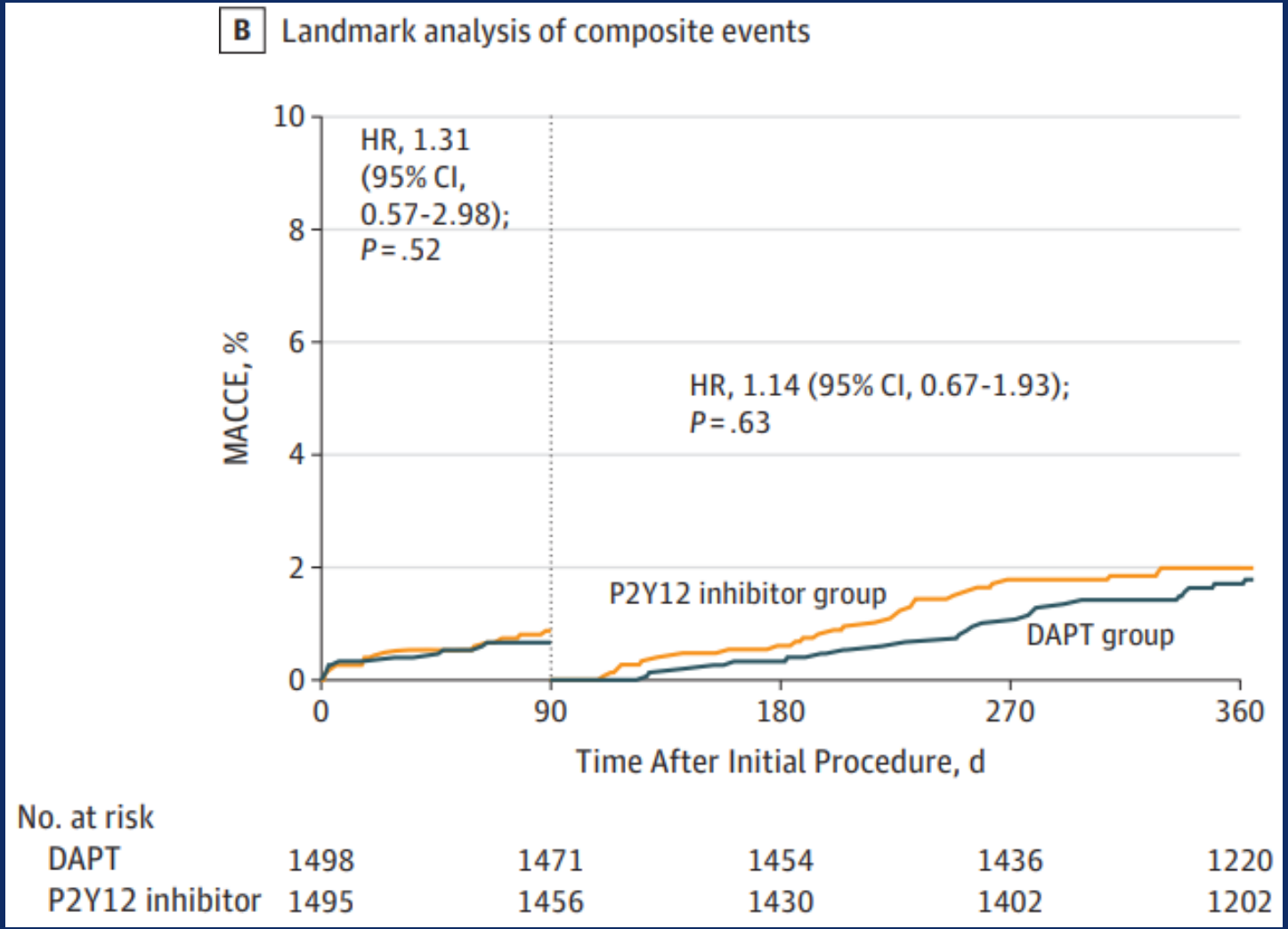


- Results of the analysis of the primary end point of major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) at 12 months.
- Cumulative rates of MACCE at 12 months were 2.9% for the P2Y12 inhibitor monotherapy group and 2.5% for the DAPT group (difference, 0.4%; *P* = .007 for noninferiority of P2Y12 monotherapy)

Joo-Yong Hahn et al. JAMA. 2019;321(24):2428-2437.

SMART-CHOICE Trial

Effect of P2Y12 Inhibitor Monotherapy vs DAPT after PCI

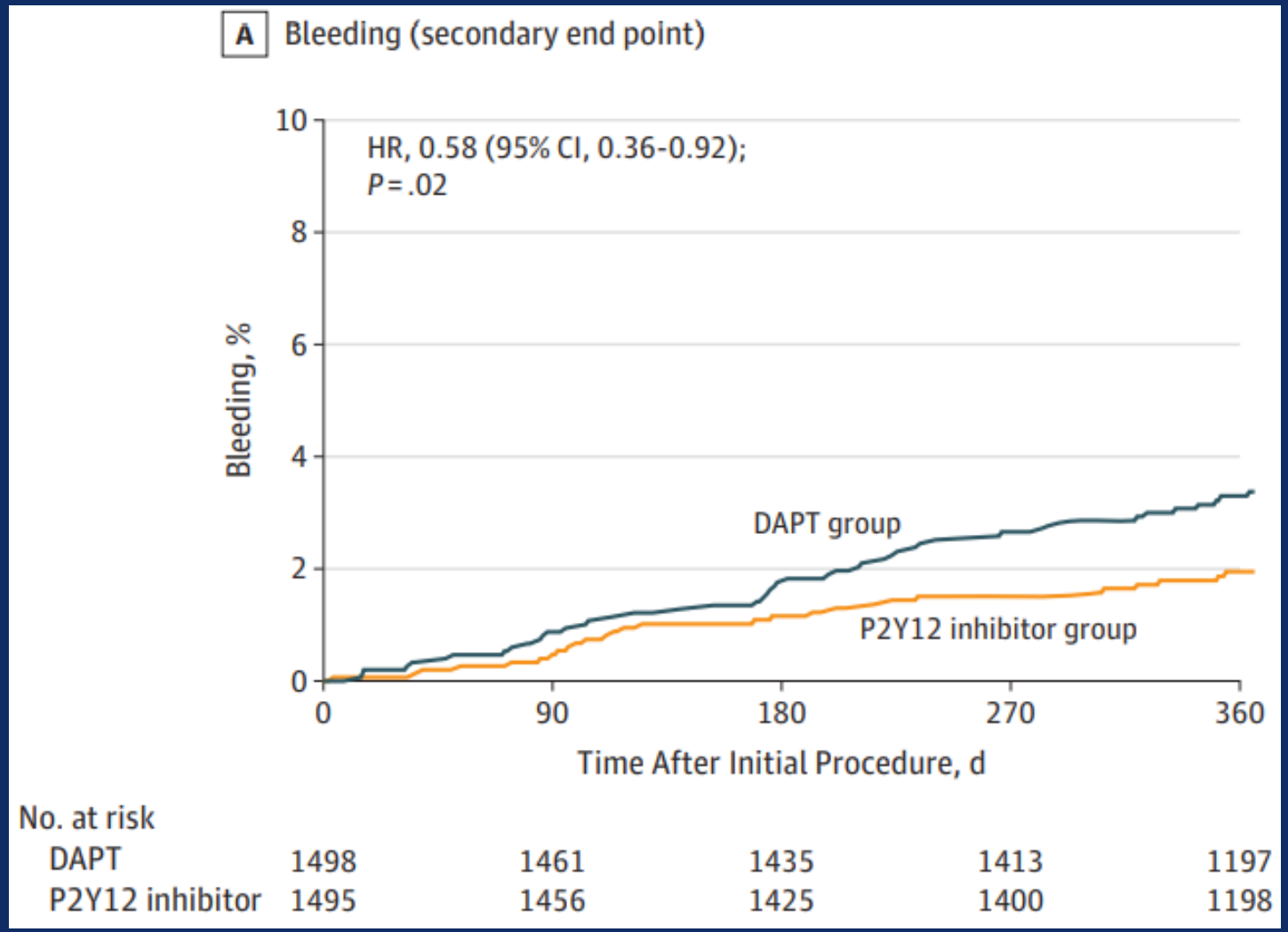


- Results of the randmark analysis at 3 months (the point after which one group received P2Y12 inhibitor only and the other received DAPT) for the primary end point.
- The risk of MACCE between 3 and 12 months was not significantly different between the group (hazard ratio, 1.14; 95% CI, 0.67-1.93; *P* = .63)

Joo-Yong Hahn et al. JAMA. 2019;321(24):2428-2437.

SMART-CHOICE Trial

Effect of P2Y12 Inhibitor Monotherapy vs DAPT after PCI

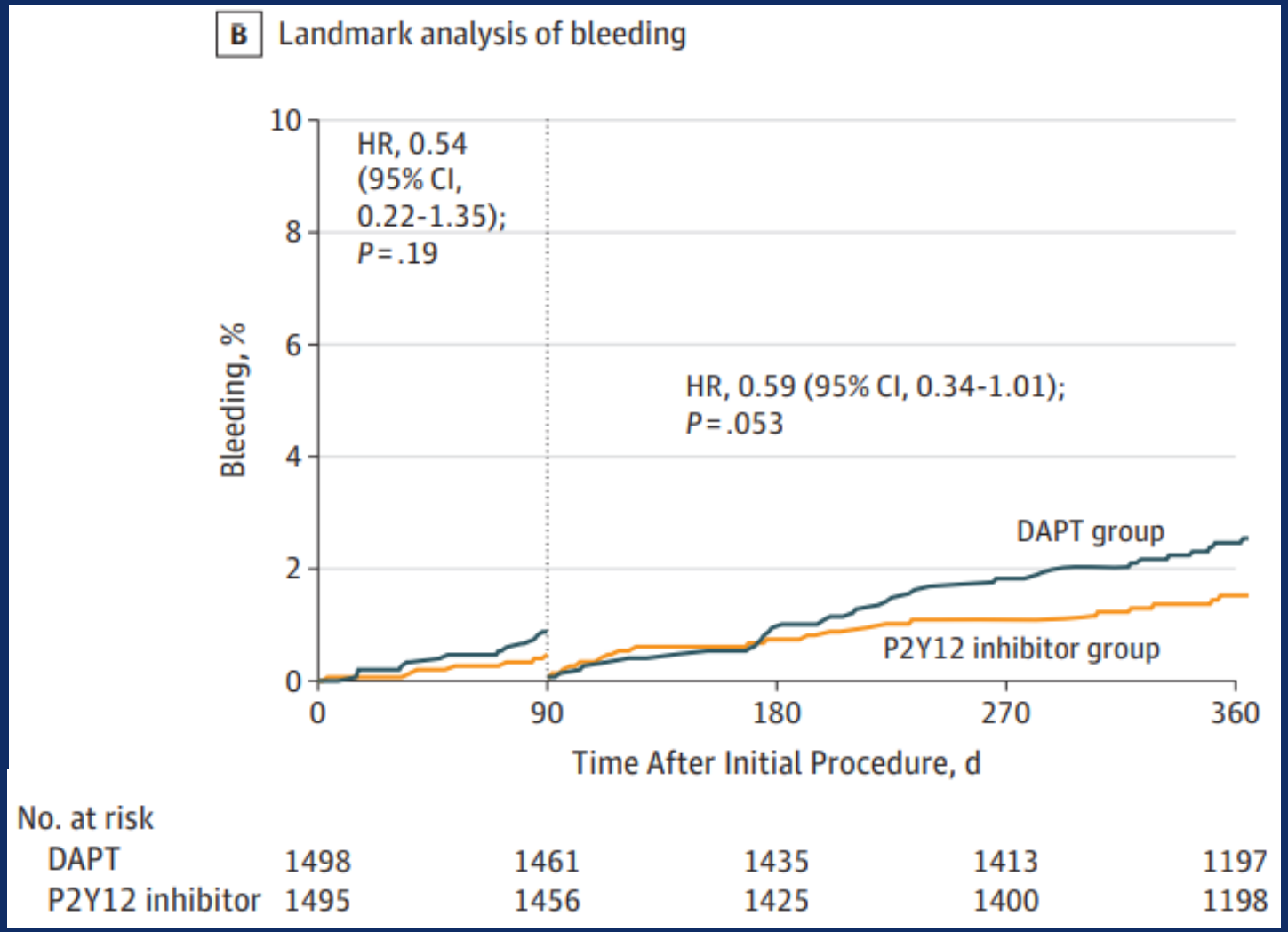


- Results of the analysis of the bleeding at 12 months.
- The rate of bleeding was significantly lower in the P2Y12 inhibitor monotherapy group than in the DAPT group (2.0% vs 3.4%; hazard ratio, 0.58 ; 95% CI, 0.36-0.92; *P* = .02)

Joo-Yong Hahn et al. JAMA. 2019;321(24):2428-2437.

SMART-CHOICE Trial

Effect of P2Y12 Inhibitor Monotherapy vs DAPT after PCI

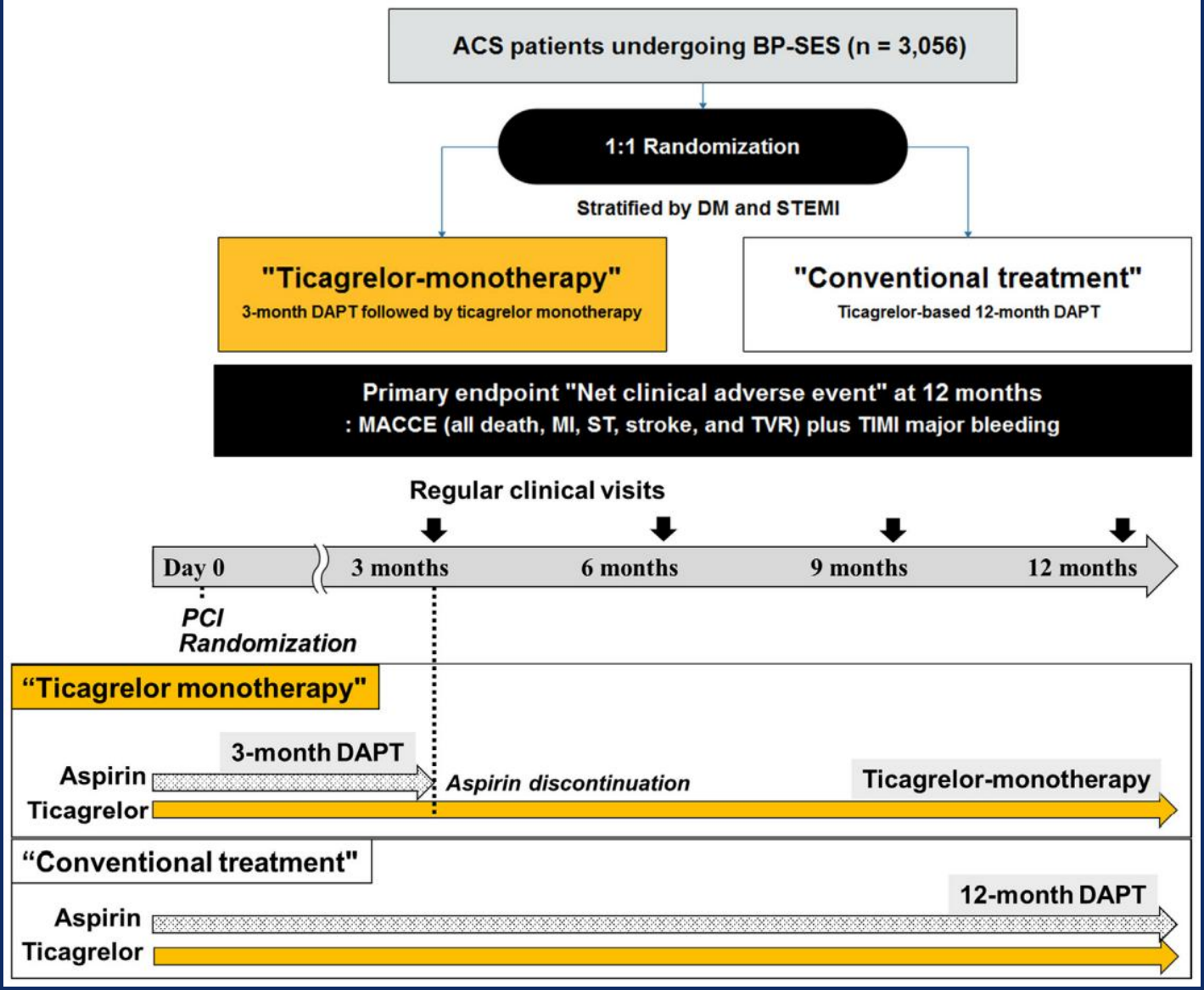


- Results of the landmark analysis at 3 months (the point after which one group received P2Y12 inhibitor only and the other received DAPT) for bleeding.
- There was no significant difference in the risk of bleeding between the groups in the post hoc 3-month landmark anlaysis (hazard ratio, 0.59; 95% CI, 0.34-1.01; *P* = 0.053)

Joo-Yong Hahn et al. JAMA. 2019;321(24):2428-2437.

TICO Trial

Effect of Ticagrelor mono vs Ticagrelor with Aspirin in patients with ACS



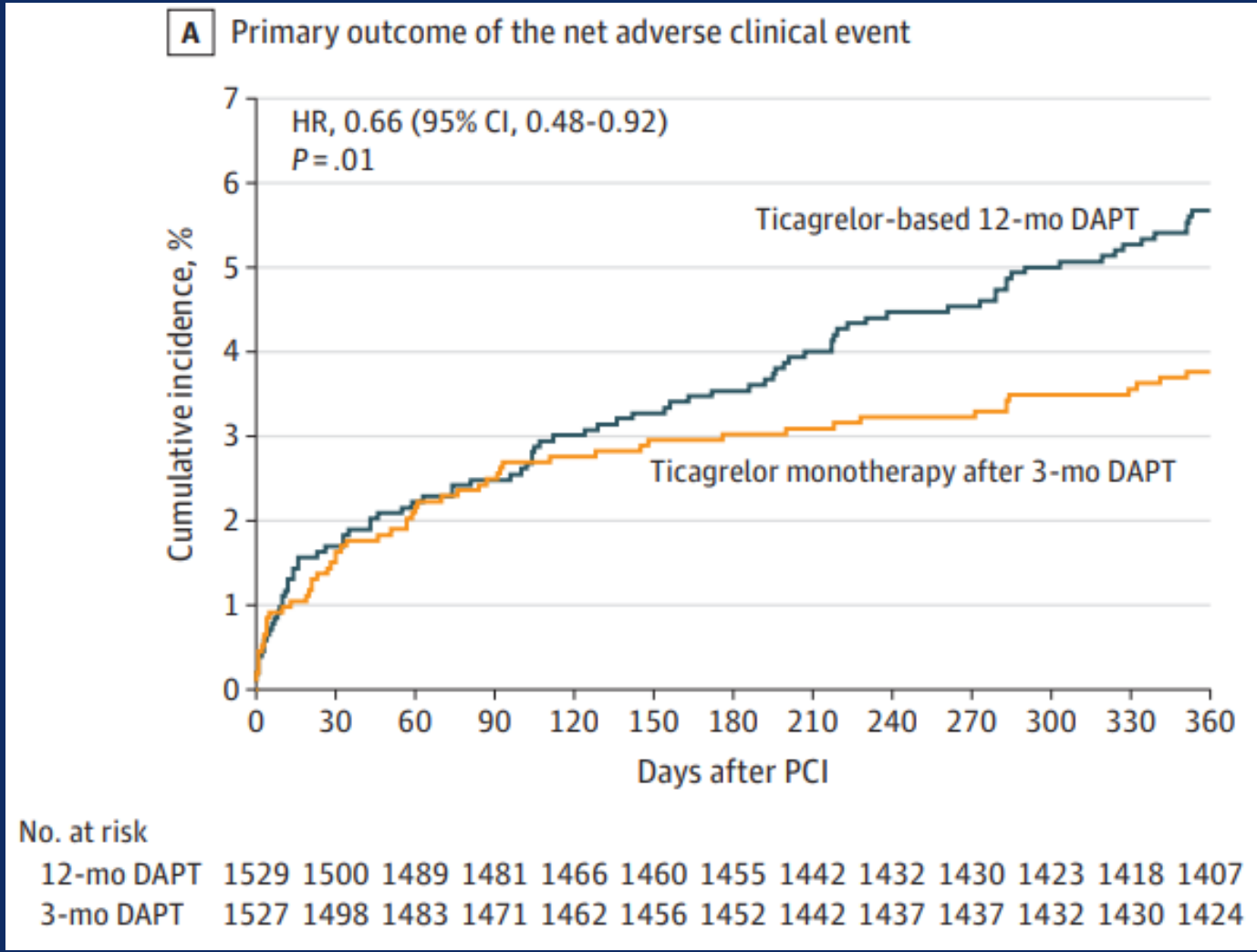
- **The primary outcome**

  A 1-year net adverse clinical event; a composite of major bleeding and adverse cardiac and cerebrovascular events (death, MI, stent thrombosis, stroke, or TVR)

Choongki Kim et al. Am Heart J. 2019;212:45-52.

TICO Trial

Effect of Ticagrelor mono vs Ticagrelor with Aspirin in patients with ACS

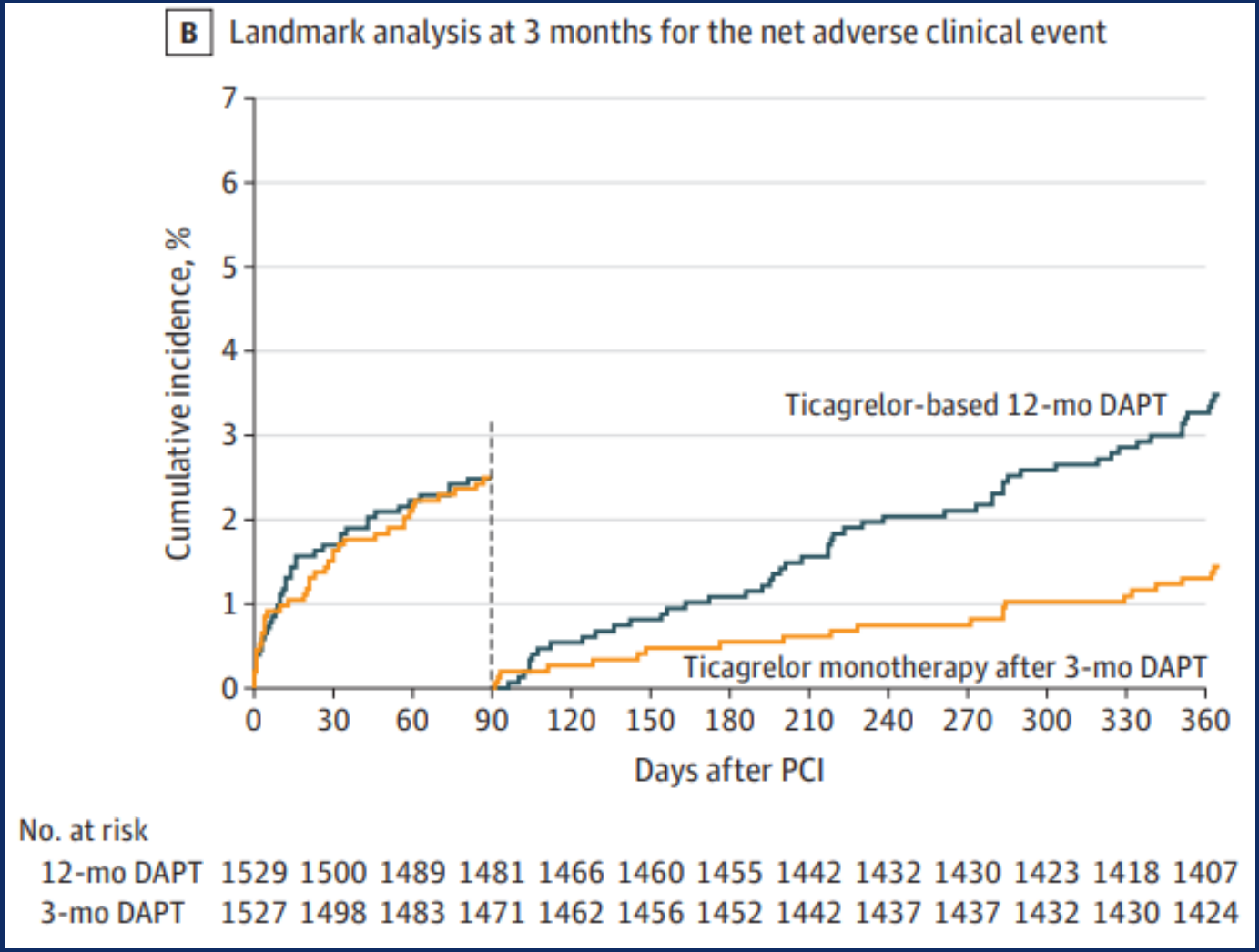


- **The primary outcome of a net adverse clinical event occurred in 59 patients (3.9%) receiving ticagrelor monotherapy after 3-month DAPT and in 89 patients (5.9%) receiving ticagrelor-based 12-month DAPT (absolute difference, -1.98% [95% CI, -3.50% to -0.45%]; HR, 0.66 [95% CI, 0.48 to 0.92]; *P* = .01)**

Byeong-Keuk Kim et al. JAMA. 2020;323(23):2407-2416.

TICO Trial

Effect of Ticagrelor mono vs Ticagrelor with Aspirin in patients with ACS

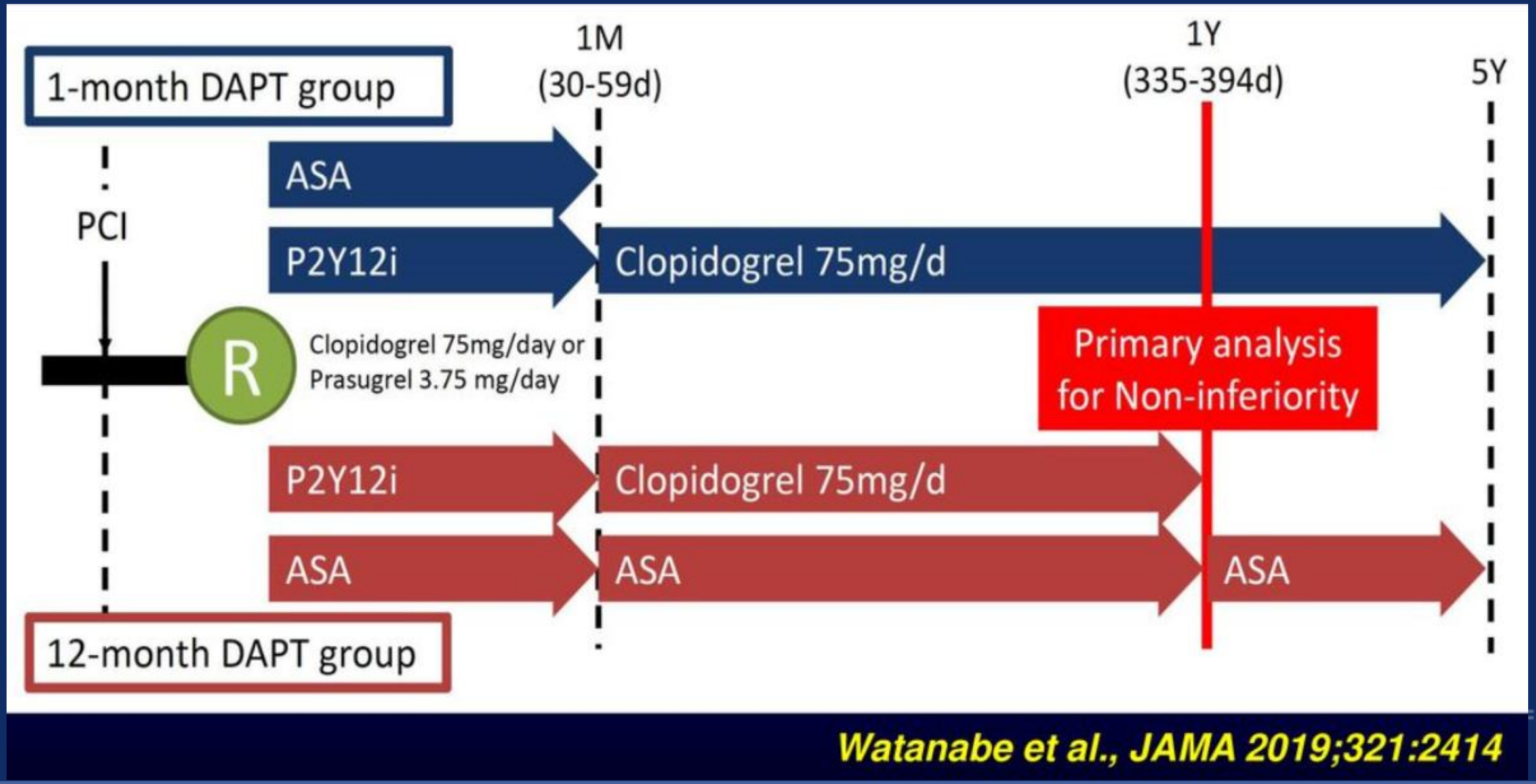


- On prespecified 3-month landmark analyses between 3 and 12 months,
  a net adverse clinical event occurred in 21 patients (1.4%) receiving ticagrelor monotherapy after 3-month DAPT and
  in 51 patients (3.5%) receiving ticagrelor-based 12-month DAPT
  (HR, 0.41 [95% CI, 0.25 to 0.68]; *P* = 0.001)

Byeong-Keuk Kim et al. JAMA. 2020;323(23):2407-2416.

STOPDAPT-2 Trial

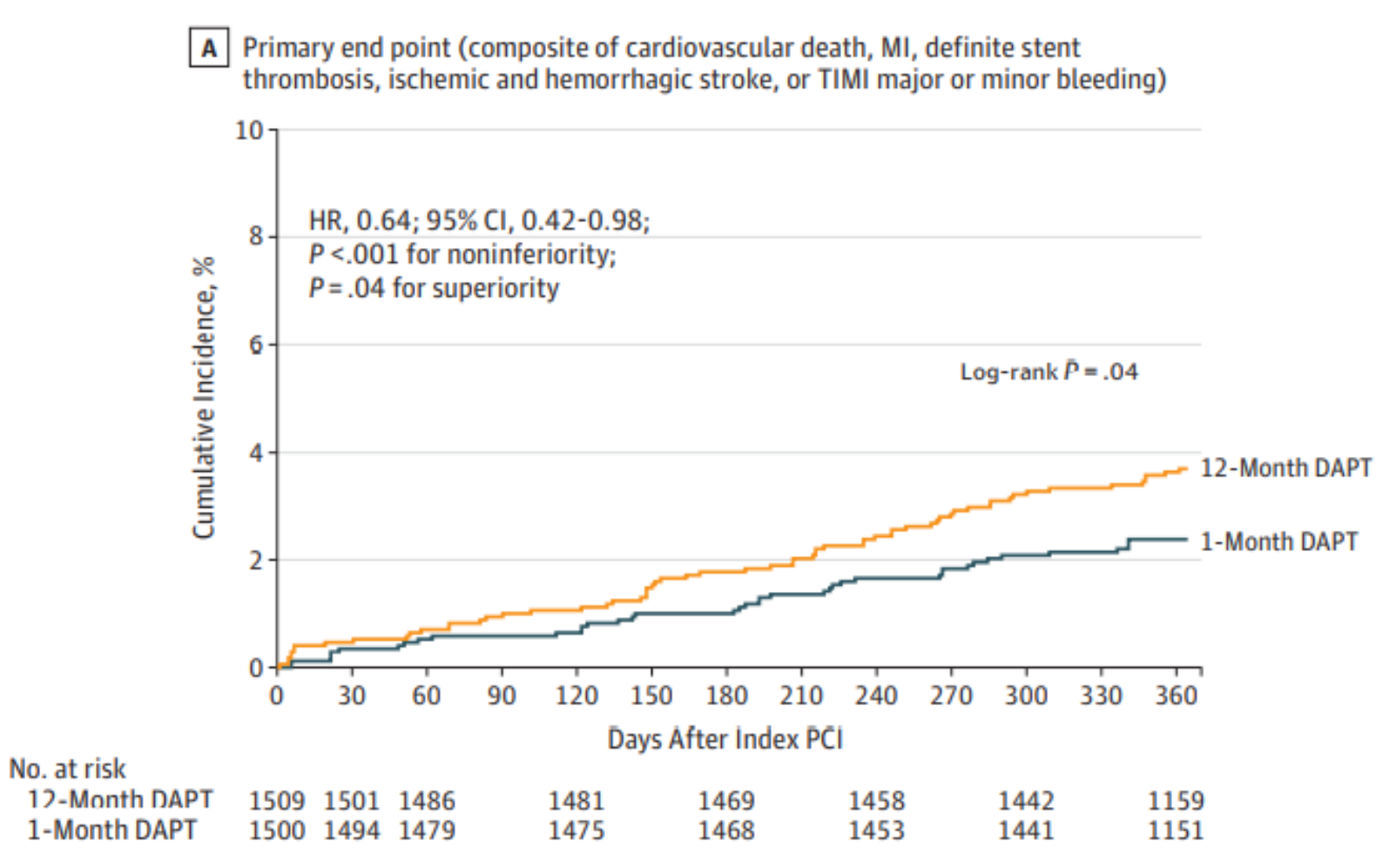
Effect of 1M DAPT followed by clopidogrel vs 12M DAPT after PCI



Watanabe et al., JAMA 2019;321:2414

STOPDAPT-2 Trial

Effect of 1M DAPT followed by clopidogrel vs 12M DAPT after PCI



- The primary end point occurred in 35 patients (2.36%) in the 1M DAPT

  occurred in 55 patients (3.70%) in the 12M DAPT

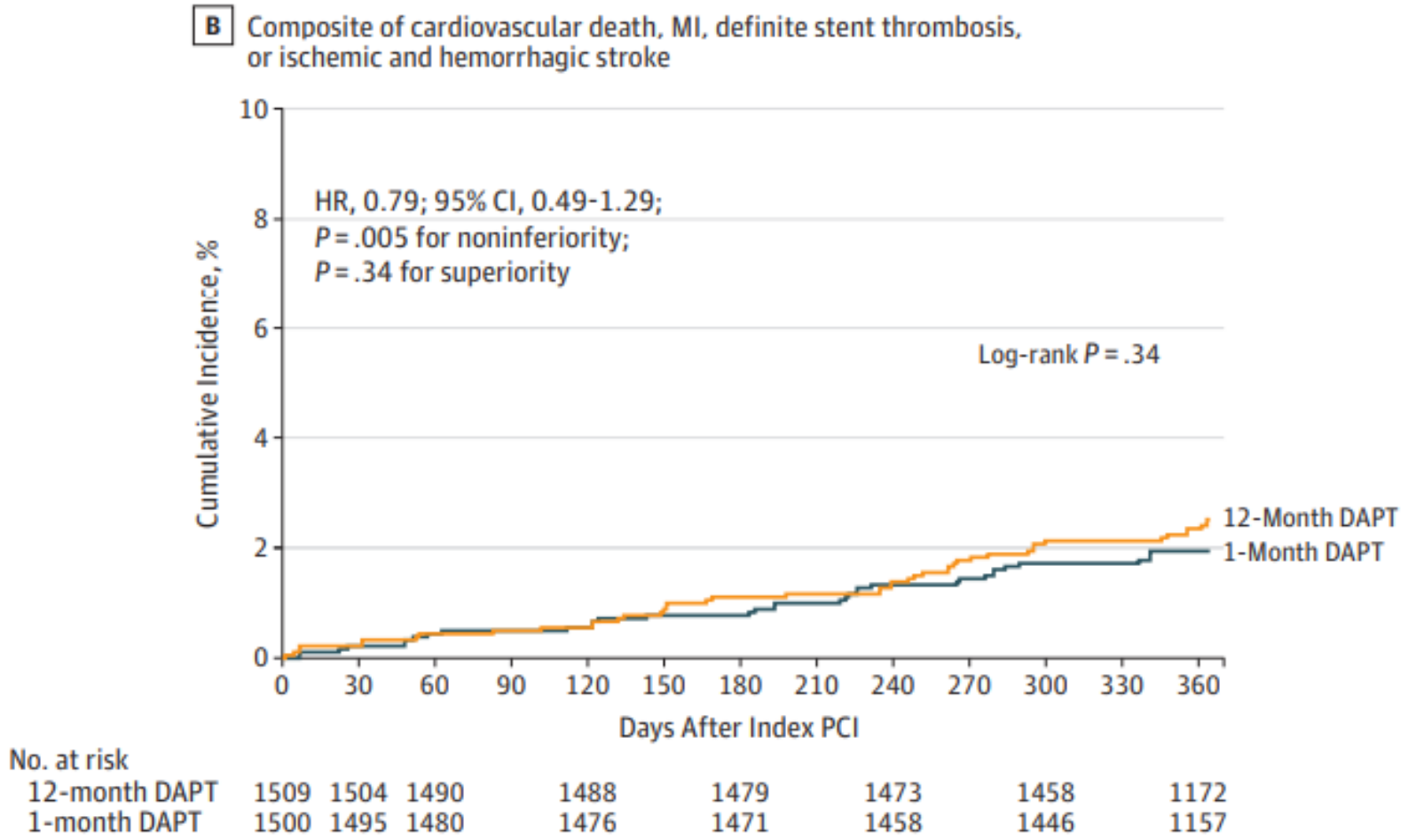
- 1M DAPT to 12M DAPT

(absolute difference, -1.34% [95% CI, -2.57% to -0.11%]; HR, 0.64 [95% CI, 0.42-0.98]; *P* < .001 for noninferiority; *P* = .04 for superiority)

Hirotoshi Watanabe et al. JAMA. 2019;321(24):2414-2427.

STOPDAPT-2 Trial

Effect of 1M DAPT followed by clopidogrel vs 12M DAPT after PCI



- For the major secondary cardiovascular end point
- 1M DAPT to 12M DAPT

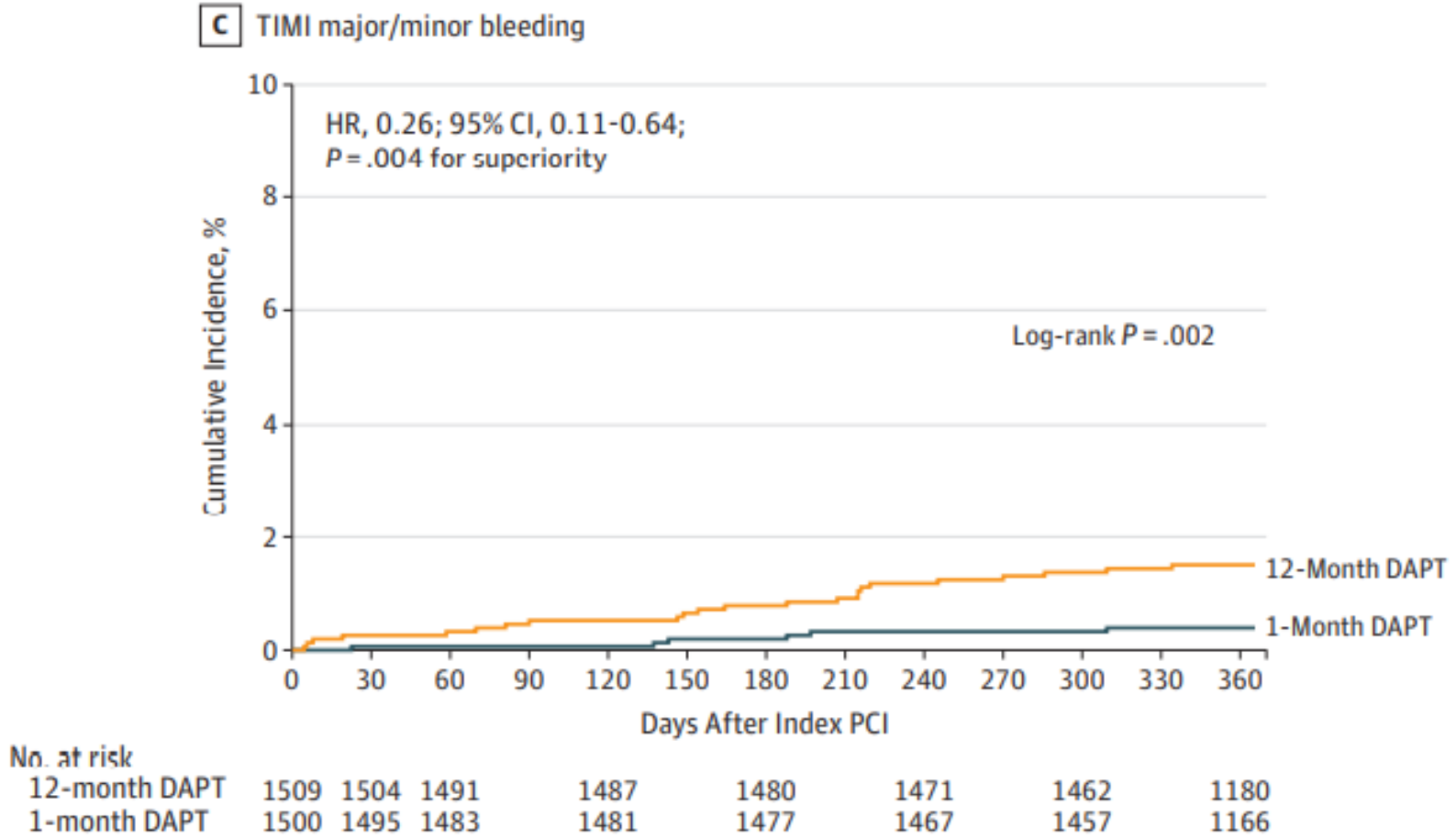
  (1.96% vs 2.51%;

  absolute difference, -0.55% [95% CI, -1.62% to -0.52%];
  HR, 0.79 [95% CI, 0.49-1.29];
  P = .005 for noninferiority;
  P = .34 for superiority)

Hirotoshi Watanabe et al. JAMA. 2019;321(24):2414-2427.

STOPDAPT-2 Trial

Effect of 1M DAPT followed by clopidogrel vs 12M DAPT after PCI



- For the major secondary bleeding end point
- 1M DAPT to 12M DAPT

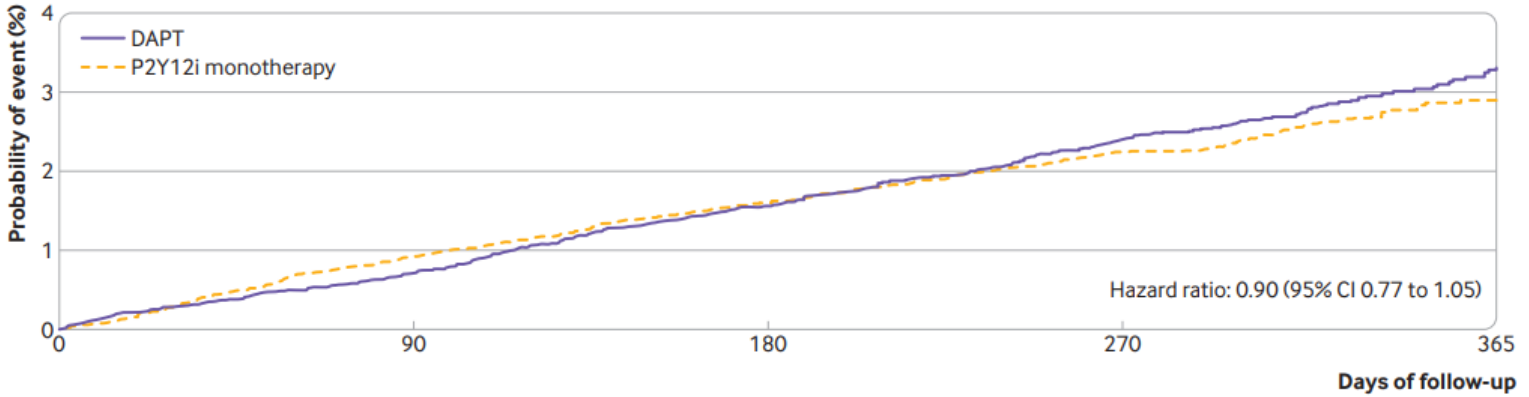
  (0.41% vs 1.54%;

  absolute difference, -1.13% [95% CI, -1.84% to -0.42%]; HR, 0.26 [95% CI, 0.11-0.64]; *P* = .004)

Hirotoshi Watanabe et al. JAMA. 2019;321(24):2414-2427.

P2Y12 inhibitor monotherapy or DAPT after PCI

: Individual patient level meta-analysis of RCTs



No at risk

DAPT				
11 674	11 527	11 388	11 000	3218
P2Y12i monotherapy				
11 634	11 447	11 319	10 954	3207

Study ID	P2Y12i monotherapy (%)	DAPT (%)	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	4/166 (2.4)	4/168 (2.4)	1.26	1.02 (0.25 to 4.06)
GLASSY (n=7509)	96/3753 (2.6)	112/3756 (3.0)	32.50	0.86 (0.65 to 1.13)
SMART-CHOICE (n=2926)	28/1455 (2.0)	27/1471 (1.9)	8.64	1.05 (0.62 to 1.79)
STOPDAPT-2 (n=3003)	36/1496 (2.4)	40/1507 (2.7)	11.91	0.91 (0.58 to 1.43)
TICO (n=3004)	13/1499 (0.9)	24/1505 (1.6)	5.30	0.54 (0.28 to 1.07)
TWILIGHT (n=6532)	126/3265 (3.9)	131/3267 (4.1)	40.38	0.96 (0.76 to 1.23)
Overall: I^2=0.0%; P=0.71			100.00	0.90 (0.77 to 1.05)

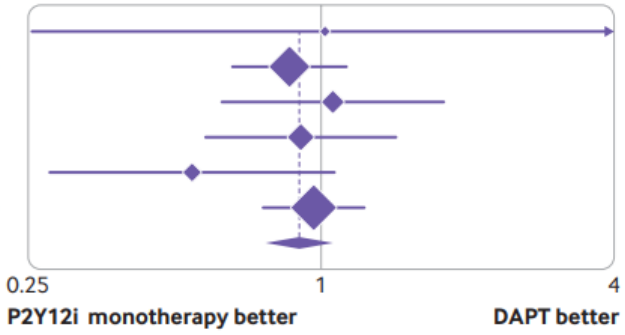


Fig 1 | Hazard ratios for individual trials and for pooled population and Kaplan-Meier estimates for primary endpoint of all cause death, myocardial infarction, or stroke in intention to treat population. Kaplan-Meier curves and hazard ratios from one step, fixed effect meta-analysis (top) and two step, fixed effect meta-analysis (bottom). DAPT=dual antiplatelet therapy; P2Y12i=$P2Y_{12}$ inhibitor monotherapy

- For primary endpoint of all cause death, myocardial infarction, or stroke in intention to treat population.

Marco Valgimigli et al. BMJ. 2021 Jun 16;373:n1332.

P2Y12 inhibitor monotherapy or DAPT after PCI
: Individual patient level meta-analysis of RCTs

	P2Y12i monotherapy (%) (n=11 634)	DAPT (%) (n=11 674)	Hazard ratio (95% CI)	P value for interaction	Hazard ratio (95% CI)
Primary outcome					
Clopidogrel	60/2618 (2.5)	65/2650 (2.7)		0.16	0.94 (0.66 to 1.33)
Newer P2Y12i	243/9016 (2.9)	273/9024 (3.4)			0.89 (0.75 to 1.06)
All cause mortality					
Clopidogrel	29/2618 (1.2)	27/2650 (1.1)		0.16	1.09 (0.65 to 1.84)
Newer P2Y12i	78/9016 (0.9)	110/9024 (1.4)			0.71 (0.53 to 0.95)
Myocardial infarction					
Clopidogrel	19/2618 (0.8)	23/2650 (1.0)		0.23	0.84 (0.46 to 1.54)
Newer P2Y12i	148/9016 (1.8)	158/9024 (1.9)			0.94 (0.75 to 1.17)
Stroke					
Clopidogrel	15/2618 (0.6)	17/2650 (0.7)		0.40	0.90 (0.45 to 1.79)
Newer P2Y12i	36/9016 (0.5)	28/9024 (0.3)			1.29 (0.79 to 2.11)
BARC 3 or 5					
Clopidogrel	19/2618 (0.8)	32/2650 (1.3)		0.41	0.60 (0.34 to 1.06)
Newer P2Y12i	78/9016 (0.9)	165/9024 (1.9)			0.47 (0.36 to 0.62)

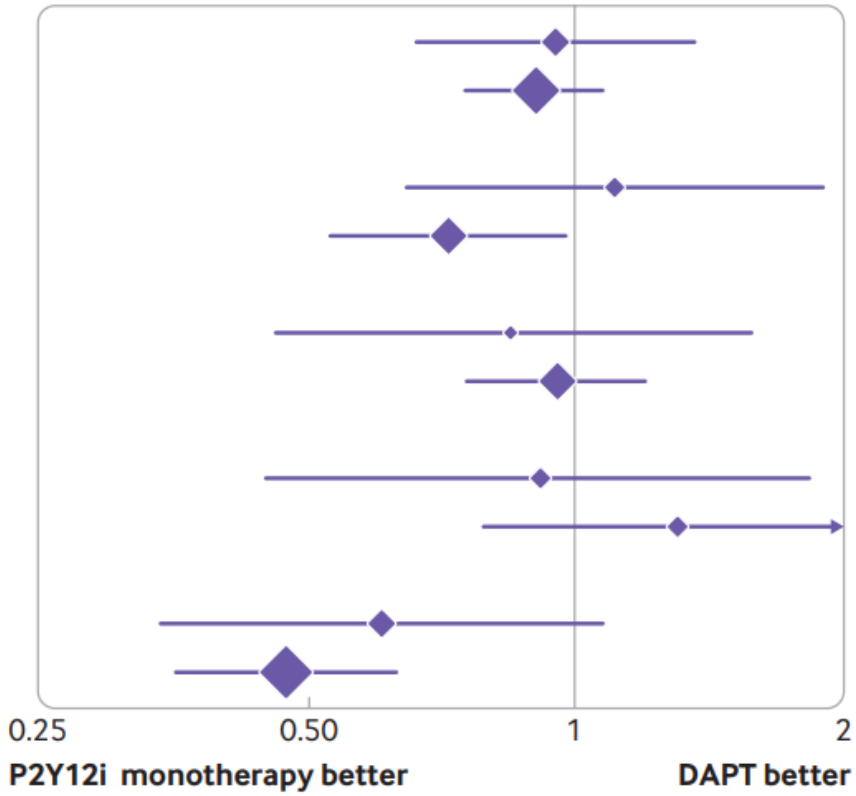
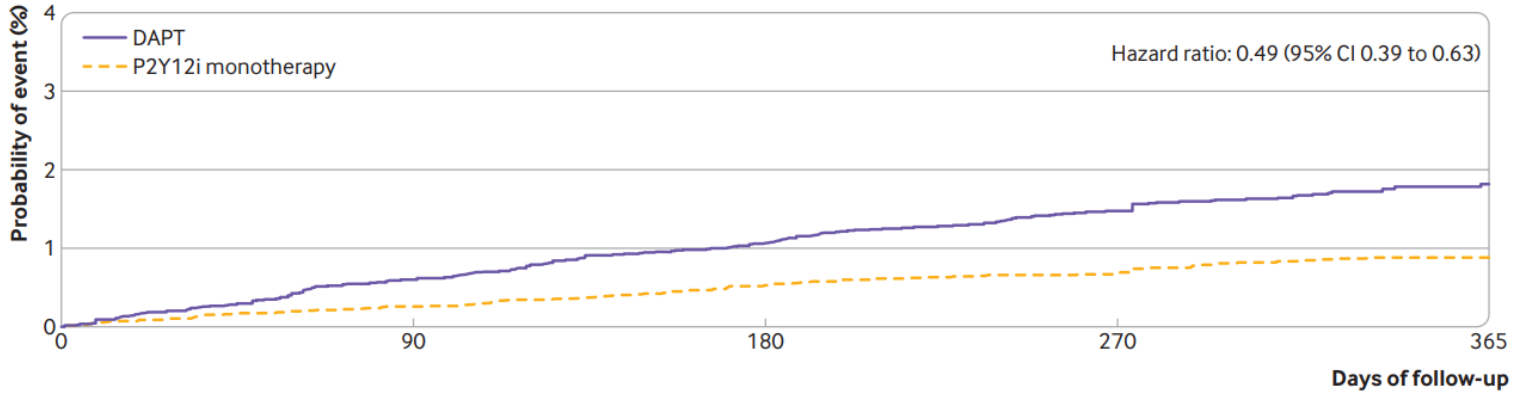


Fig 4 | Primary endpoint or its components and key safety endpoint stratified by use of clopidogrel or newer $P2Y_{12}$ inhibitors in experimental arm of intention to treat population. BARC=Bleeding Academy Research Consortium; DAPT=dual antiplatelet therapy

Marco Valgimigli et al. BMJ. 2021 Jun 16;373:n1332.

P2Y12 inhibitor monotherapy or DAPT after PCI

: Individual patient level meta-analysis of RCTs



No at risk

DAPT				
11 674	11 511	11 382	11 006	3243
P2Y12i monotherapy				
11 634	11 487	11 380	11 033	3270

Study ID	P2Y12i monotherapy (%)	DAPT (%)	Relative risk (95% CI)	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	-	-		-	-
GLASSY (n=7509)	34/3753 (0.9)	53/3756 (1.4)		28.85	0.64 (0.42 to 0.99)
SMART-CHOICE (n=2926)	13/1455 (1.0)	18/1471 (1.4)		14.32	0.74 (0.36 to 1.50)
STOPDAPT-2 (n=3003)	7/1496 (0.5)	21/1507 (1.4)		10.63	0.33 (0.14 to 0.79)
TICO (n=3004)	13/1499 (0.9)	42/1505 (2.8)		17.68	0.31 (0.17 to 0.57)
TWILIGHT (n=6532)	30/3265 (0.9)	63/3267 (2.0)		28.53	0.47 (0.31 to 0.73)
Overall: I^2=29.3%; P=0.23				100.00	0.49 (0.36 to 0.67)

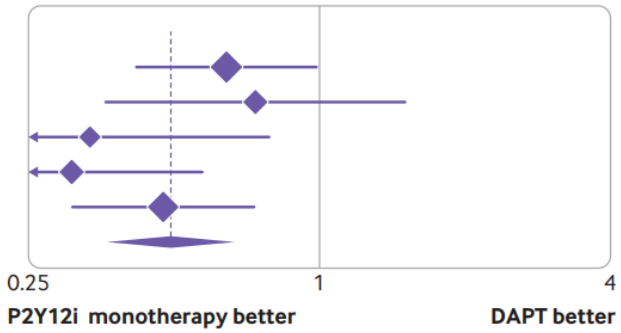


Fig 5 | Hazard ratios for individual trials and for pooled population and Kaplan-Meier estimates for key safety endpoint of Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding in intention to treat population. Kaplan-Meier curves and hazard ratios from one step, fixed effect meta-analysis (top) and two step, fixed effect meta-analysis (bottom). DAPT=dual antiplatelet therapy

- For safety endpoint of BARC type 3 or type 5 in intention to treat population.

Marco Valgimigli et al. BMJ. 2021 Jun 16;373:n1332.

T-Pass Trial

Stopping Aspirin Within 1 Month After Stenting for Ticagrelor Monotherapy in Acute Coronary Syndrome

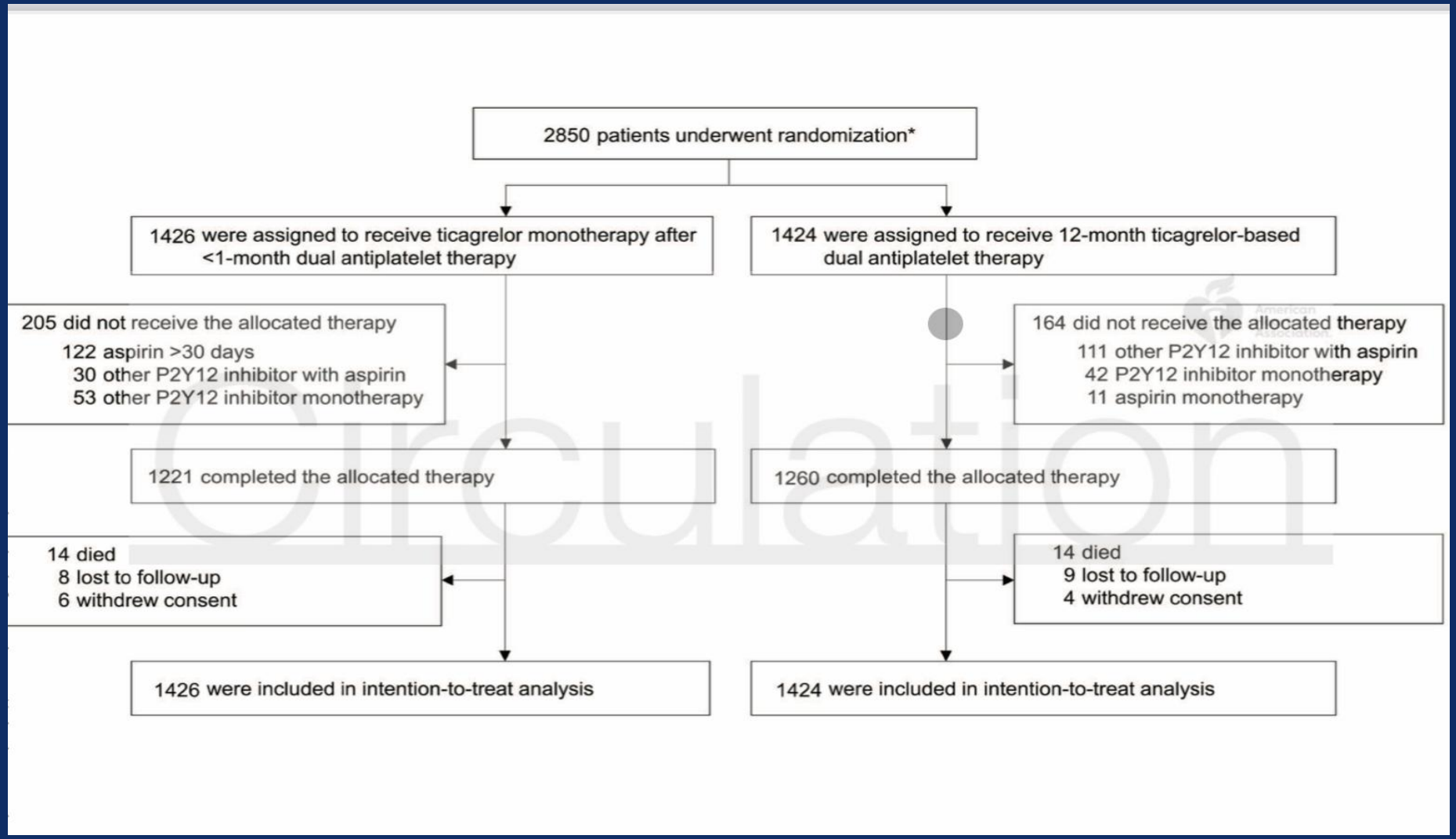
- **Aim:** asess non-inferiority of < 1 month DAPT followed by ticagrelol monotherapy vs 12 month DAPT in ACS.

- **Design:** non inferiority RCT of 2850 patients with ACS who underwent PCI with DES in 24 south Korean centres.

- **primary endpoint:** composite of all-cause death, myocardial infarction, definite or probable stent thrombosis, stroke, and major bleeding at 1 year after the index procedure

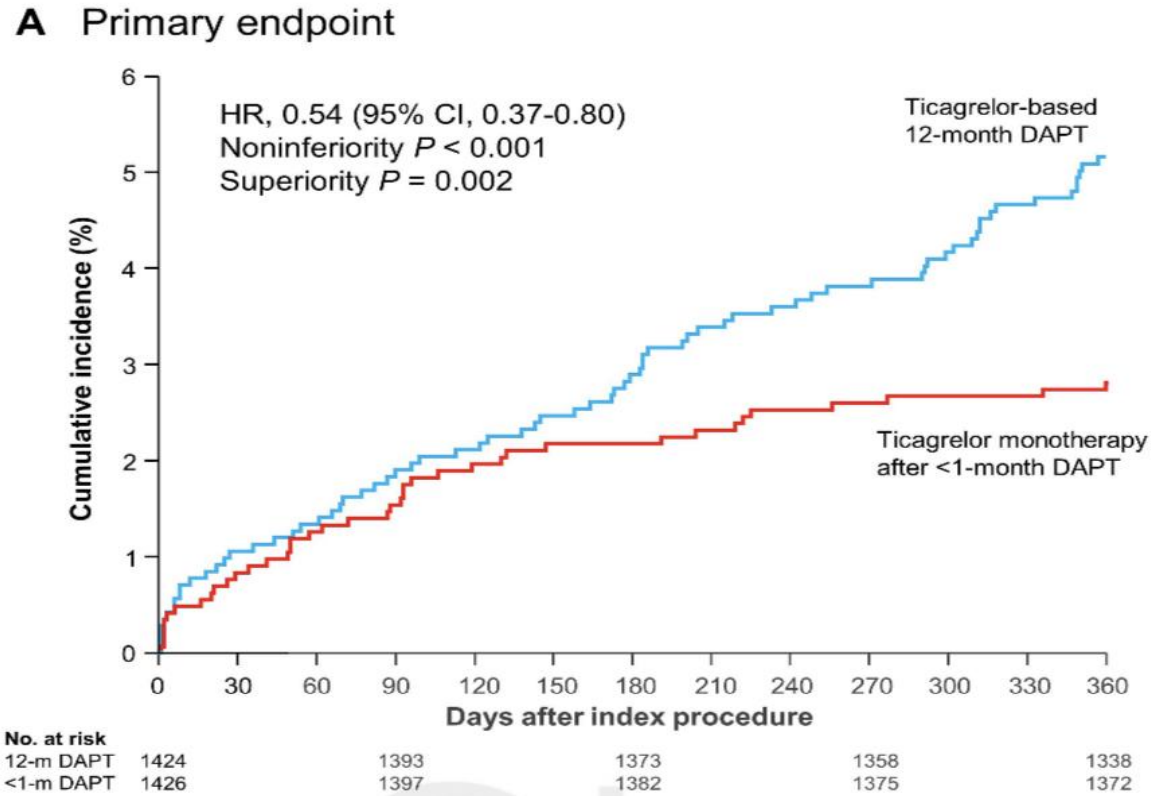
Sung-Jin Hong, Circulation. 2023

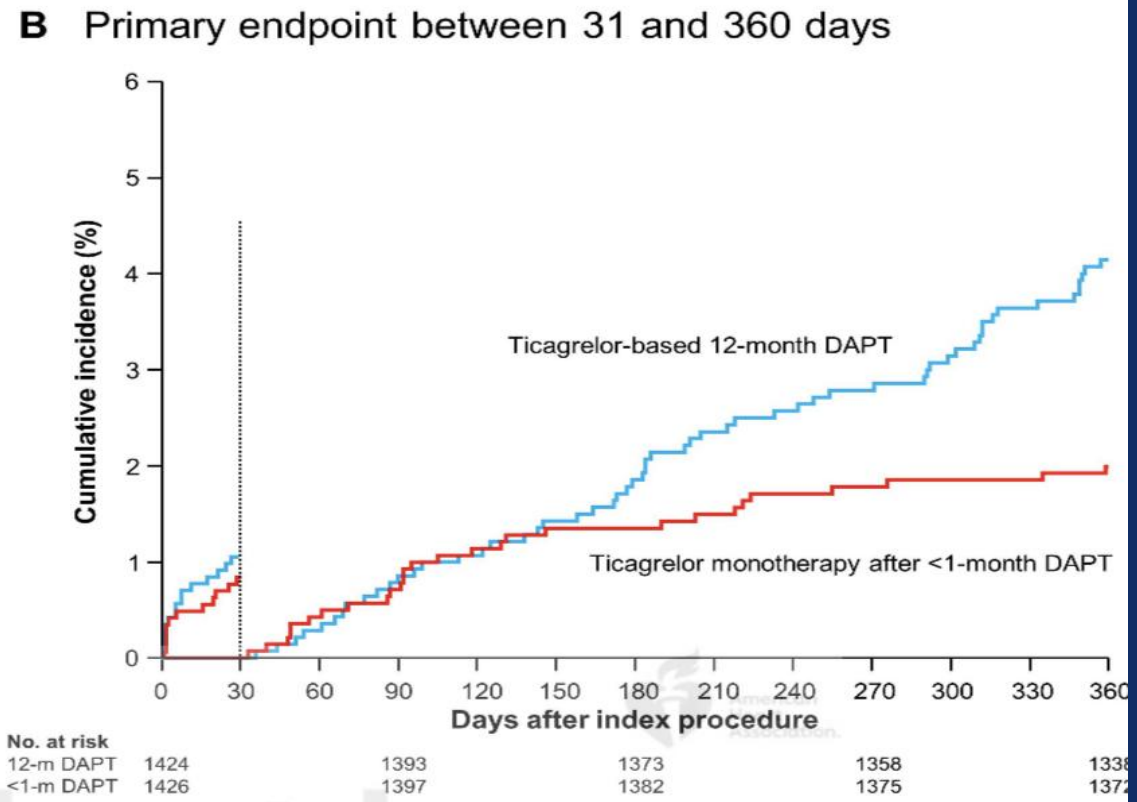
T-Pass Trial



Sung-Jin Hong, Circulation. 2023

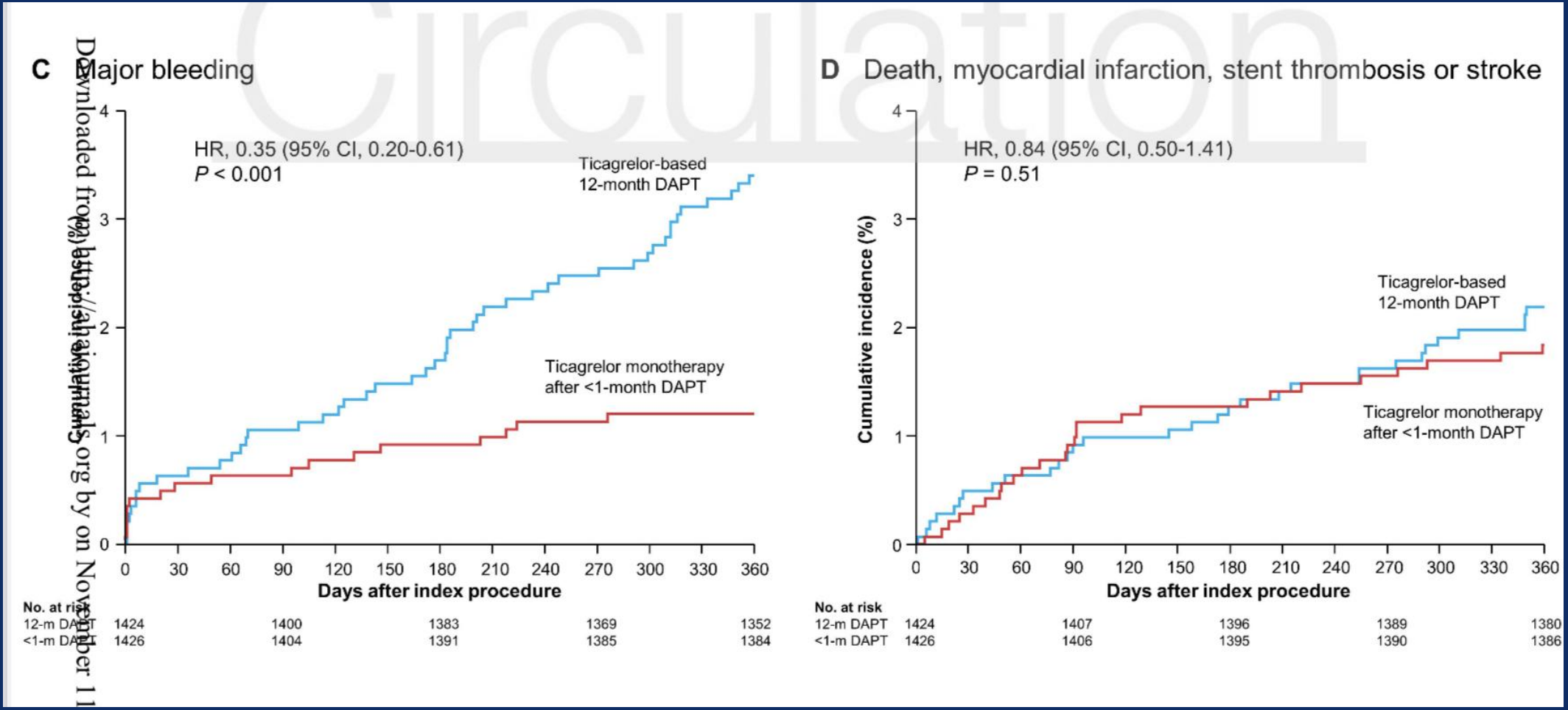
T-Pass Trial





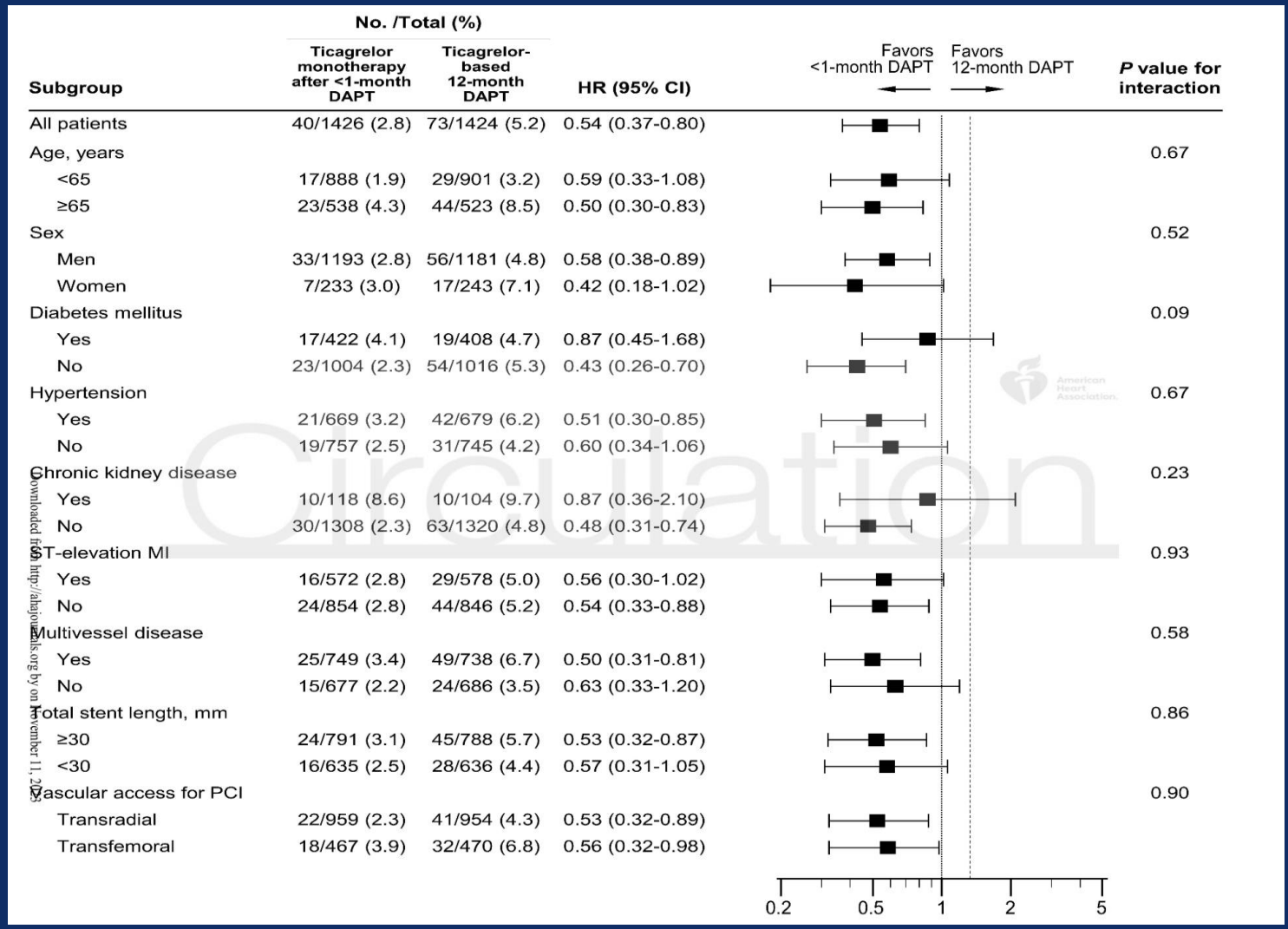
Sung-Jin Hong, Circulation. 2023

T-Pass Trial



Sung-Jin Hong, Circulation. 2023

T-Pass Trial



Subgroup	No. /Total (%) Ticagrelor monotherapy after <1-month DAPT	Ticagrelor-based 12-month DAPT	HR (95% CI)	*P* value for interaction
All patients	40/1426 (2.8)	73/1424 (5.2)	0.54 (0.37-0.80)	
Age, years				0.67
<65	17/888 (1.9)	29/901 (3.2)	0.59 (0.33-1.08)	
≥65	23/538 (4.3)	44/523 (8.5)	0.50 (0.30-0.83)	
Sex				0.52
Men	33/1193 (2.8)	56/1181 (4.8)	0.58 (0.38-0.89)	
Women	7/233 (3.0)	17/243 (7.1)	0.42 (0.18-1.02)	
Diabetes mellitus				0.09
Yes	17/422 (4.1)	19/408 (4.7)	0.87 (0.45-1.68)	
No	23/1004 (2.3)	54/1016 (5.3)	0.43 (0.26-0.70)	
Hypertension				0.67
Yes	21/669 (3.2)	42/679 (6.2)	0.51 (0.30-0.85)	
No	19/757 (2.5)	31/745 (4.2)	0.60 (0.34-1.06)	
Chronic kidney disease				0.23
Yes	10/118 (8.6)	10/104 (9.7)	0.87 (0.36-2.10)	
No	30/1308 (2.3)	63/1320 (4.8)	0.48 (0.31-0.74)	
ST-elevation MI				0.93
Yes	16/572 (2.8)	29/578 (5.0)	0.56 (0.30-1.02)	
No	24/854 (2.8)	44/846 (5.2)	0.54 (0.33-0.88)	
Multivessel disease				0.58
Yes	25/749 (3.4)	49/738 (6.7)	0.50 (0.31-0.81)	
No	15/677 (2.2)	24/686 (3.5)	0.63 (0.33-1.20)	
Total stent length, mm				0.86
≥30	24/791 (3.1)	45/788 (5.7)	0.53 (0.32-0.87)	
<30	16/635 (2.5)	28/636 (4.4)	0.57 (0.31-1.05)	
Vascular access for PCI				0.90
Transradial	22/959 (2.3)	41/954 (4.3)	0.53 (0.32-0.89)	
Transfemoral	18/467 (3.9)	32/470 (6.8)	0.56 (0.32-0.98)	

Sung-Jin Hong, Circulation. 2023

ULTIMATE-DAPT Trial

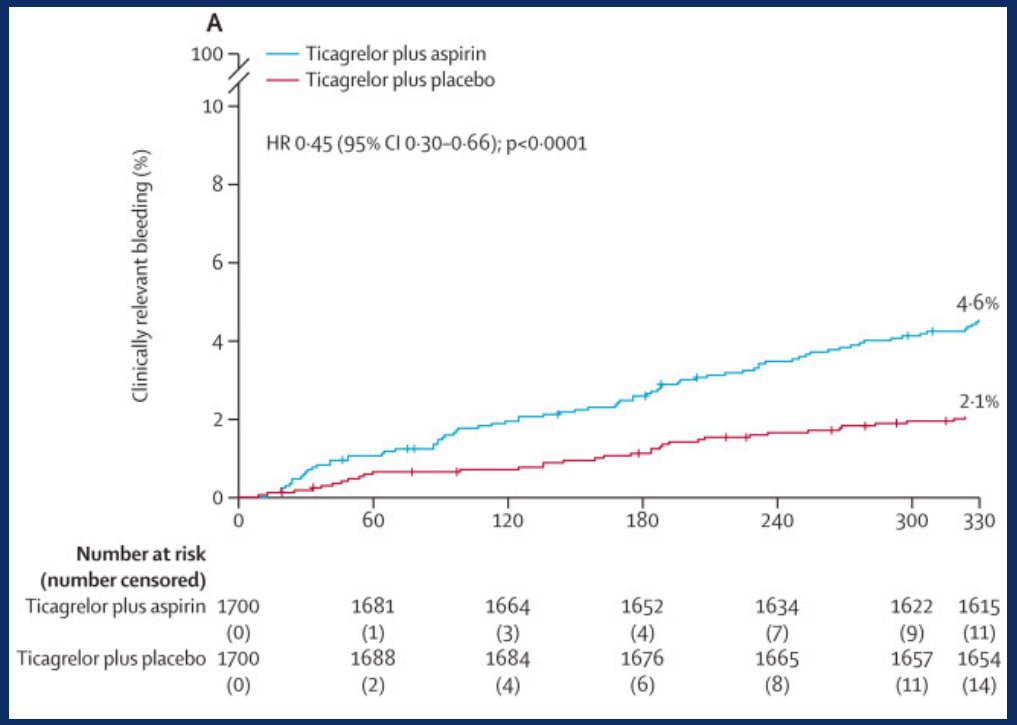
One-month Ticagrelor Monotherapy after PCI in Acute Coronary Syndrome

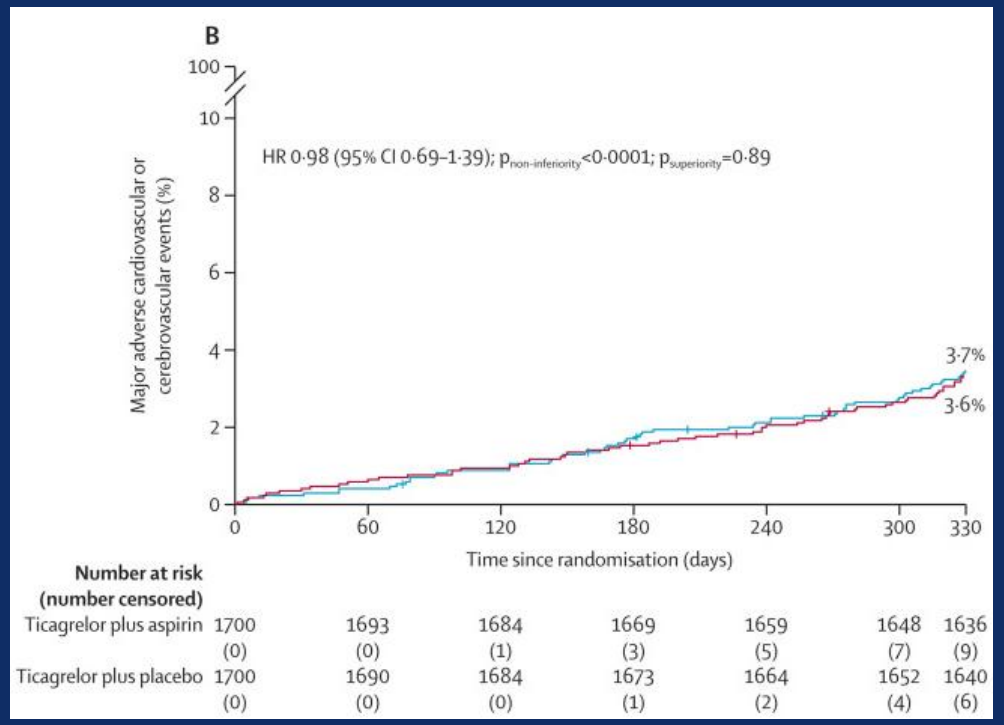
- Asess of 30days DAPT followed by ticagrelol monotherapy vs 12 month DAPT in ACS.

- Primary Endpoint:
  Effectiveness : Clinically-relevant bleeding (BARC types 2, 3, or 5), Powered for Superiority testing
  Safety : Composite MACCE, including cardiac death, MI, ischemic stroke, definite stent thrombosis, or clinically-driven TVR, Powered for Non-Inferiority testing

ULTIMATE-DAPT Trial

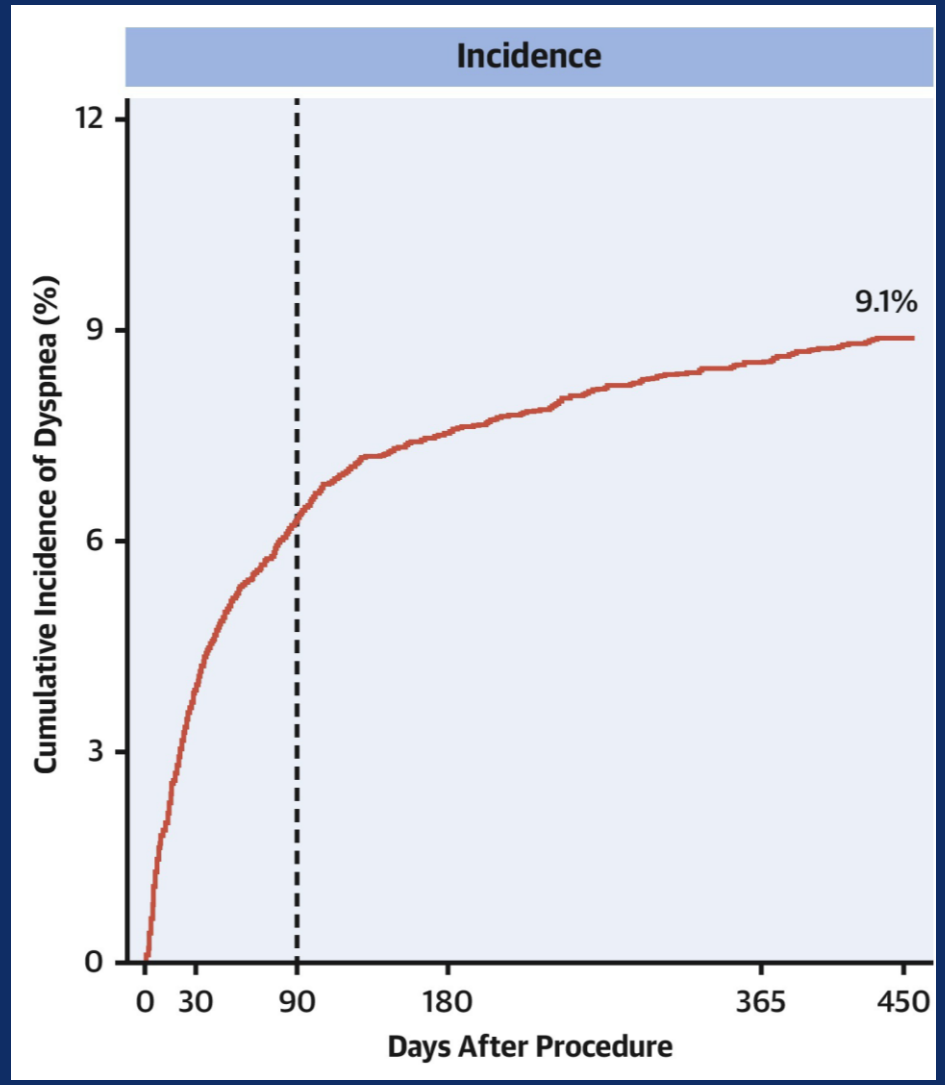
One-month Ticagrelor Monotherapy after PCI in Acute Coronary Syndrome



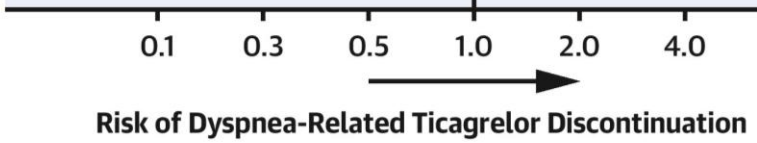


Treatment with Ticagrelor alone between 1 and 12 months will Decrease Clinically-Relevant and Major Bleeding while Providing Similar Protection from MACCE compared with ticagrelor plus aspirin

Twilight- Ticagrelol induced Dyspnea



Predictors	HR (95% CI)	*P* Value
Race		< 0.001
White	Ref.	
Asian	0.26 (0.18-0.38)	
Black	0.68 (0.45-1.03)	
Others	1.05 (0.66-1.66)	
Female	1.18 (0.99-1.40)	0.061
CKD	1.19 (1.00-1.42)	0.053
Prior PCI	1.21 (1.04-1.41)	0.015
Current Smoker	1.22 (1.04-1.43)	0.012
Hypercholesterolemia	1.23 (1.00-1.49)	0.042
Peripheral artery disease	1.32 (1.05-1.66)	0.017
Prior CABG	1.34 (1.10-1.62)	0.003
BMI, kg/m^2		<0.001
BMI ≥25 to <30	Ref.	
25≤ BMI <30	1.13 (0.91-1.40)	
BMI ≥30	1.56 (1.26-1.94)	
Age, years		<0.001
Age <65	Ref.	
Age ≥65 to <75	1.70 (1.43-2.03)	
Age ≥75	2.24 (1.81-2.78)	



Angiolillo DJ, et al. J Am Cardio 2023;16(20): 2514-2524

Aspirin versus Clopidogrel

CAPRIE Trial

Clopidogrel vs Aspirin in patients at risk of ischaemic events

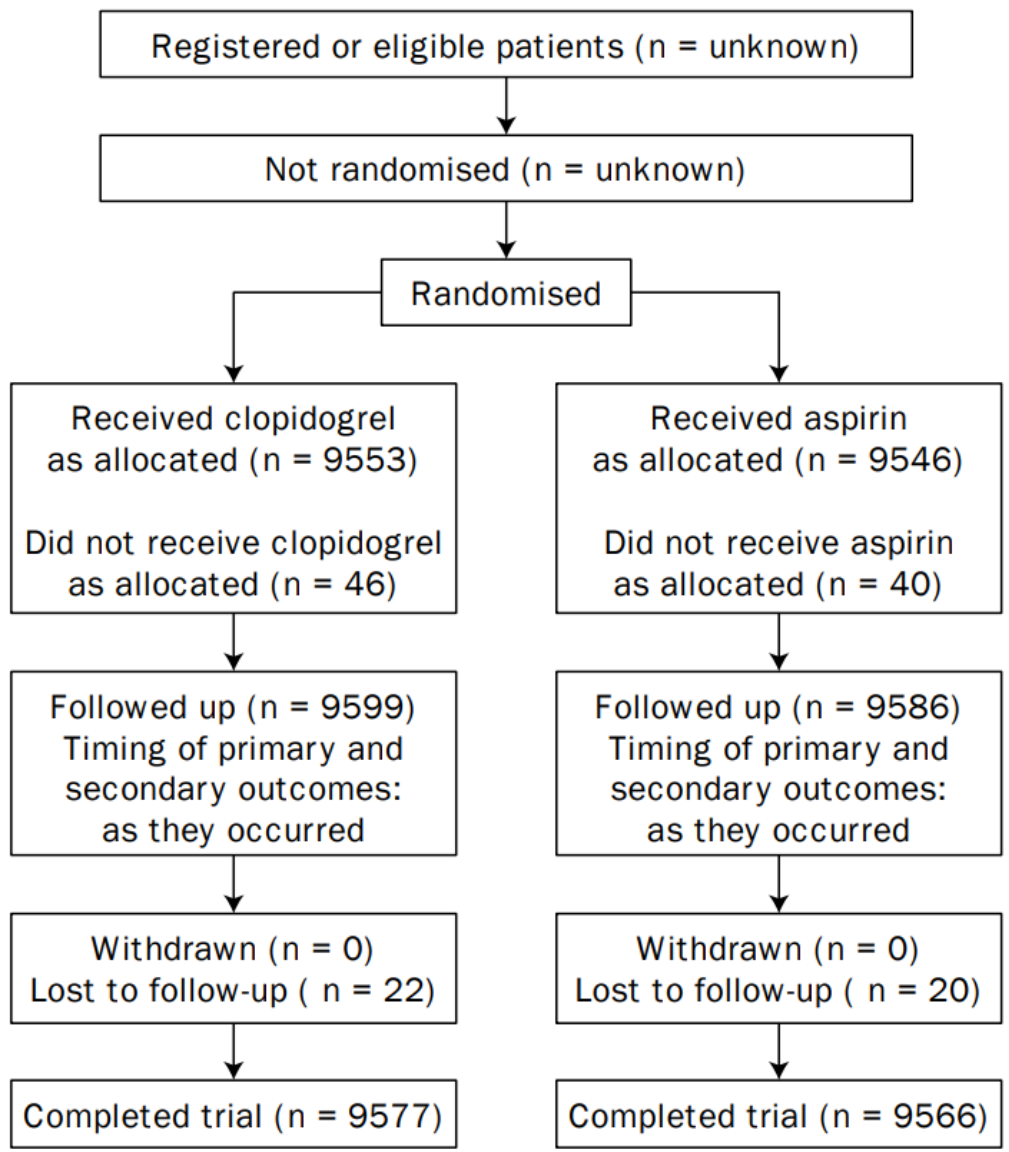


Figure 2: **Participant progress through trial**

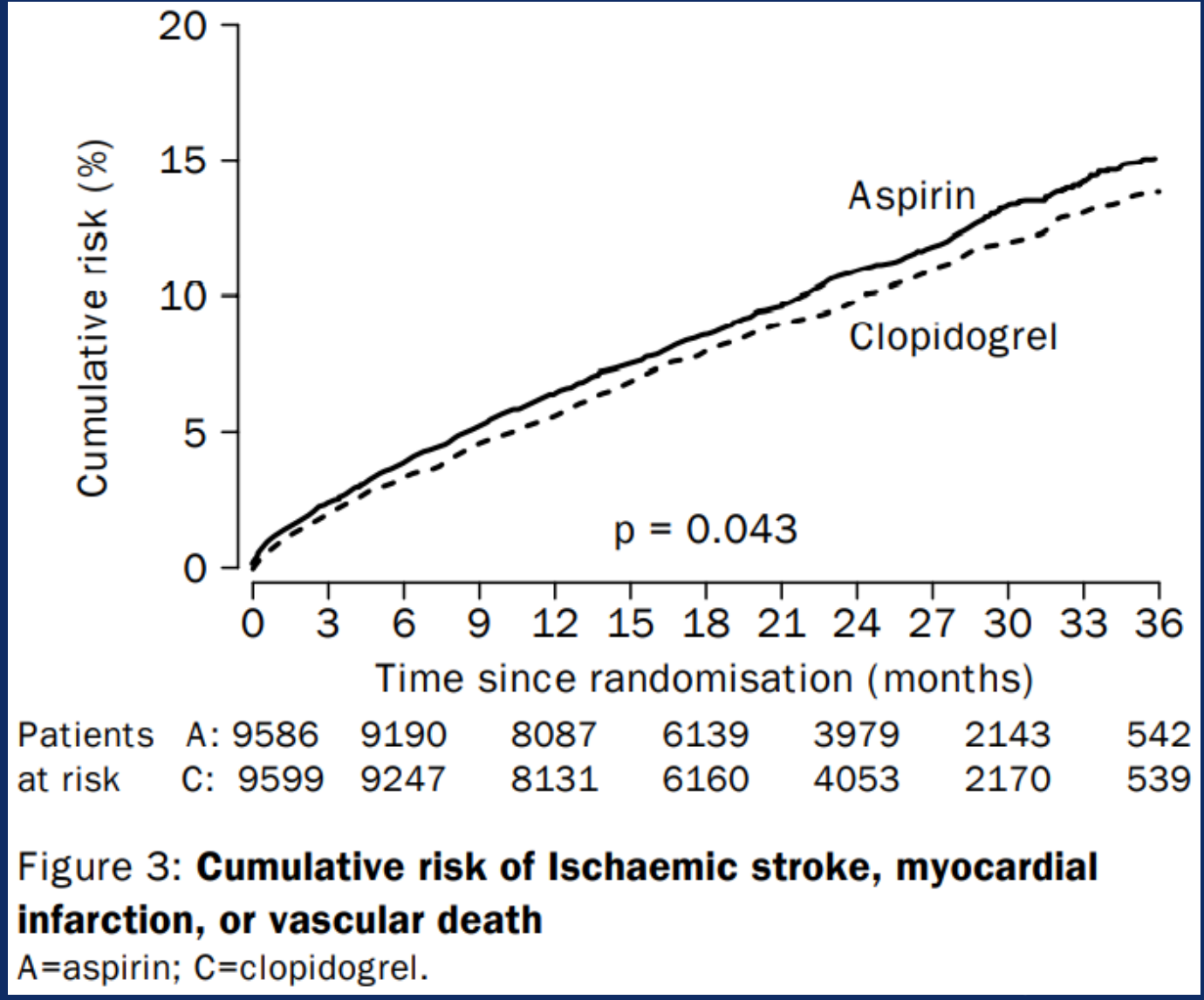


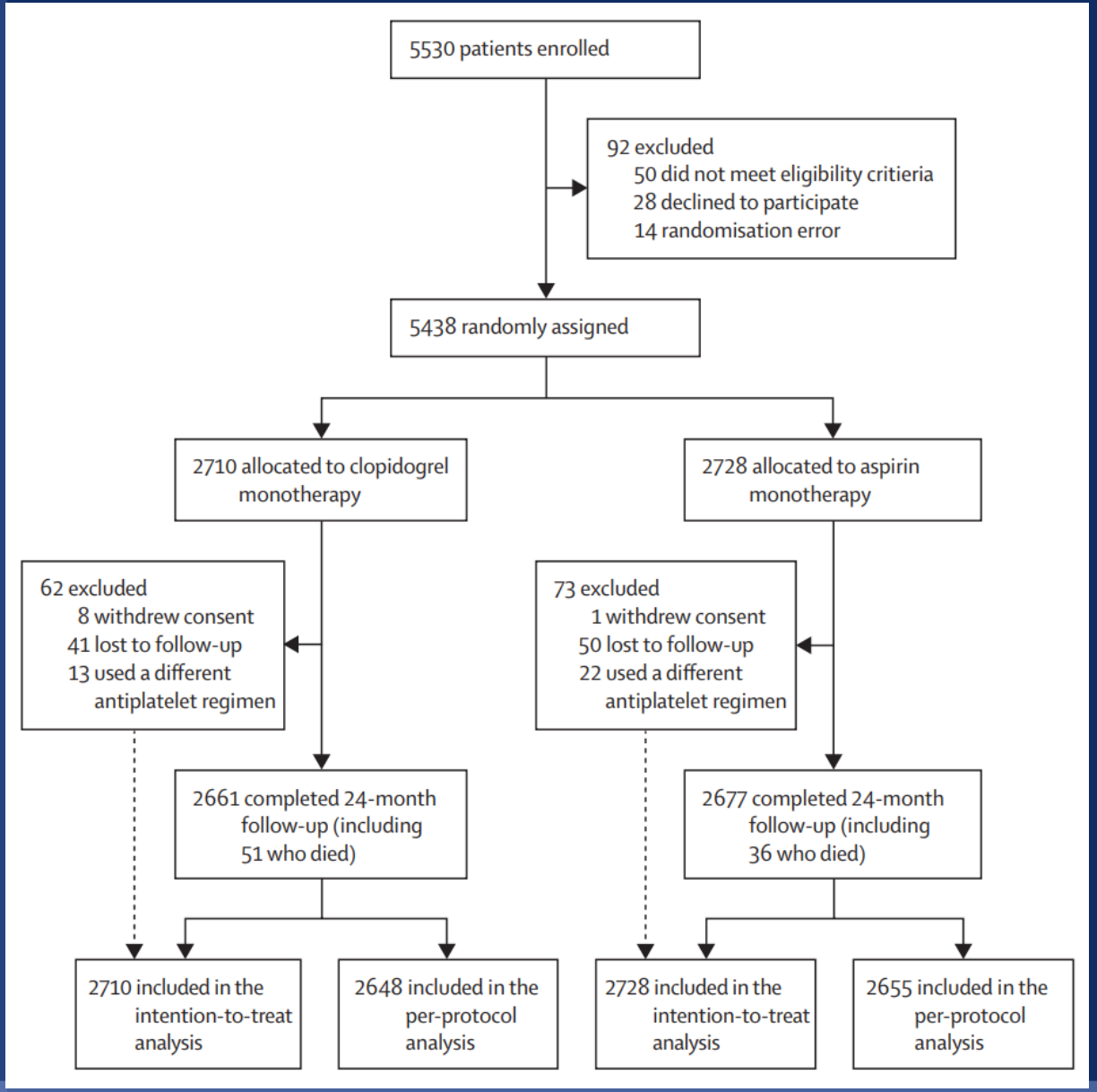
Figure 3: **Cumulative risk of Ischaemic stroke, myocardial infarction, or vascular death**

A=aspirin; C=clopidogrel.

M Gent et al. Lancet. 1996 Nov 16;348(9038):1329-39.

HOST-EXAM Trial

Aspirin vs Clopidogrel for chronic maintenance monotherapy after PCI



- **Participants**

  ≥ 20 years old

  underwent PCI with DES and maintained DAPT without any clinical events within 6-18 months after PCI

- **exclusion) any ischaemic and major bleeding complications (non-fatal MI, any repeat revascularization, readmission due to cardiac cause, and major bleeding**

Bon-Kwon Koo et al. Lancet. 2021 Jun 26;397(10293):2487-2496.

HOST-EXAM Trial

Aspirin vs Clopidogrel for chronic maintenance monotherapy after PCI

	Clopidogrel (n=2710)	Aspirin (n=2728)	Hazard ratio (95% CI)*	p value
Primary composite endpoint†	152 (5·7%)	207 (7·7%)	0·73 (0·59–0·90)	0·003
Thrombotic composite endpoint‡	99 (3·7%)	146 (5·5%)	0·68 (0·52–0·87)	0·003
Any bleeding (BARC type ≥2)§	61 (2·3%)	87 (3·3%)	0·70 (0·51–0·98)	0·036
All-cause death¶	51 (1·9%)	36 (1·3%)	1·43 (0·93–2·19)	0·101
Cardiac death	19 (0·7%)	14 (0·5%)	1·37 (0·69–2·73)	0·374
Non-cardiac death	32 (1·2%)	22 (0·8%)	1·47 (0·85–2·52)	0·167
Non-fatal myocardial infarction	18 (0·7%)	28 (1·0%)	0·65 (0·36–1·17)	0·150
Stroke	18 (0·7%)	43 (1·6%)	0·42 (0·24–0·73)	0·002
Ischaemic stroke	14 (0·5%)	26 (1·0%)	0·54 (0·28–1·04)	0·064
Haemorrhagic stroke	4 (0·2%)	17 (0·6%)	0·24 (0·08–0·70)	0·010
Readmission due to ACS	66 (2·5%)	109 (4·1%)	0·61 (0·45–0·82)	0·001
Major bleeding (BARC type ≥3)	33 (1·2%)	53 (2·0%)	0·63 (0·41–0·97)	0·035
Any revascularisation	56 (2·1%)	69 (2·6%)	0·82 (0·57–1·16)	0·261
Target lesion revascularisation	24 (0·9%)	36 (1·4%)	0·67 (0·40–1·12)	0·130
Target vessel revascularisation	37 (1·4%)	48 (1·8%)	0·78 (0·50–1·19)	0·245
Definite or probable stent thrombosis	10 (0·4%)	16 (0·6%)	0·63 (0·29–1·39)	0·251
Any minor gastrointestinal complications	272 (10·2%)	320 (11·9%)	0·85 (0·72–1·00)	0·048

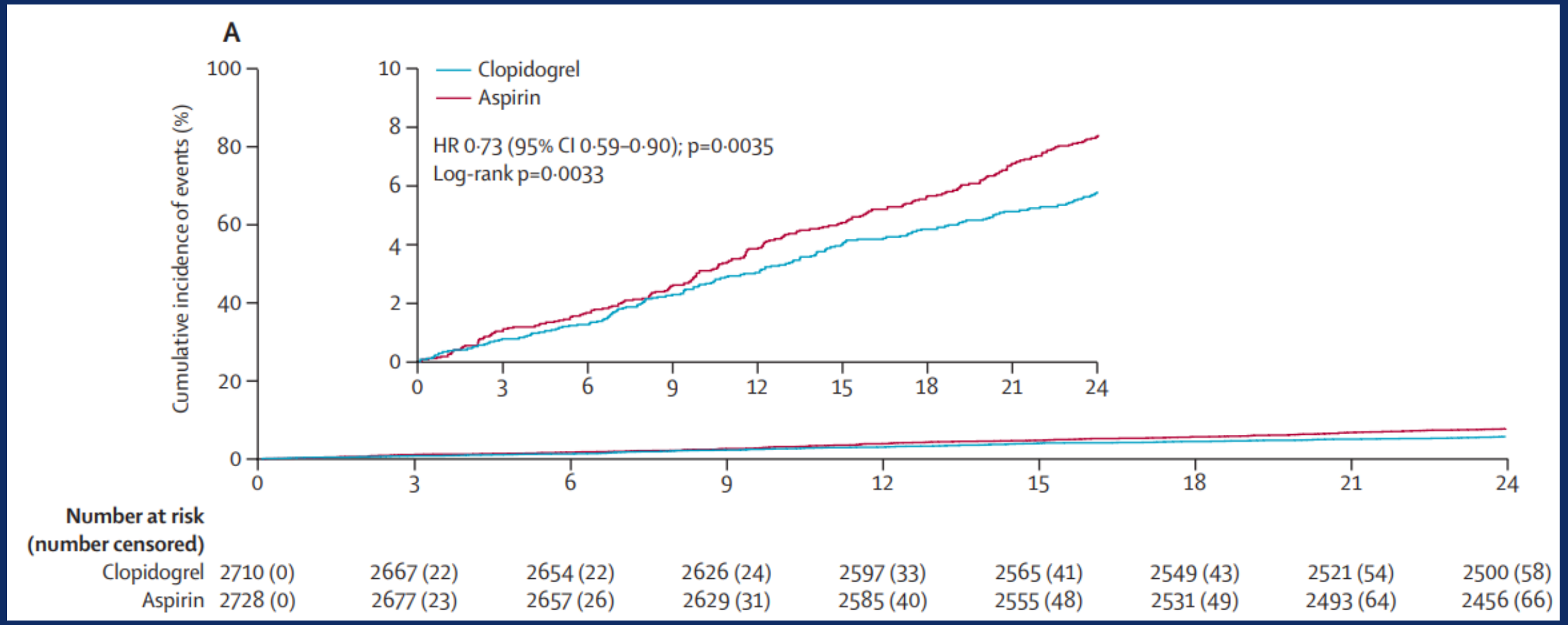
Bon-Kwon Koo et al. Lancet. 2021 Jun 26;397(10293):2487-2496.

HOST-EXAM Trial

30th TCTAP2025

Aspirin vs Clopidogrel for chronic maintenance monotherapy after PCI

- A) The cumulative incidence of the primary endpoint, consisting of all-cause death, non-fatal MI, stroke, readmission due to ACS, and major bleeding (BARC 3 or more) complications



Number at risk (number censored)									
Clopidogrel	2710 (0)	2667 (22)	2654 (22)	2626 (24)	2597 (33)	2565 (41)	2549 (43)	2521 (54)	2500 (58)
Aspirin	2728 (0)	2677 (23)	2657 (26)	2629 (31)	2585 (40)	2555 (48)	2531 (49)	2493 (64)	2456 (66)

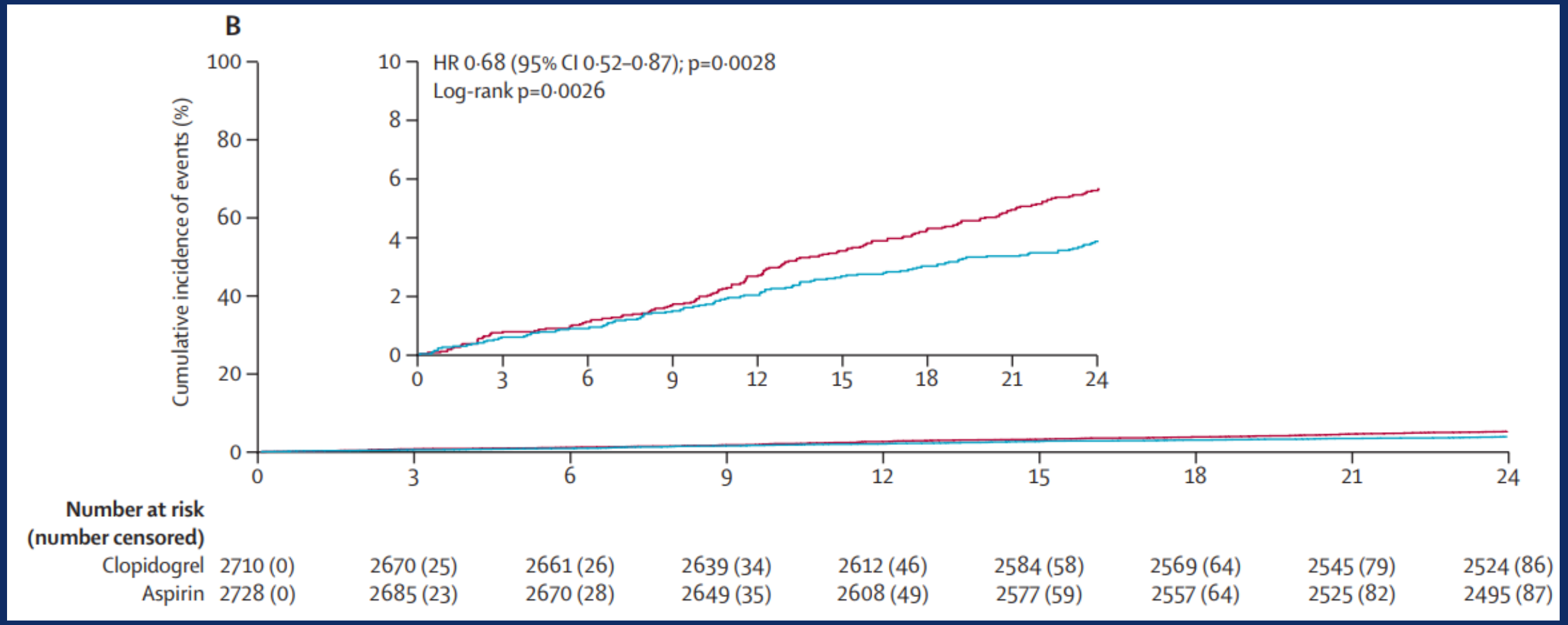
Bon-Kwon Koo et al. Lancet. 2021 Jun 26;397(10293):2487-2496.

HOST-EXAM Trial

30th TCTAP2025

Aspirin vs Clopidogrel for chronic maintenance monotherapy after PCI

- **B) The cumulative incidence of the secondary composite thrombotic endpoint, consisting of cardiac death, non-fatal MI, ischaemic stroke, readmission due to ACS, or definite or probable stent thrombosis**



Number at risk (number censored)									
Clopidogrel	2710 (0)	2670 (25)	2661 (26)	2639 (34)	2612 (46)	2584 (58)	2569 (64)	2545 (79)	2524 (86)
Aspirin	2728 (0)	2685 (23)	2670 (28)	2649 (35)	2608 (49)	2577 (59)	2557 (64)	2525 (82)	2495 (87)

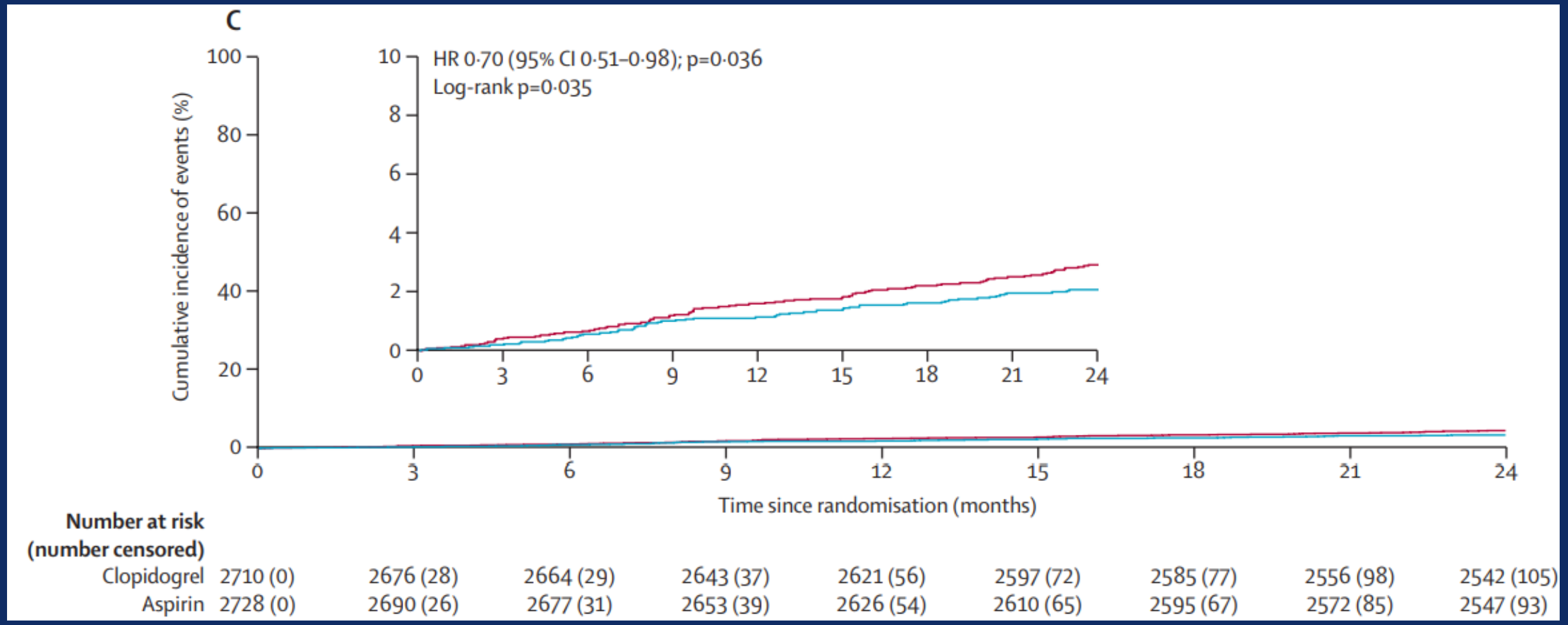
Bon-Kwon Koo et al. Lancet. 2021 Jun 26;397(10293):2487-2496.

HOST-EXAM Trial

30th TCTAP2025

Aspirin vs Clopidogrel for chronic maintenance monotherapy after PCI

- C) The cumulative incidence of any bleeding events.



Number at risk (number censored)									
Clopidogrel	2710 (0)	2676 (28)	2664 (29)	2643 (37)	2621 (56)	2597 (72)	2585 (77)	2556 (98)	2542 (105)
Aspirin	2728 (0)	2690 (26)	2677 (31)	2653 (39)	2626 (54)	2610 (65)	2595 (67)	2572 (85)	2547 (93)

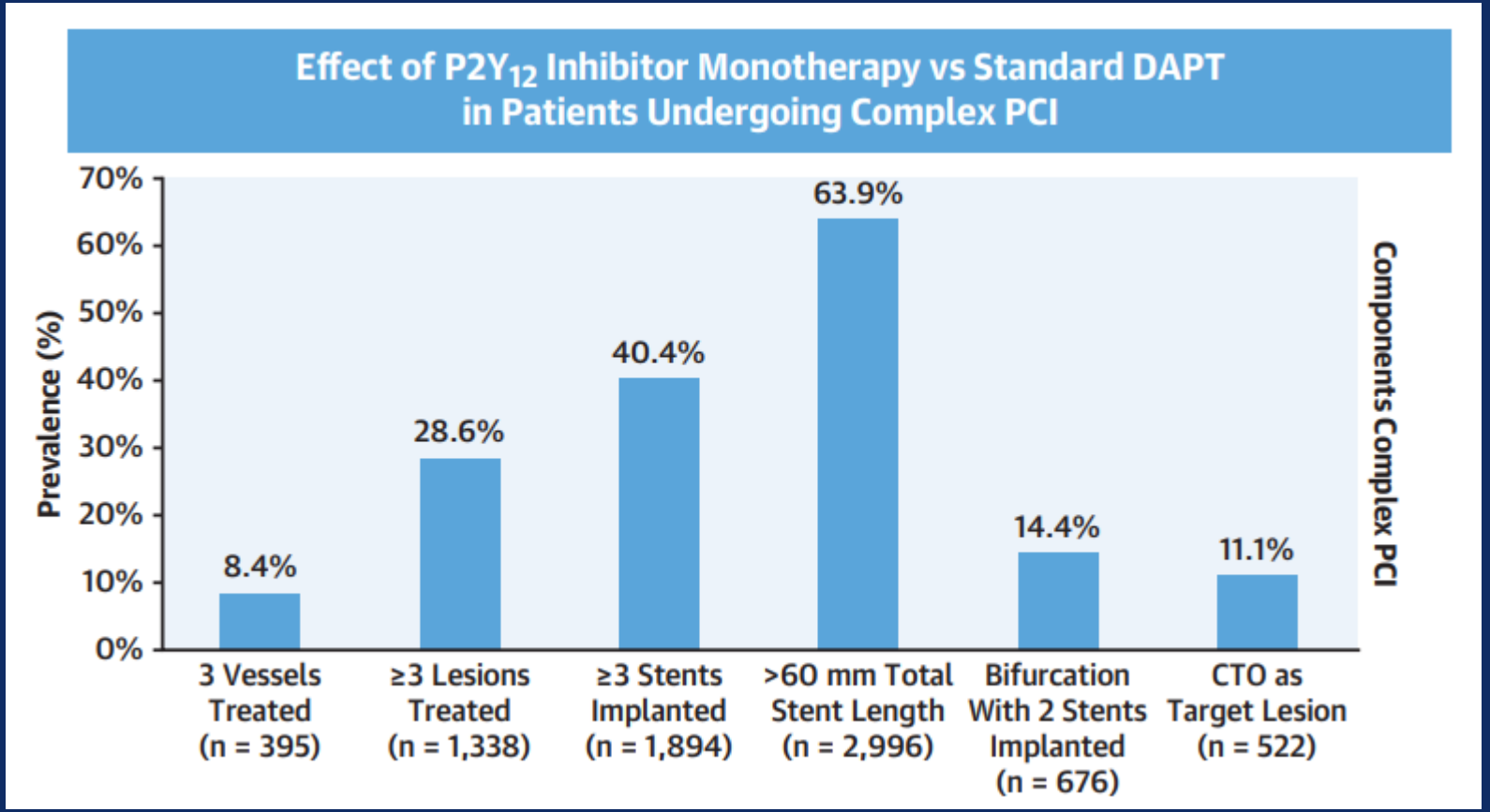
Bon-Kwon Koo et al. Lancet. 2021 Jun 26;397(10293):2487-2496.

P2Y12 Inhibitor Monotherapy or DAPT after Complex PCI: Sidney-2 Meta-Analysis of RCTs.

- Safety and efficacy with P2Y12 inhibitor monotherapy after initial period of DAPT(1 to 3 months)

versus

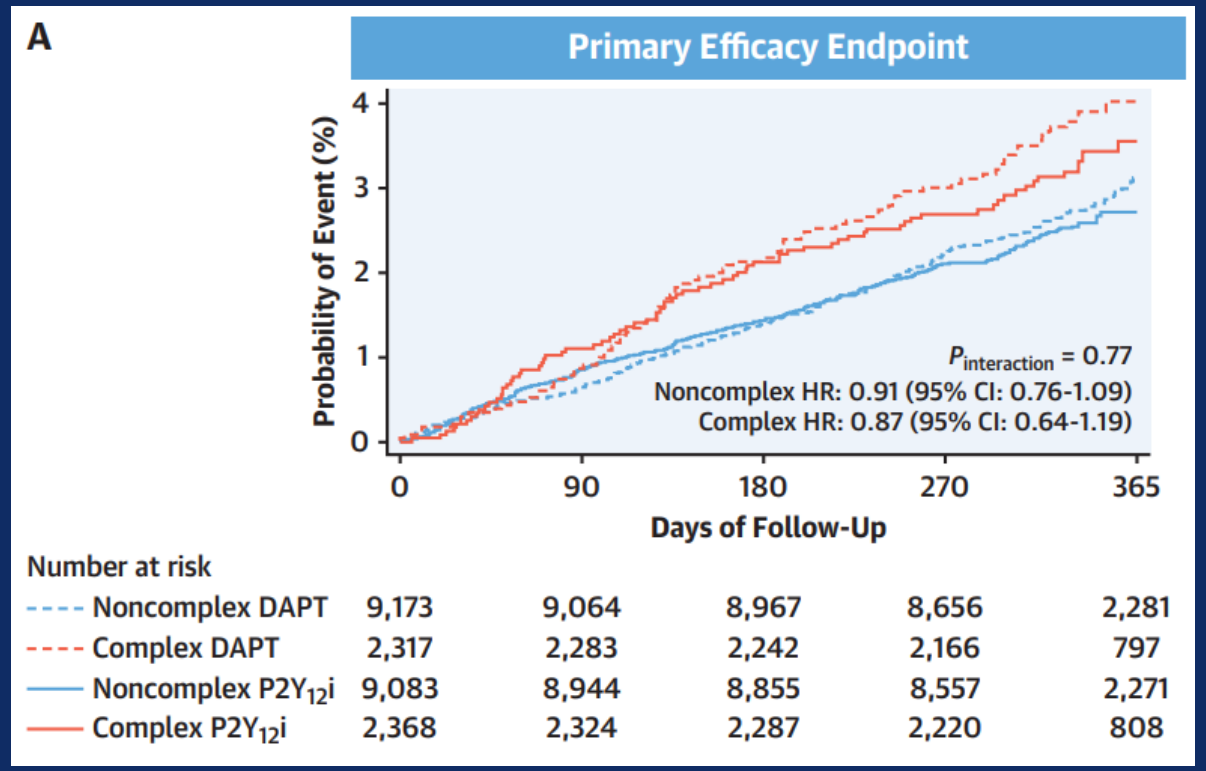
Standard DAPT in patients undergoing complex and noncomplex PCI



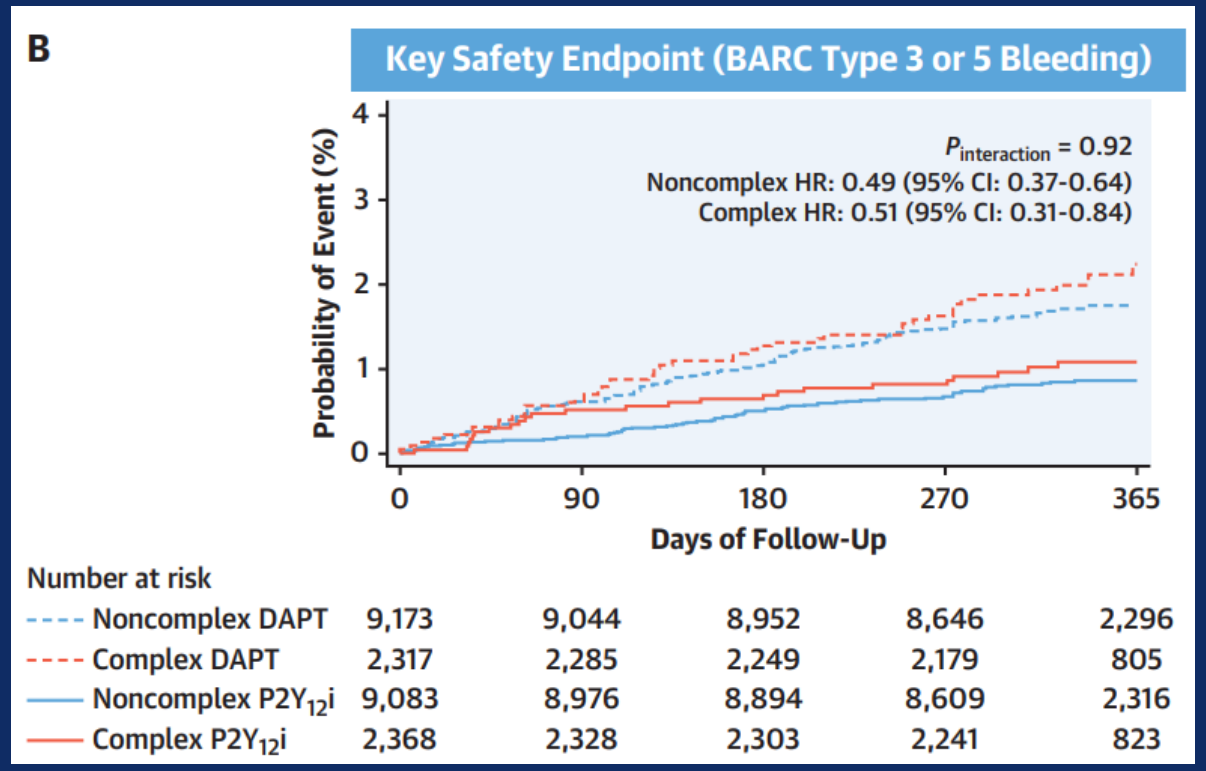
Felice Gragnano et al. J Am Coll Cardiol. 2023 Feb, 81(6)537-552.

P2Y12 Inhibitor Monotherapy or DAPT after Complex PCI: Sidney-2 Meta-Analysis of RCTs.

- A) Primary Efficacy Endpoint (All-cause death, MI, and Stroke)



- B) Key Safety Endpoint (BARC Type 3 or 5 Bleeding)

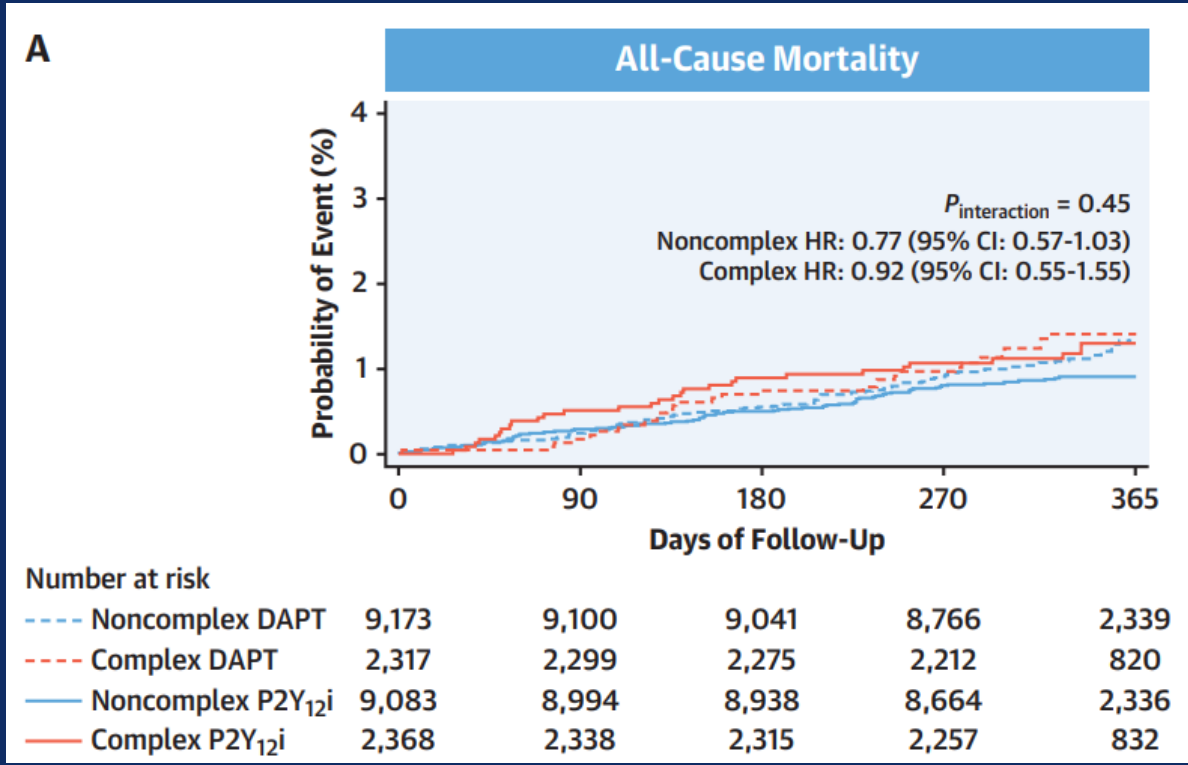


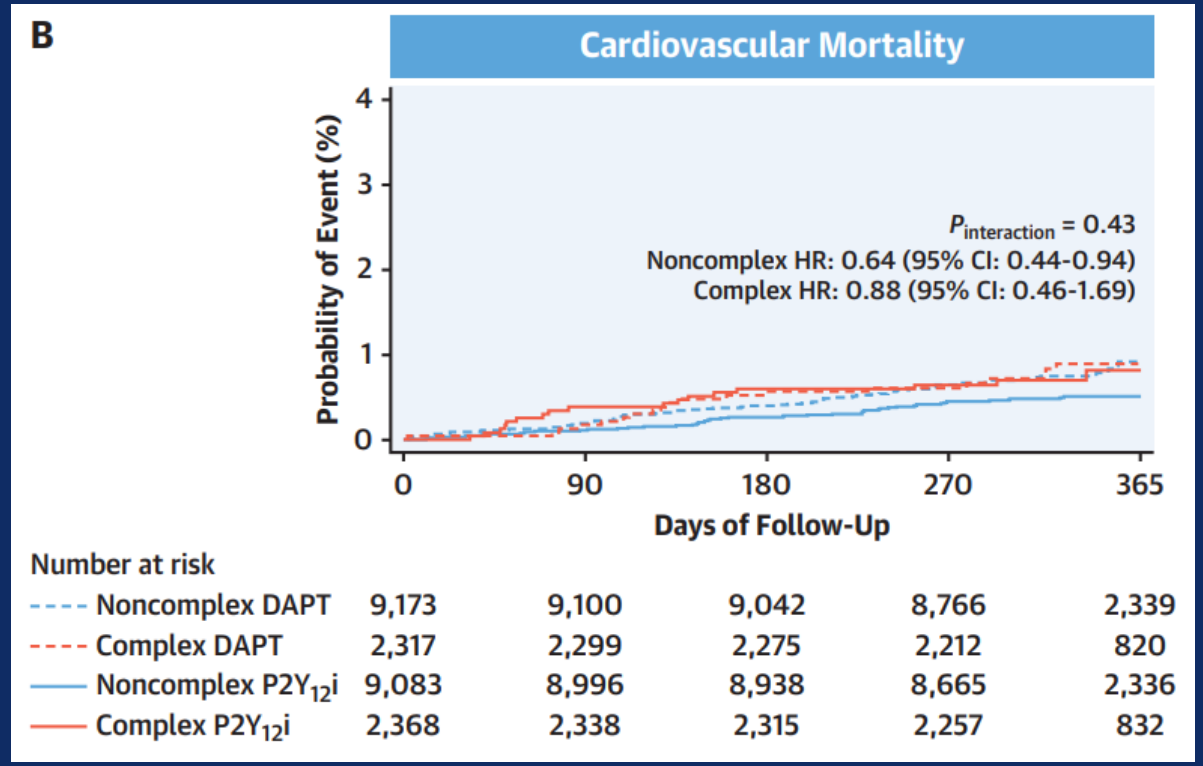
Felice Gragnano et al. J Am Coll Cardiol. 2023 Feb, 81(6)537-552.

P2Y12 Inhibitor Monotherapy or DAPT after Complex PCI: Sidney-2 Meta-Analysis of RCTs.

- A) All-Cause Mortality

B) Cardiovascular Mortality

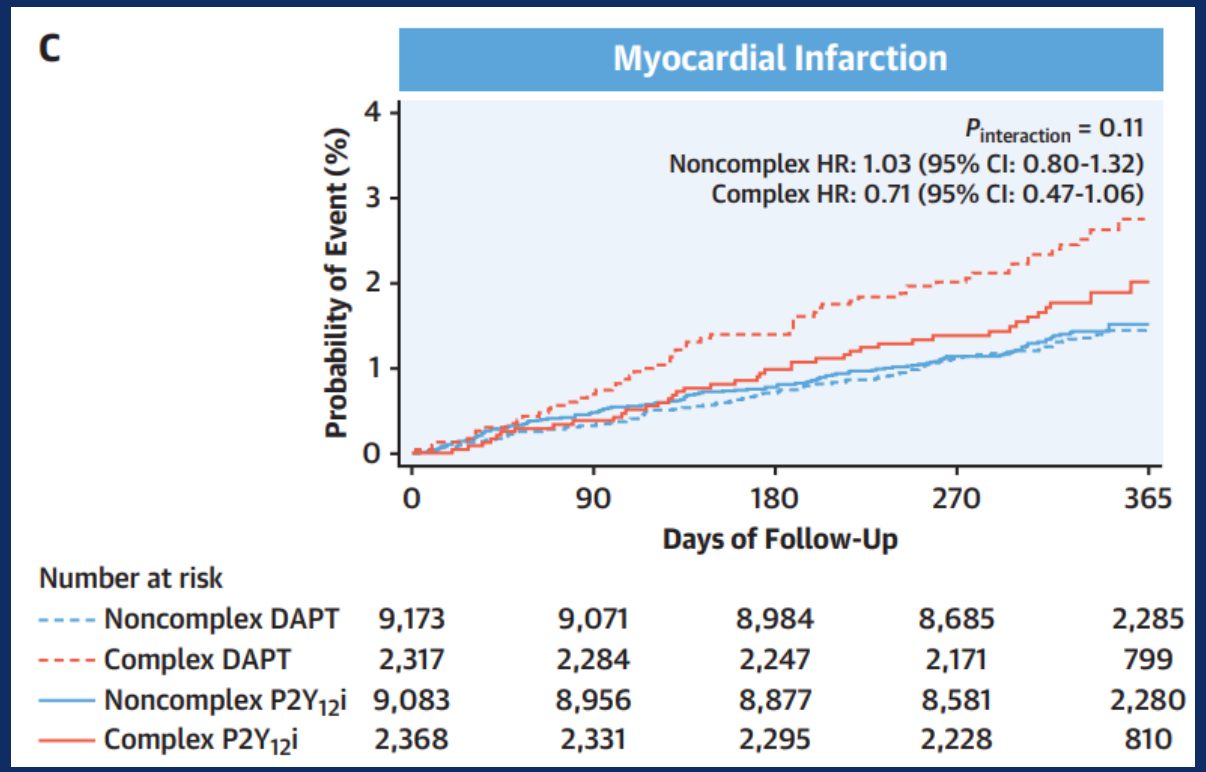


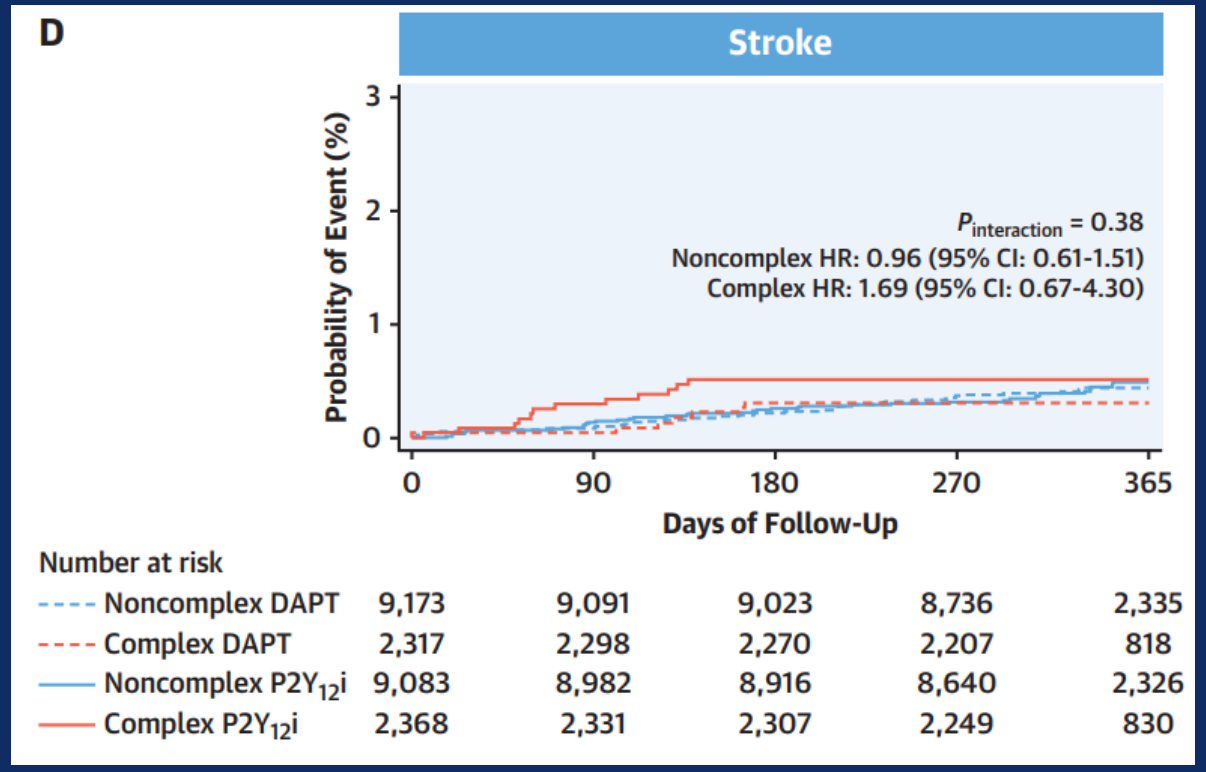


Felice Gragnano et al. J Am Coll Cardiol. 2023 Feb, 81(6)537-552.

P2Y12 Inhibitor Monotherapy or DAPT after Complex PCI: Sidney-2 Meta-Analysis of RCTs.

- C) Myocardial Infarction
- D) Stroke

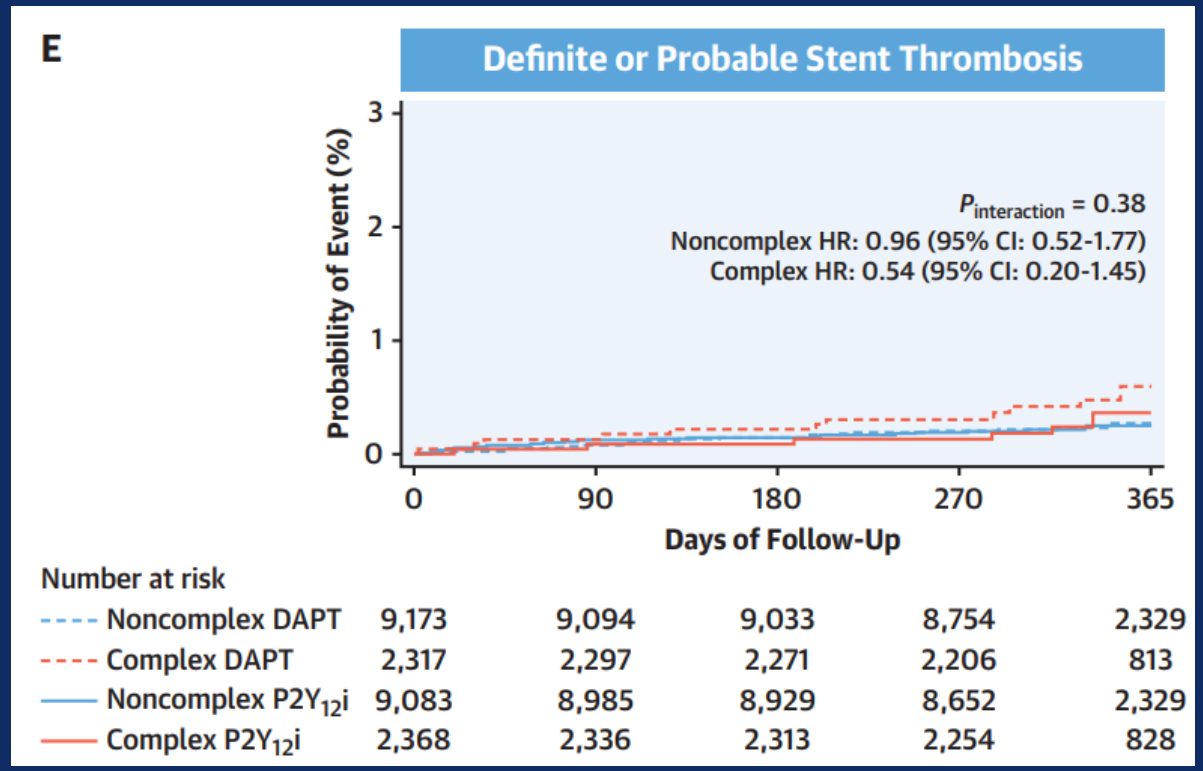


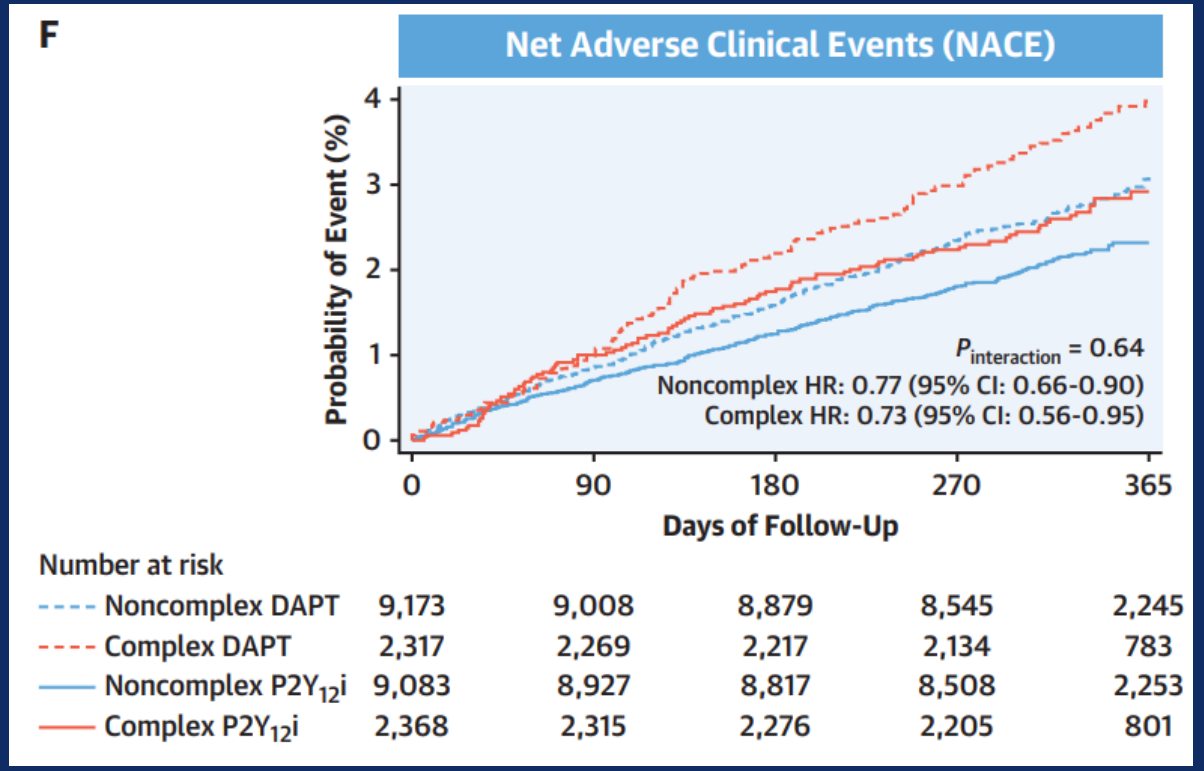


Felice Gragnano et al. J Am Coll Cardiol. 2023 Feb, 81(6)537-552.

P2Y12 Inhibitor Monotherapy or DAPT after Complex PCI: Sidney-2 Meta-Analysis of RCTs.

- E) Definite or Probable Stent Thrombosis
- F) Net Adverse Clinical Events (NACE)





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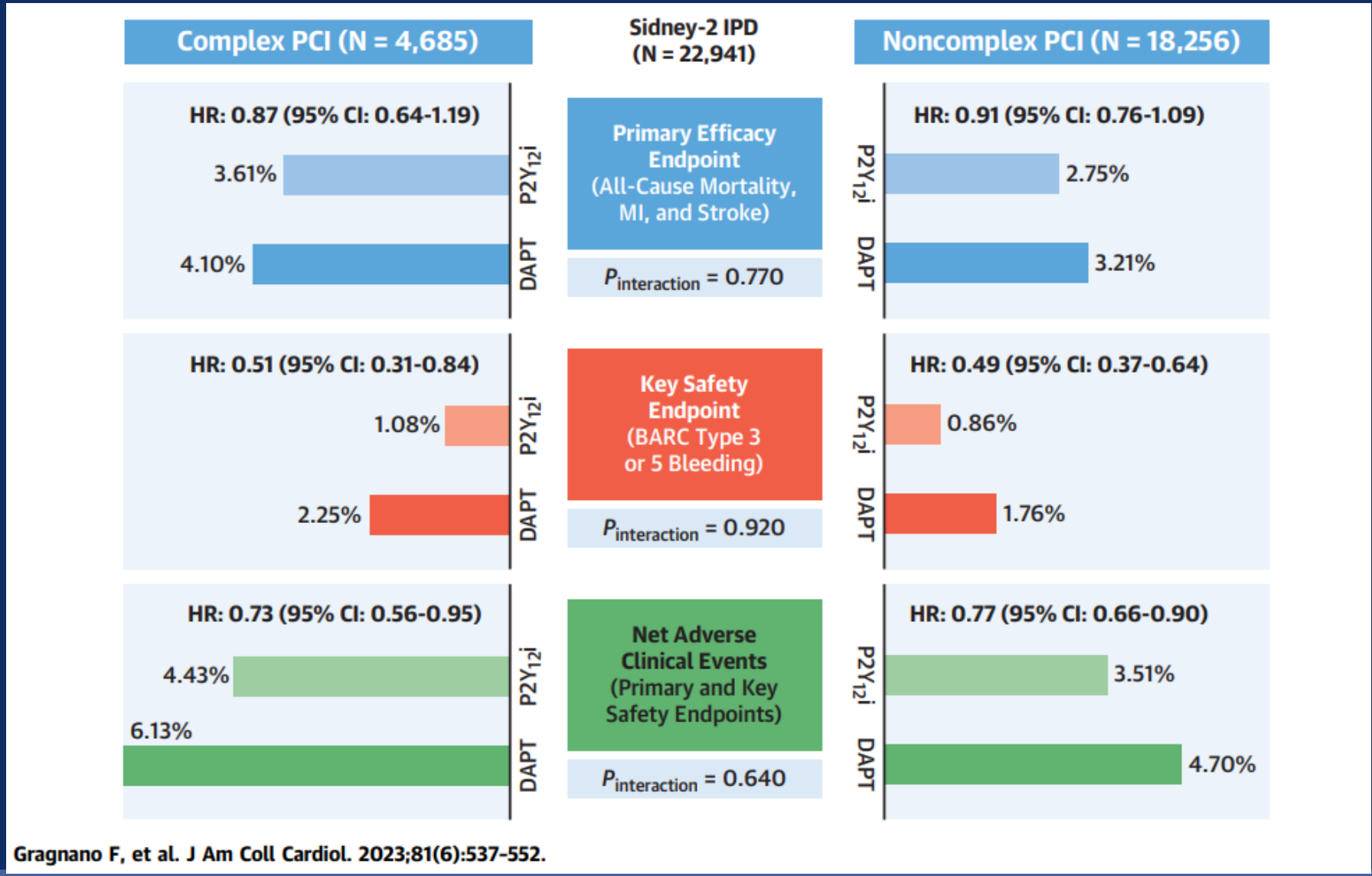
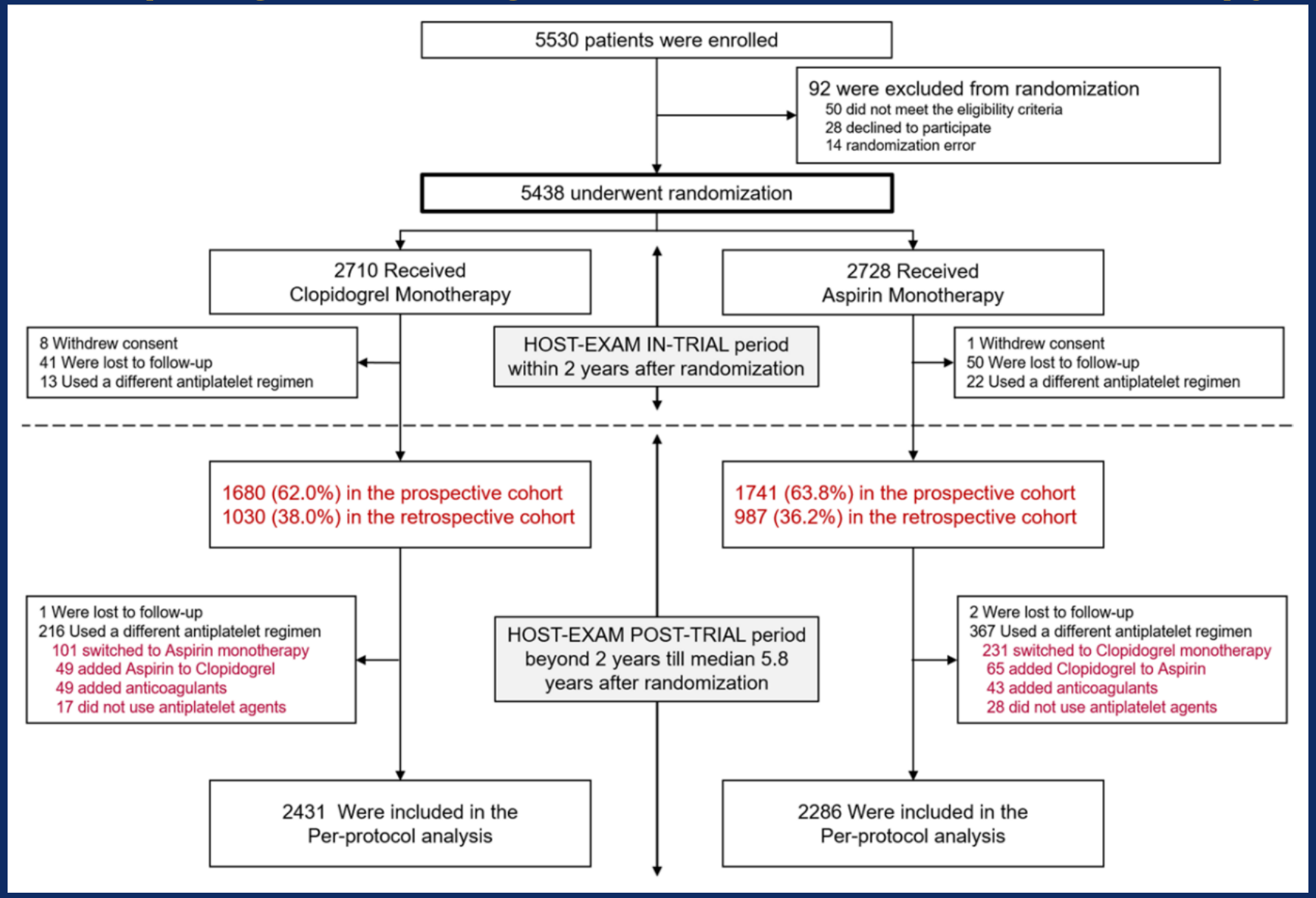
P2Y12 Inhibitor Monotherapy or DAPT after Complex PCI: Sidney-2 Meta-Analysis of RCTs.



Gragnano F, et al. J Am Coll Cardiol. 2023;81(6):537-552.

HOST-EXAM Extended Study

Aspirin vs Clopidogrel for long term maintenance monotherapy after PCI

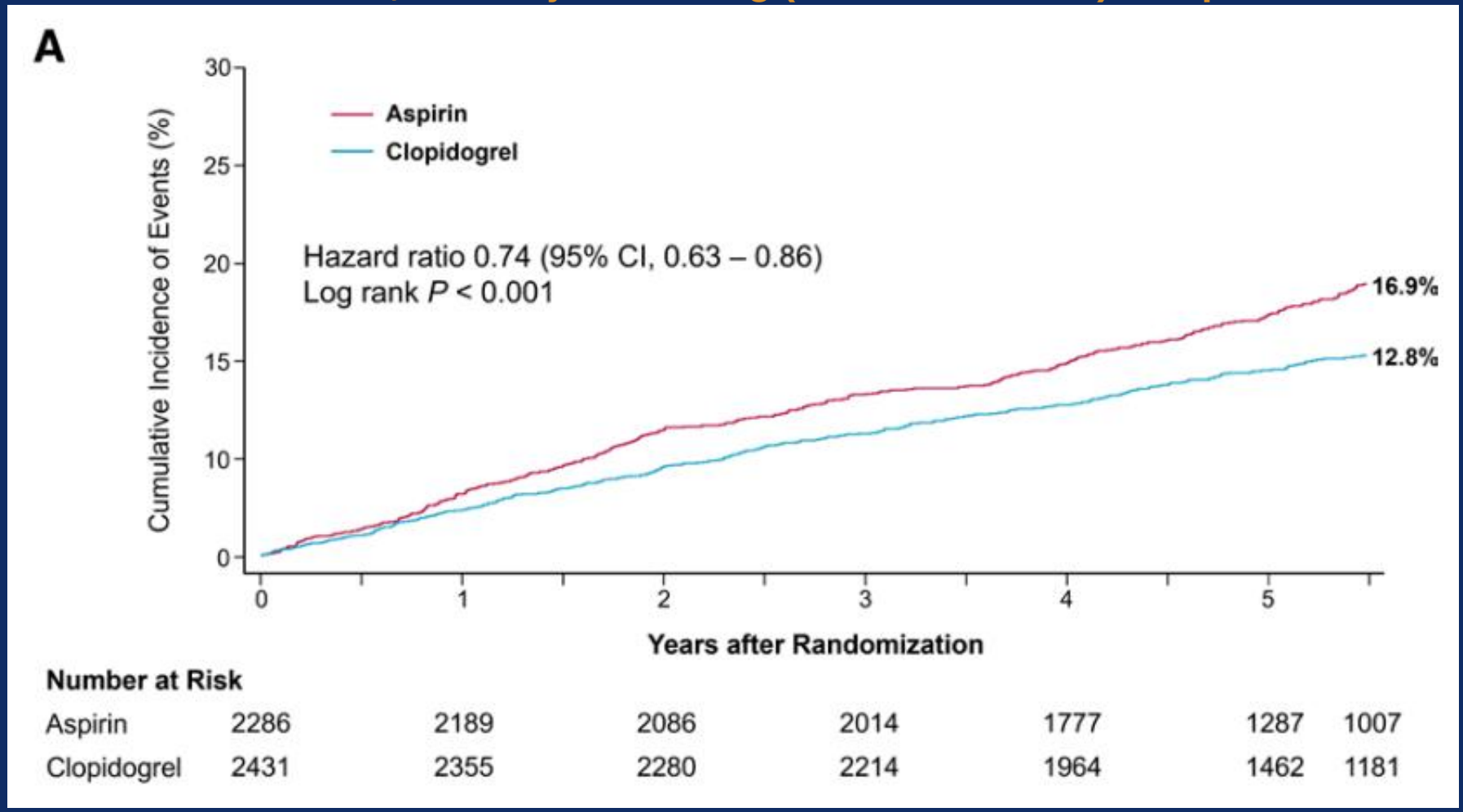


Jeehoon Kang et al. Circulation. 2023;147:108-117.

HOST-EXAM Extended Study

Aspirin vs Clopidogrel for long term maintenance monotherapy after PCI

- A) The cumulative incidence of the primary endpoint, consisting of all-cause death, non-fatal MI, stroke, readmission due to ACS, and major bleeding (BARC 3 or more) complications



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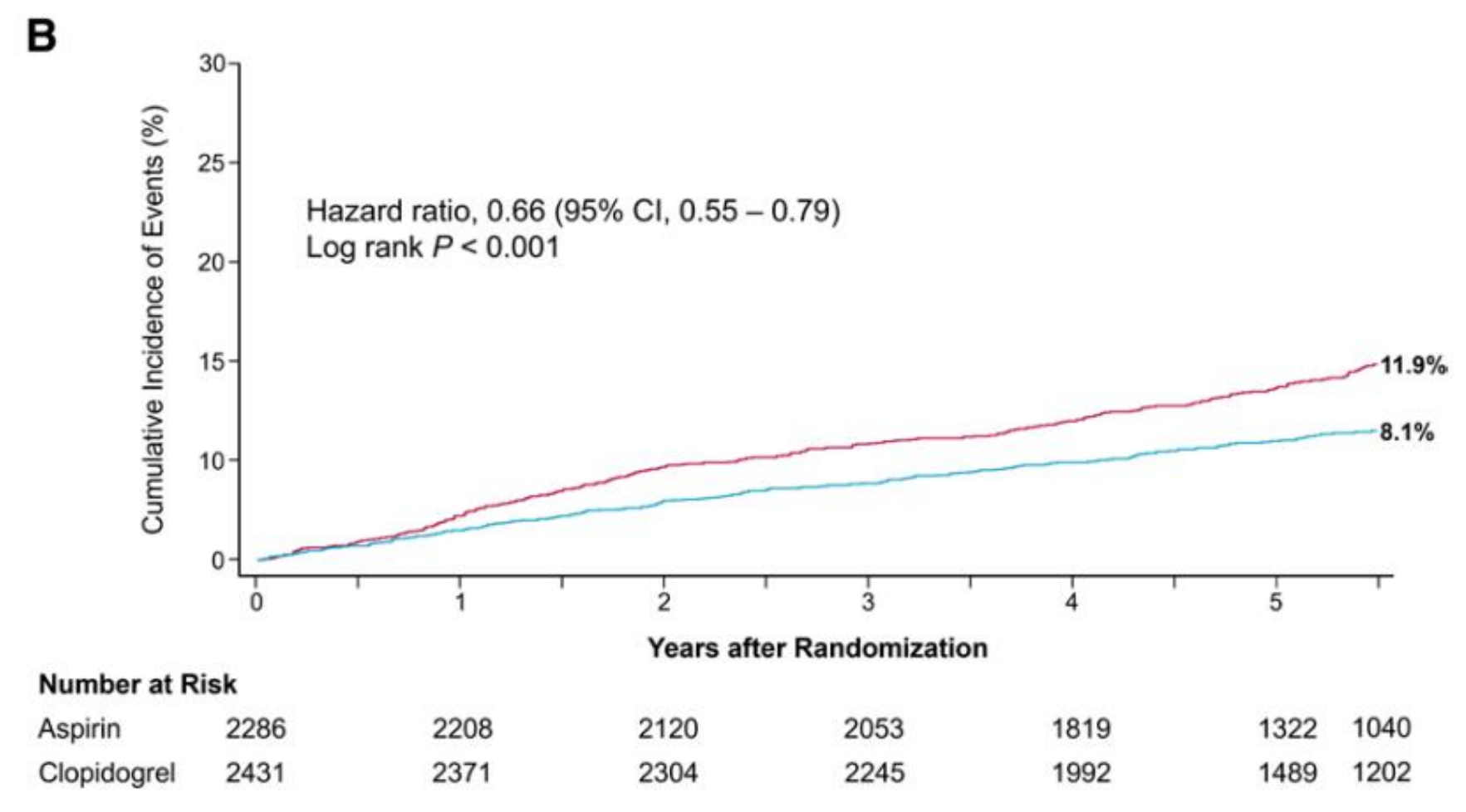
HOST-EXAM Extended Study

Aspirin vs Clopidogrel for long term maintenance monotherapy after PCI

- B) The cumulative incidence of the secondary composite thrombotic endpoint, consisting of cardiac death, non-fatal MI, ischaemic stroke, readmission due to ACS, or definite or probable stent thrombosis

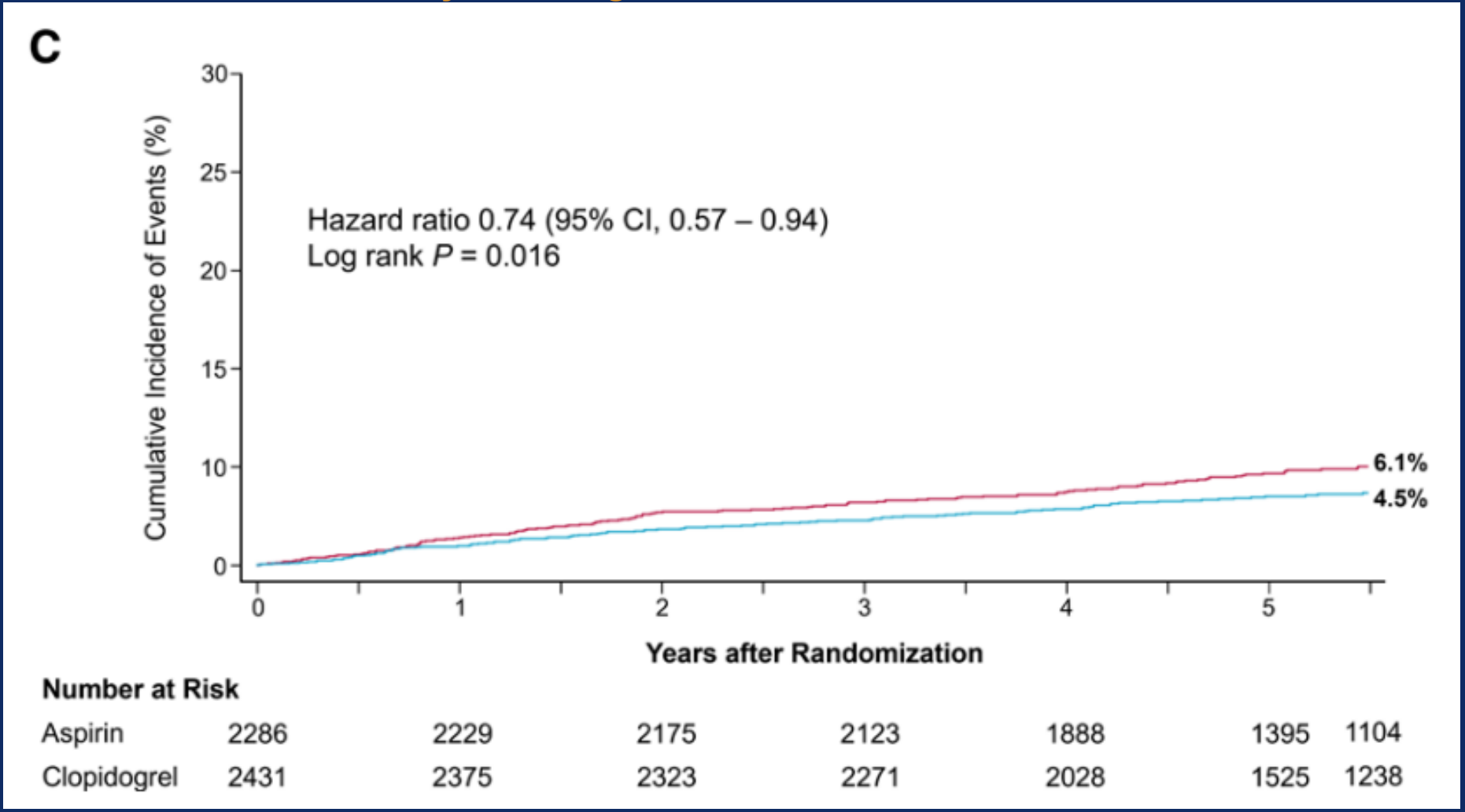


Jeehoon Kang et al. Circulation. 2023;147:108-117.

HOST-EXAM Extended Study

Aspirin vs Clopidogrel for long term maintenance monotherapy after PCI

- C) The cumulative incidence of any bleeding events.

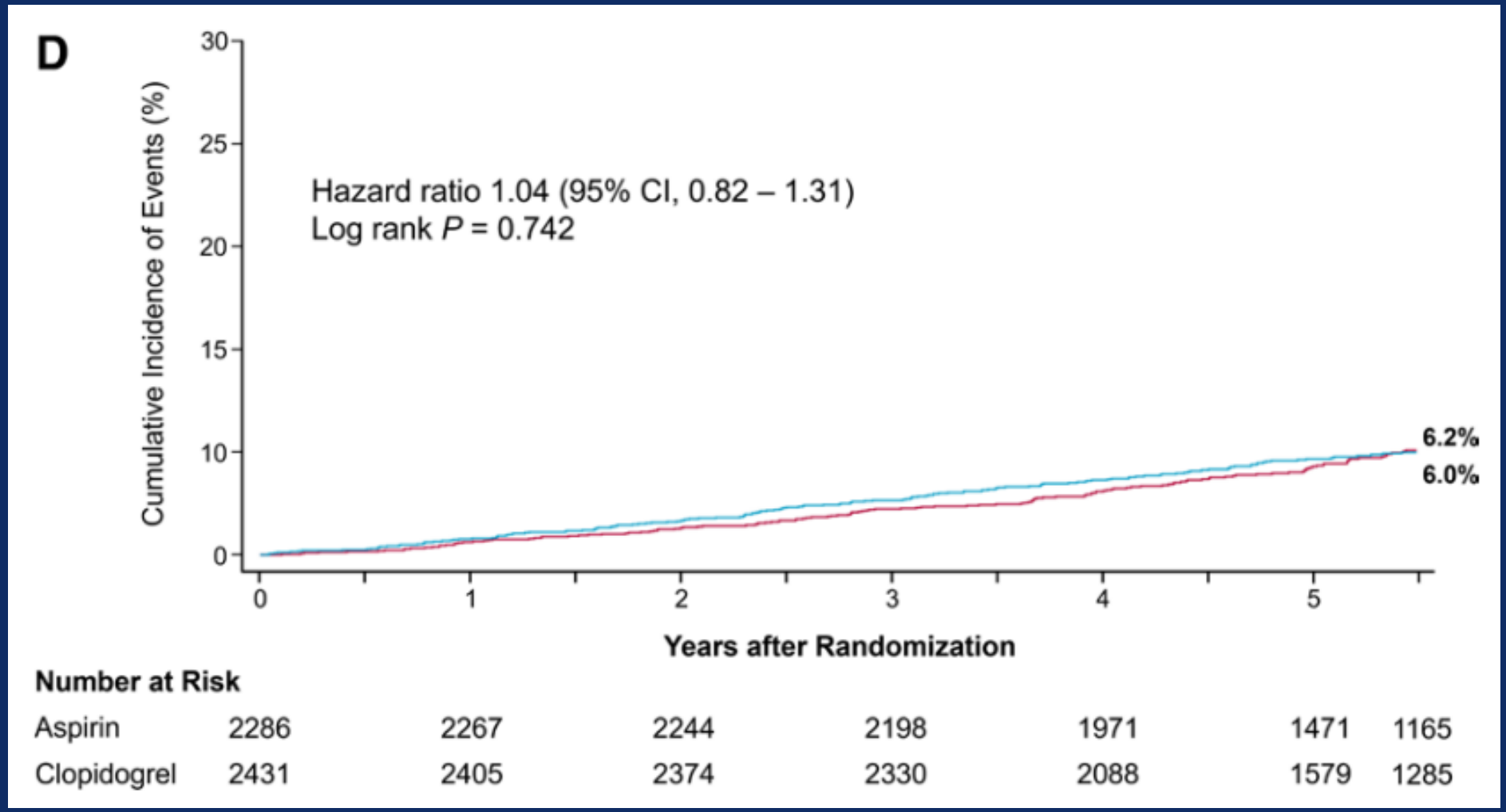


Jeehoon Kang et al. Circulation. 2023;147:108-117.

HOST-EXAM Extended Study

Aspirin vs Clopidogrel for long term maintenance monotherapy after PCI

- D) The cumulative incidence of all-cause death.

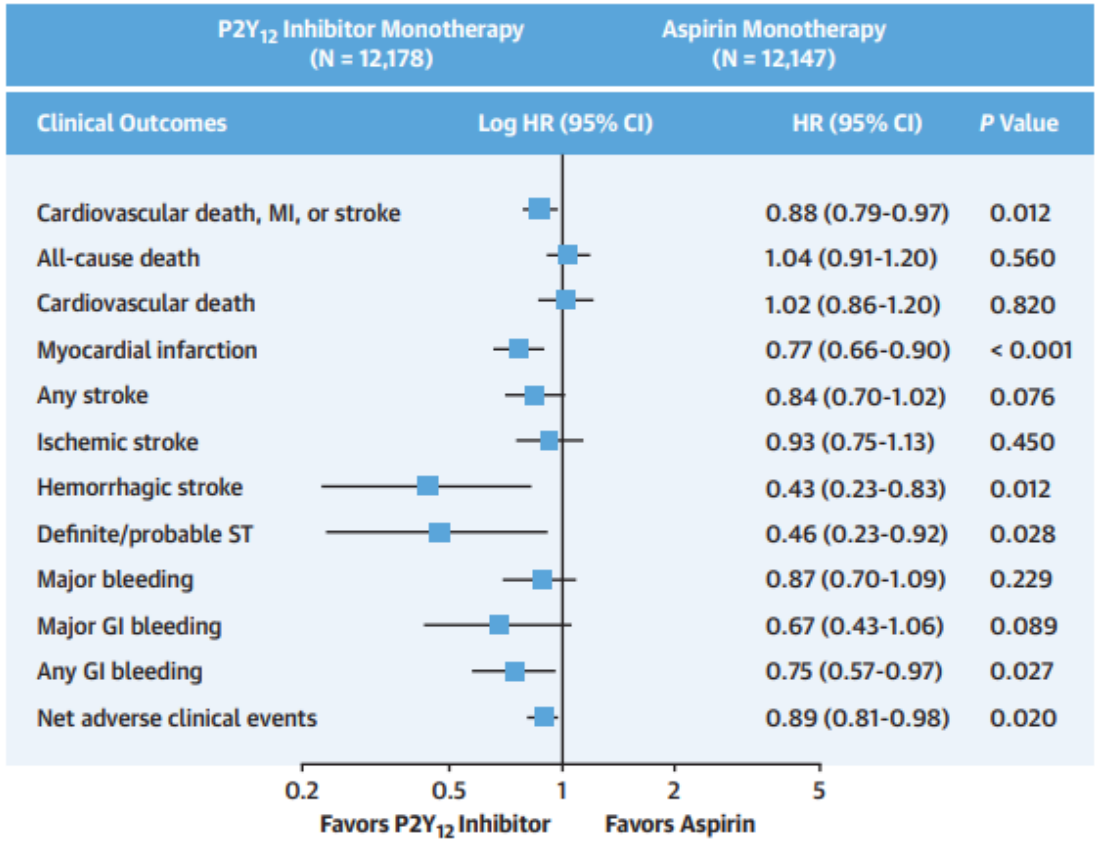


Jeehoon Kang et al. Circulation. 2023;147:108-117.

P2Y12 Inhibitor or Aspirin Monotherapy for Secondary Prevention of Coronary Events ; PANTHER Meta-Analysis

- Safety and efficacy with P2Y12 inhibitor monotherapy versus aspirin in patients with CAD

CENTRAL ILLUSTRATION $P2Y_{12}$ Inhibitor Monotherapy Versus Aspirin Monotherapy in Patients With Coronary Artery Disease

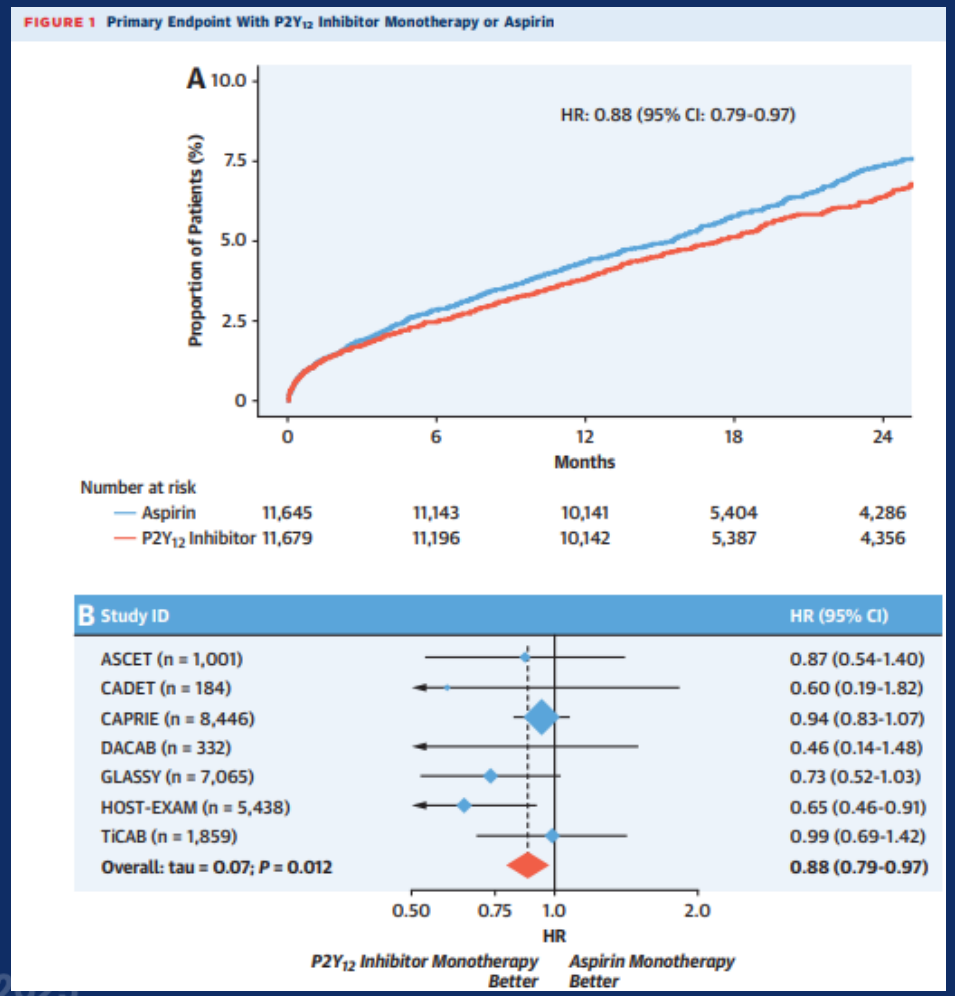


Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

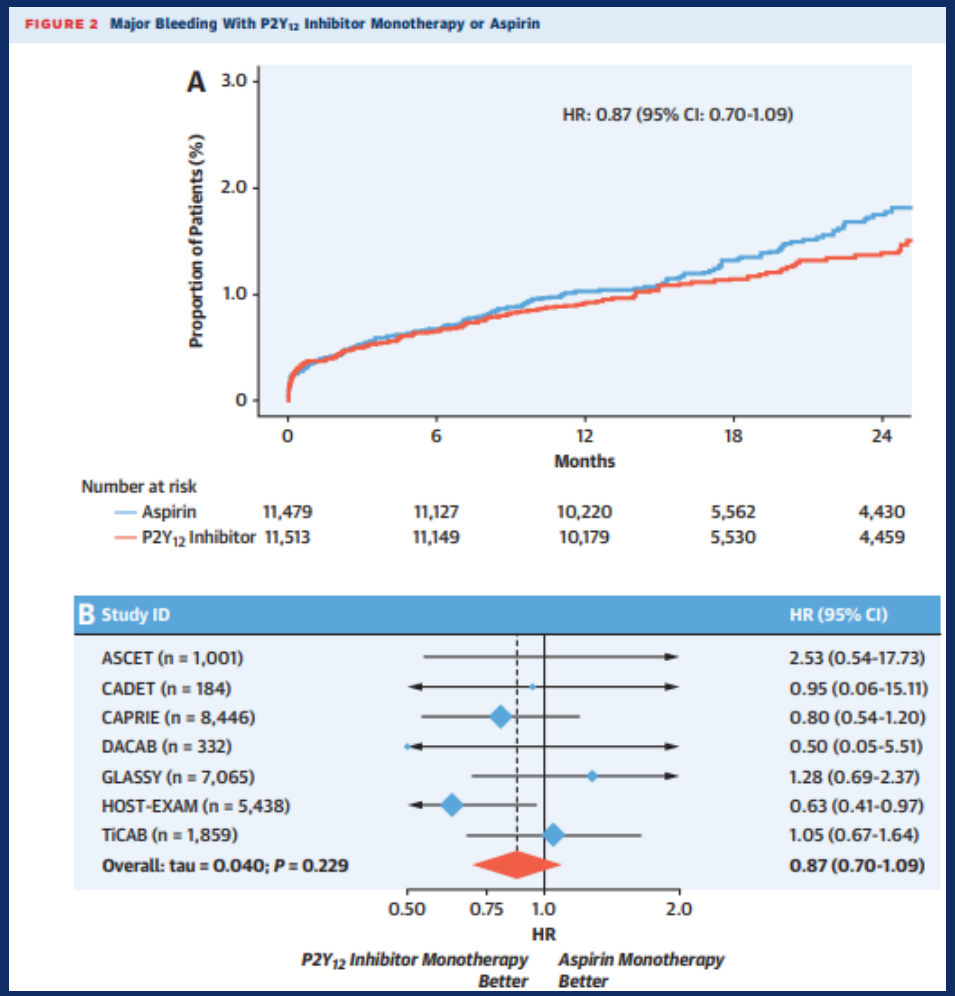
Felice Gragnano et al. J Am Coll Cardiol. 2023 Jul, 82(2):89-105.

P2Y12 Inhibitor or Aspirin Monotherapy for Secondary Prevention of Coronary Events ; PANTHER Meta-Analysis

A) Primary Endpoint



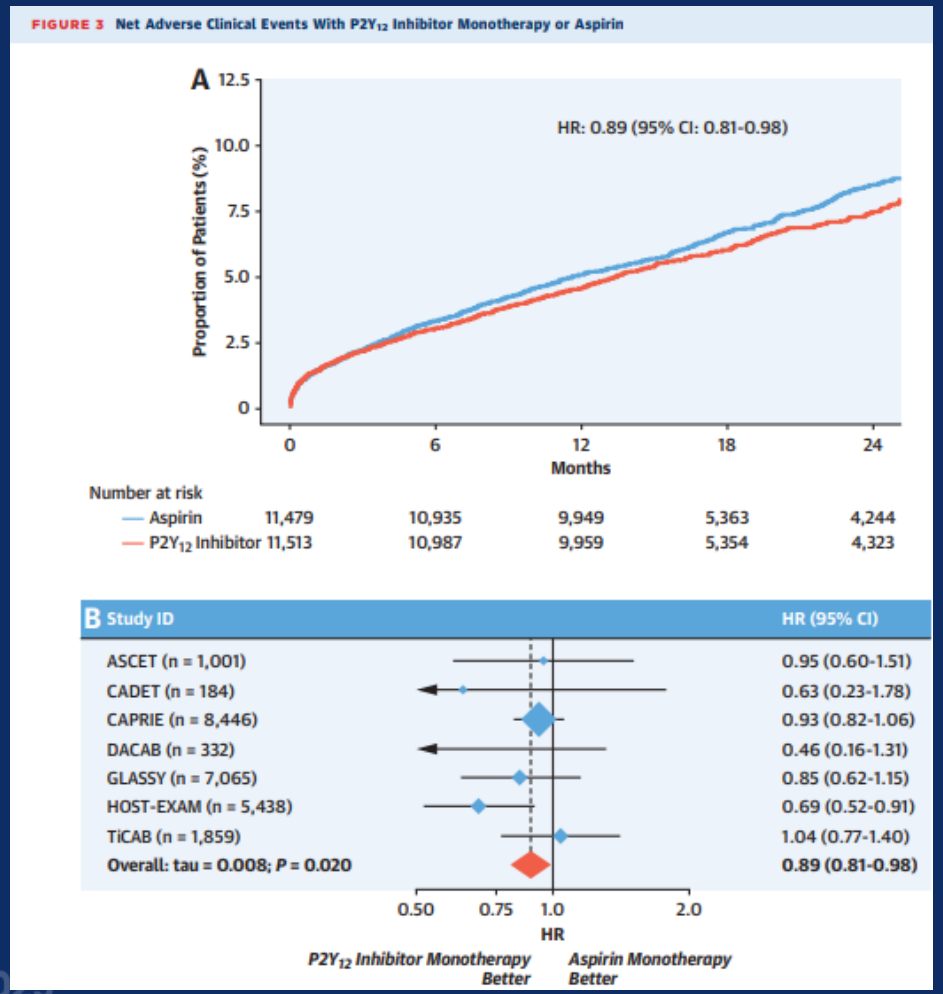
B) Major Bleeding



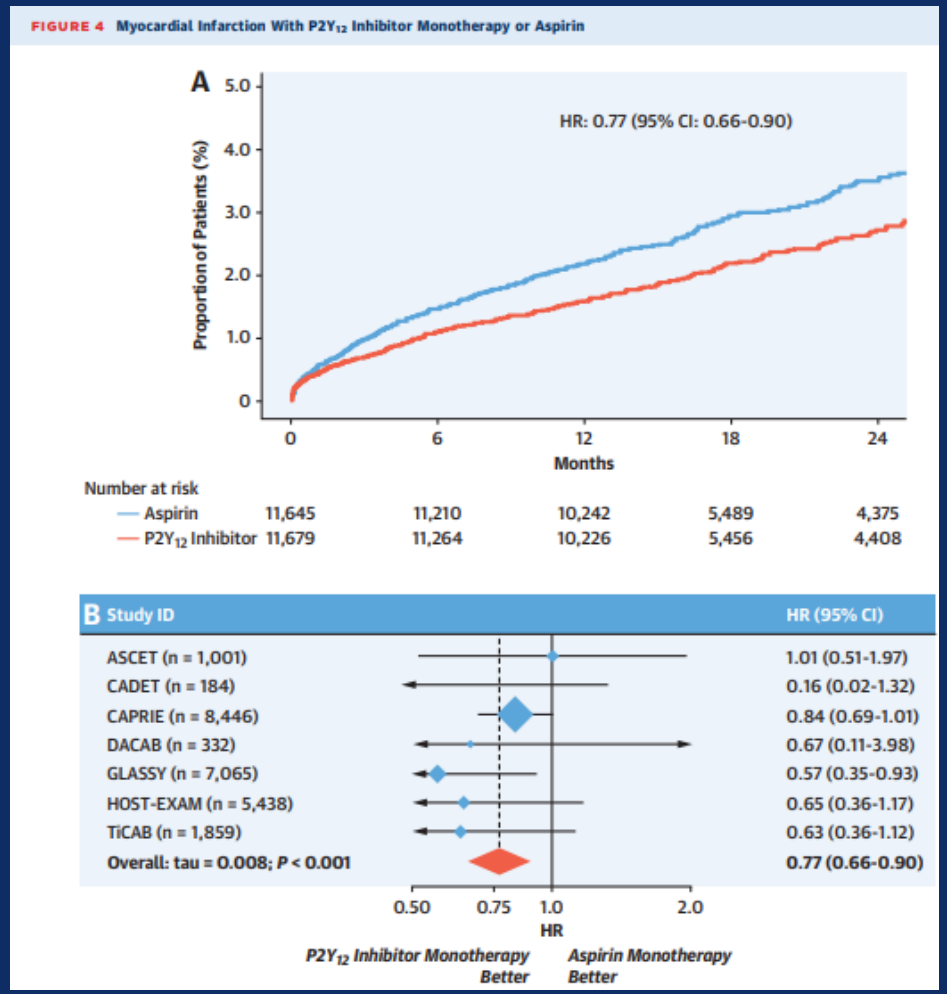
Felice Gragnano et al. J Am Coll Cardiol. 2023 Jul, 82(2):89-105.

P2Y12 Inhibitor or Aspirin Monotherapy for Secondary Prevention of Coronary Events ; PANTHER Meta-Analysis

C) Net Adverse Clinical Events (NACE)



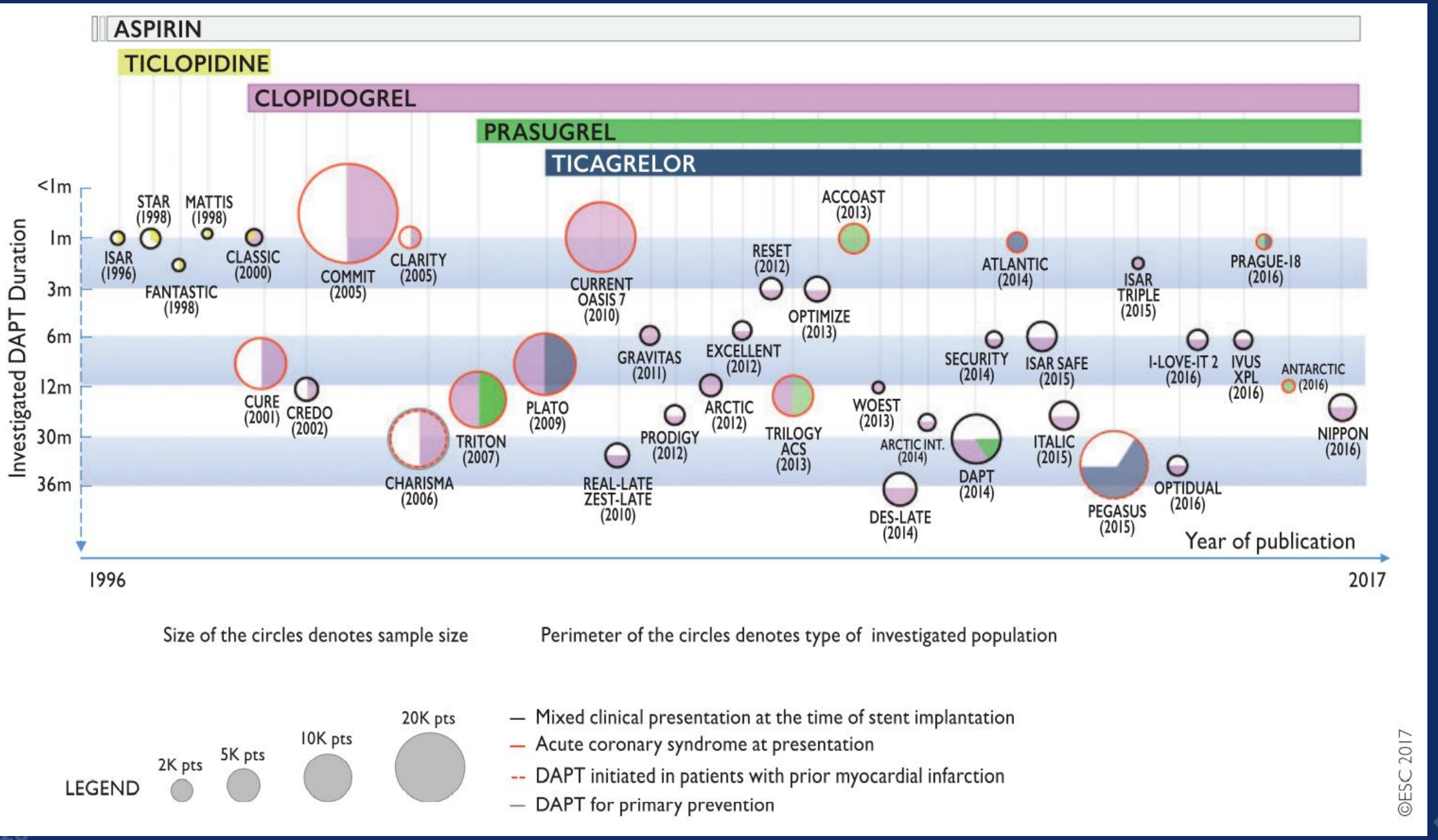
D) Myocardial infarction



Felice Gragnano et al. J Am Coll Cardiol. 2023 Jul, 82(2):89-105.

Antiplatelet Therapy in CAD

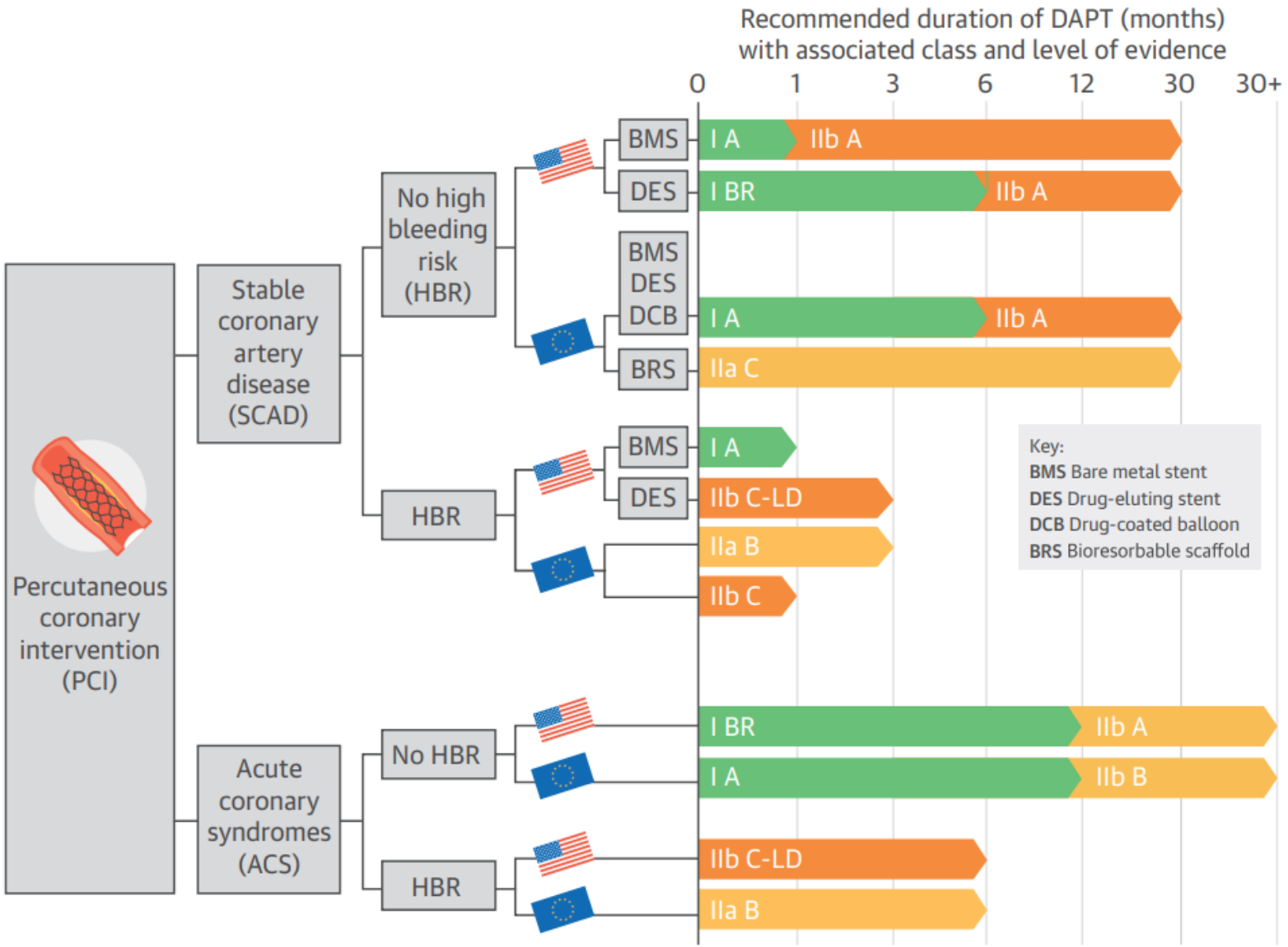
Antiplatelet Therapy in CAD



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

Antiplatelet Therapy in CAD

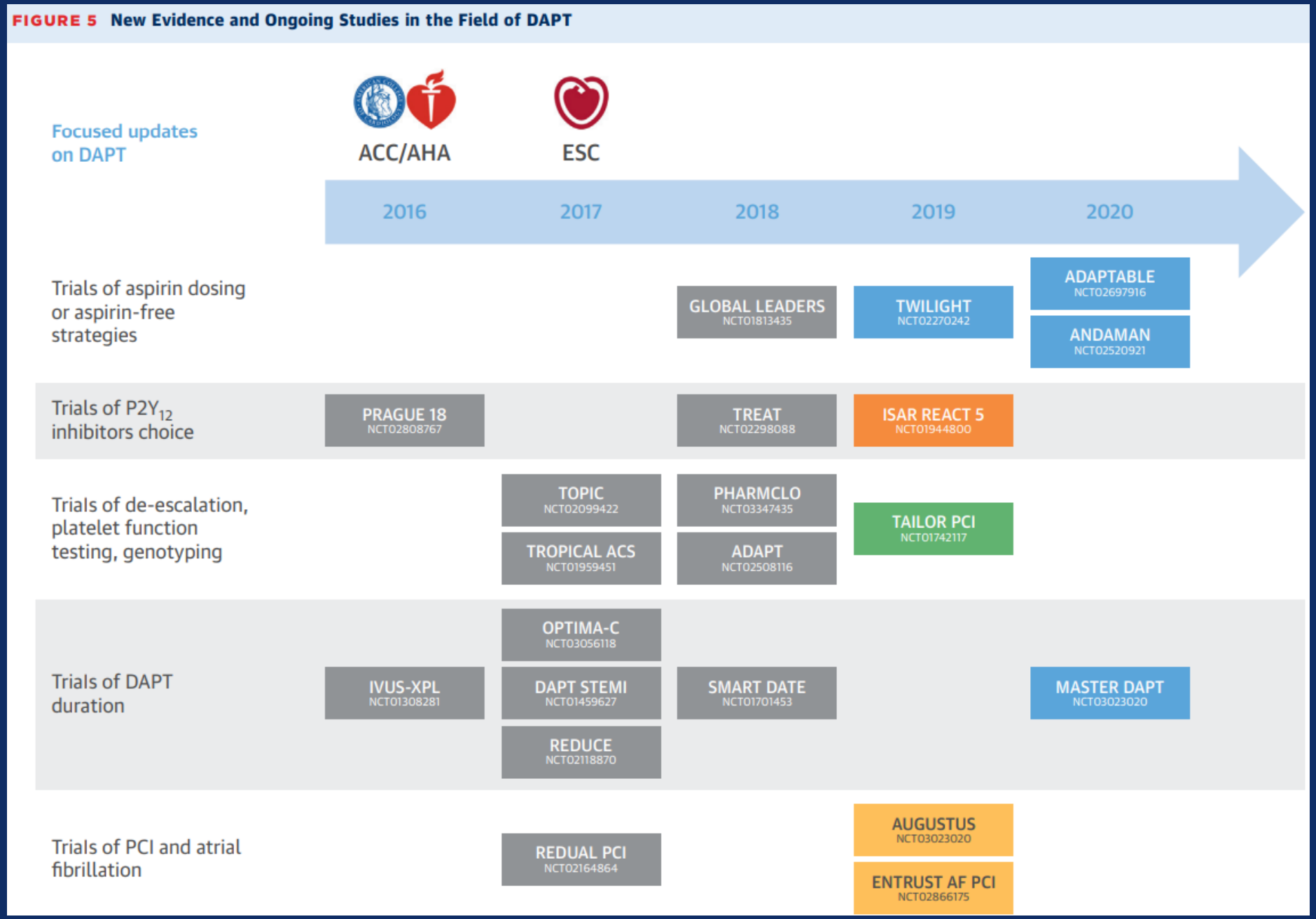
CENTRAL ILLUSTRATION **Recommendations for Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention**



Capodanno, D. et al. J Am Coll Cardiol. 2018;72(23):2915-31.

Antiplatelet Therapy in CAD

FIGURE 5 New Evidence and Ongoing Studies in the Field of DAPT



TAILORED-CHIP Trial

Tailored P2Y12 Strategy for CHIP patients

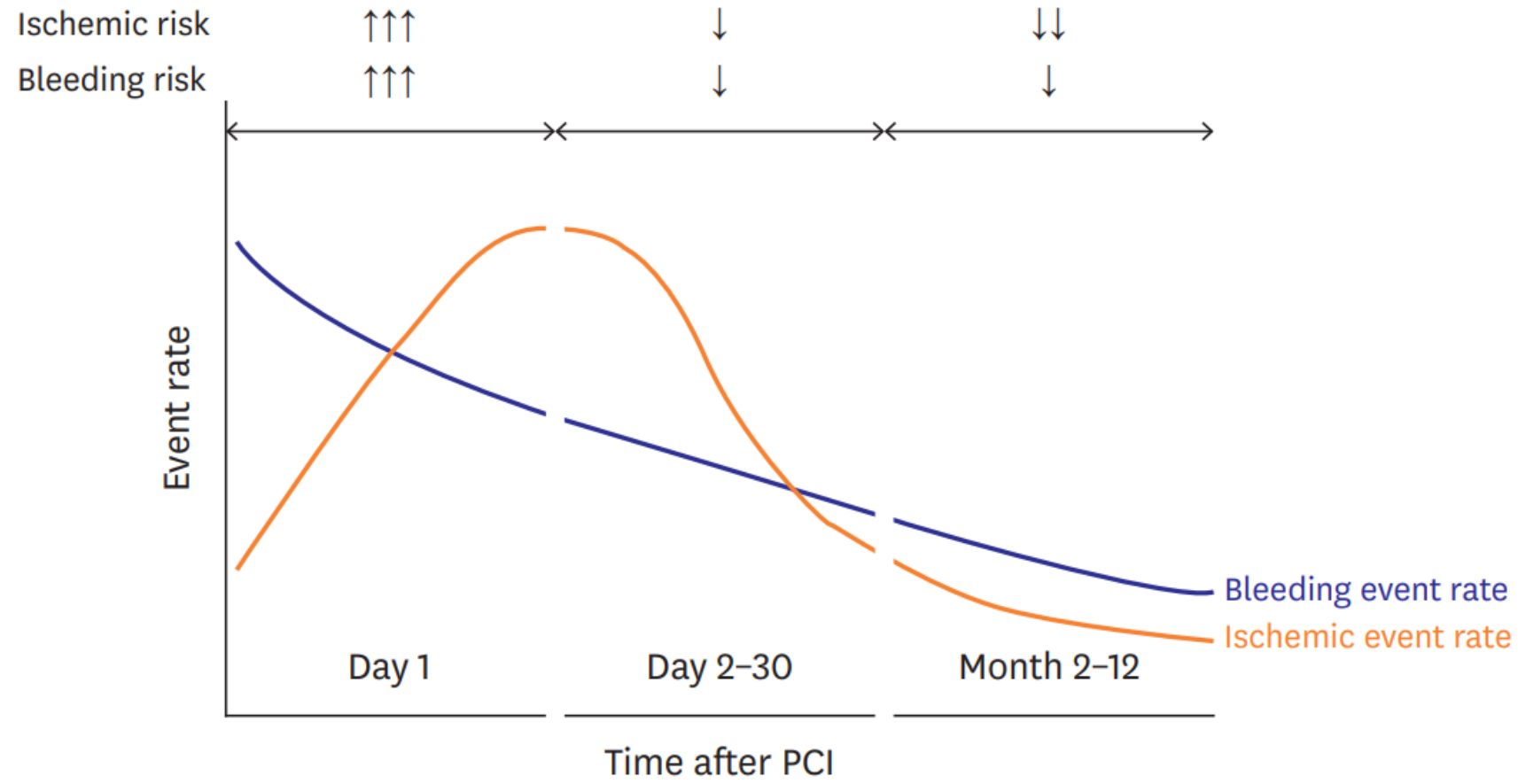


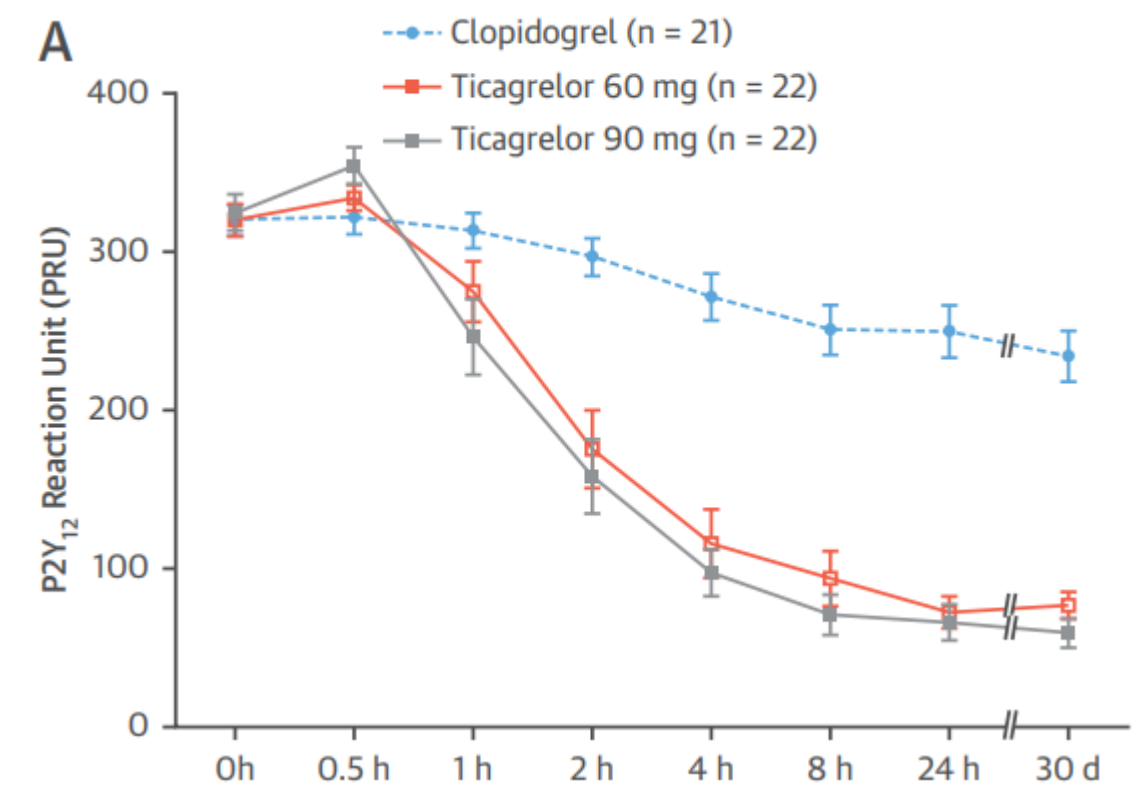
Figure 1. Timing of ischemic versus bleeding events after PCI. Ischemic and bleeding rates after PCI are displayed dependent on time. Whereas ischemic rates reach a plateau during the first month, bleeding rates steadily decline. In the second month, ischemic events substantially decrease resulting in an exuberant bleeding risk in the later phase post-PCI.
PCI = percutaneous coronary intervention.

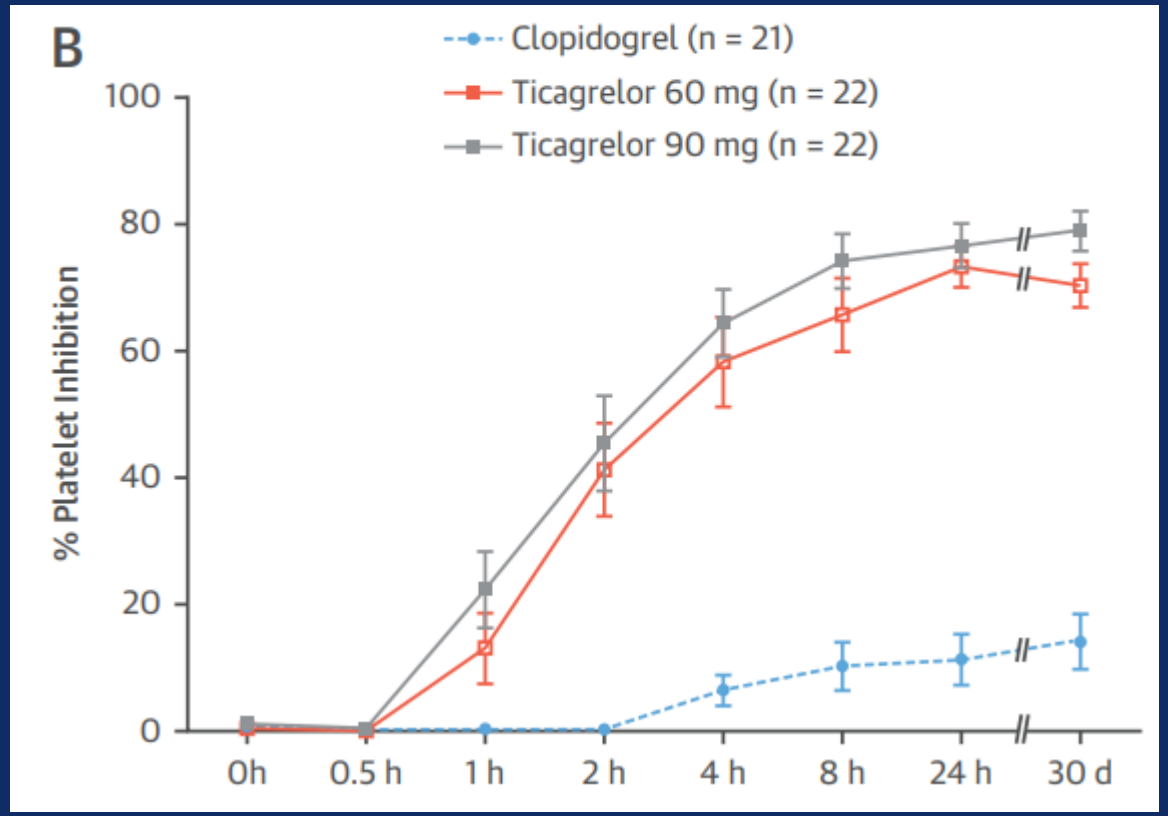
Danny Kupka et al. Korean Circ J. 2018 Oct;48(10):863-872.

30th TCTAP2025

TAILORED-CHIP Trial

Tailored P2Y12 Strategy for CHIP patients





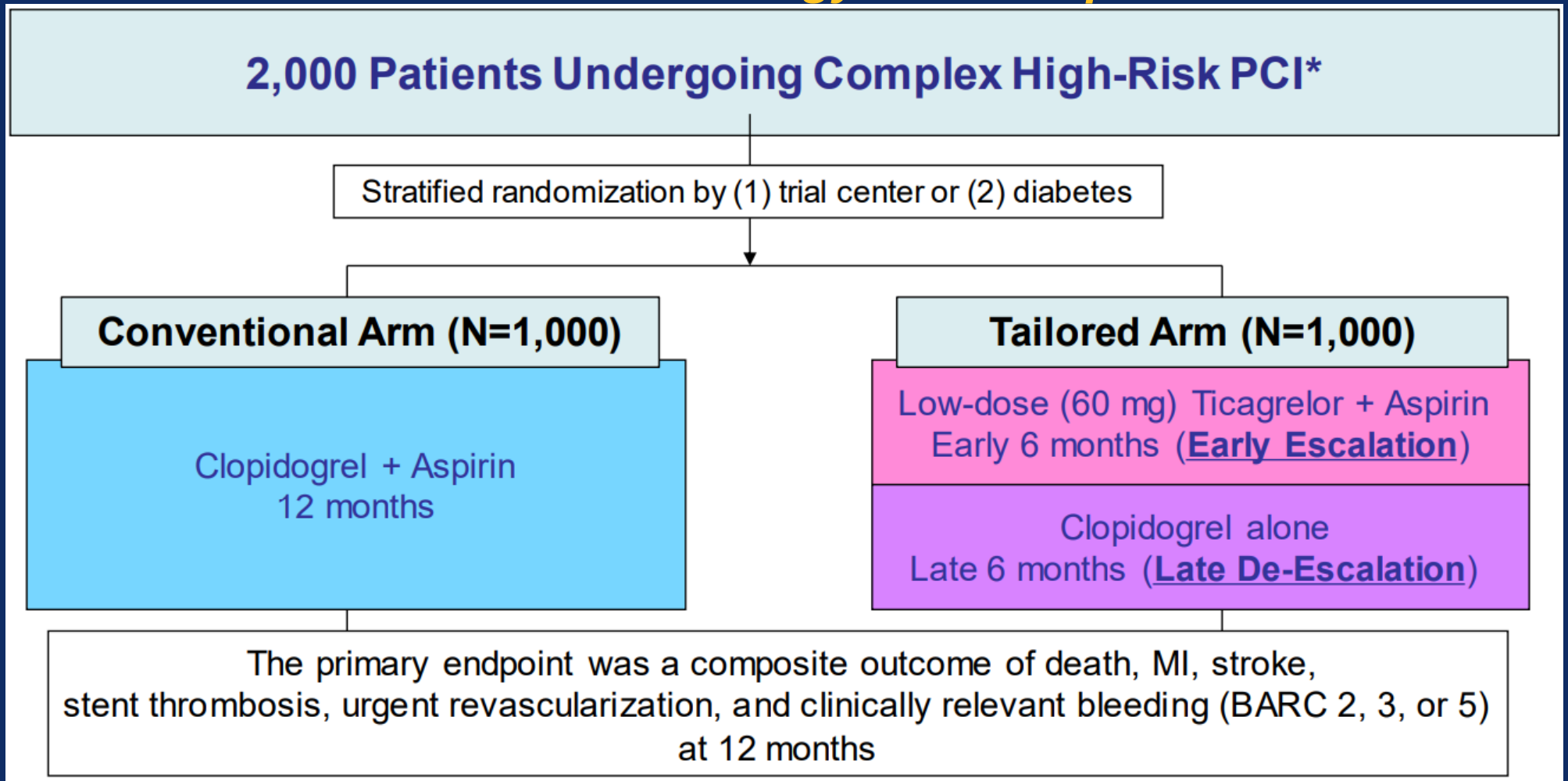
- **Ticagrelor 60 mg might provide better safety and tolerability than ticagrelor 90 mg with similar efficacy in East Asian patients with ACS. From OPTIMA trial**

CVRF

Duk-Woo Park et al. J Am Coll Cardiol. 2018 Apr 10;71(14):1594-1595.

TAILORED-CHIP Trial

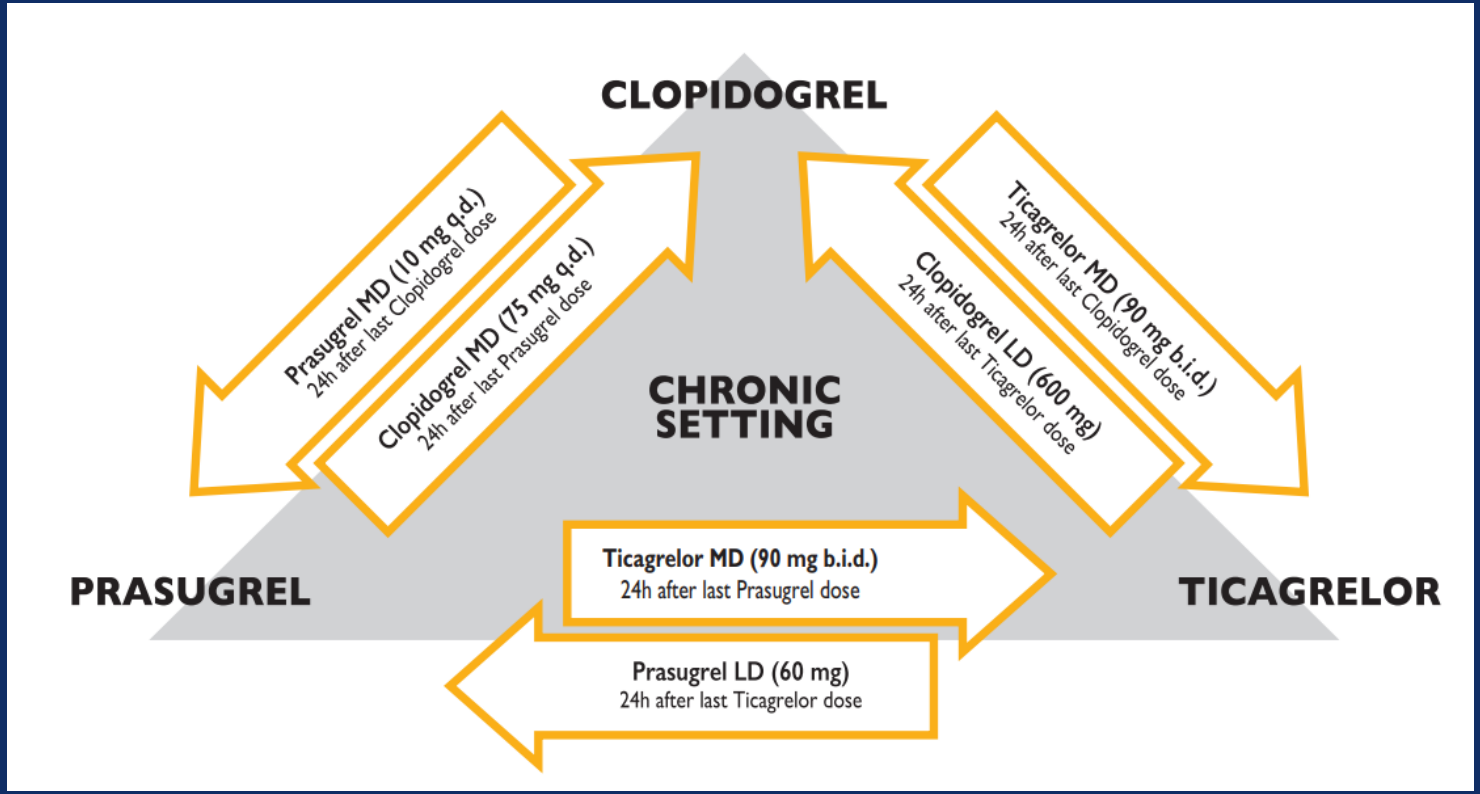
Tailored P2Y12 Strategy for CHIP patients



***Complex High-Risk PCI**

: Left main PCI, chronic total occlusion, bifurcation requiring two-stent technique, severe calcification, diffuse long lesion (lesion length ≥ 30mm), multivessel PCI (≥ 2 vessels requiring stent implantation), ≥3 requiring stents implantation, ≥3 lesions will be treated, predicted total stent length for revascularization >60mm, diabetes, CKD (Cr-clearance <60ml/min) or severe LV dysfunction (EF <40%).

P2Y12 inhibitor: Switching Ticagrelor to Clopidogrel at 6 month



"At 24 hours from last dose of ticagrelor, clopidogrel 600 mg loading dose should be given"

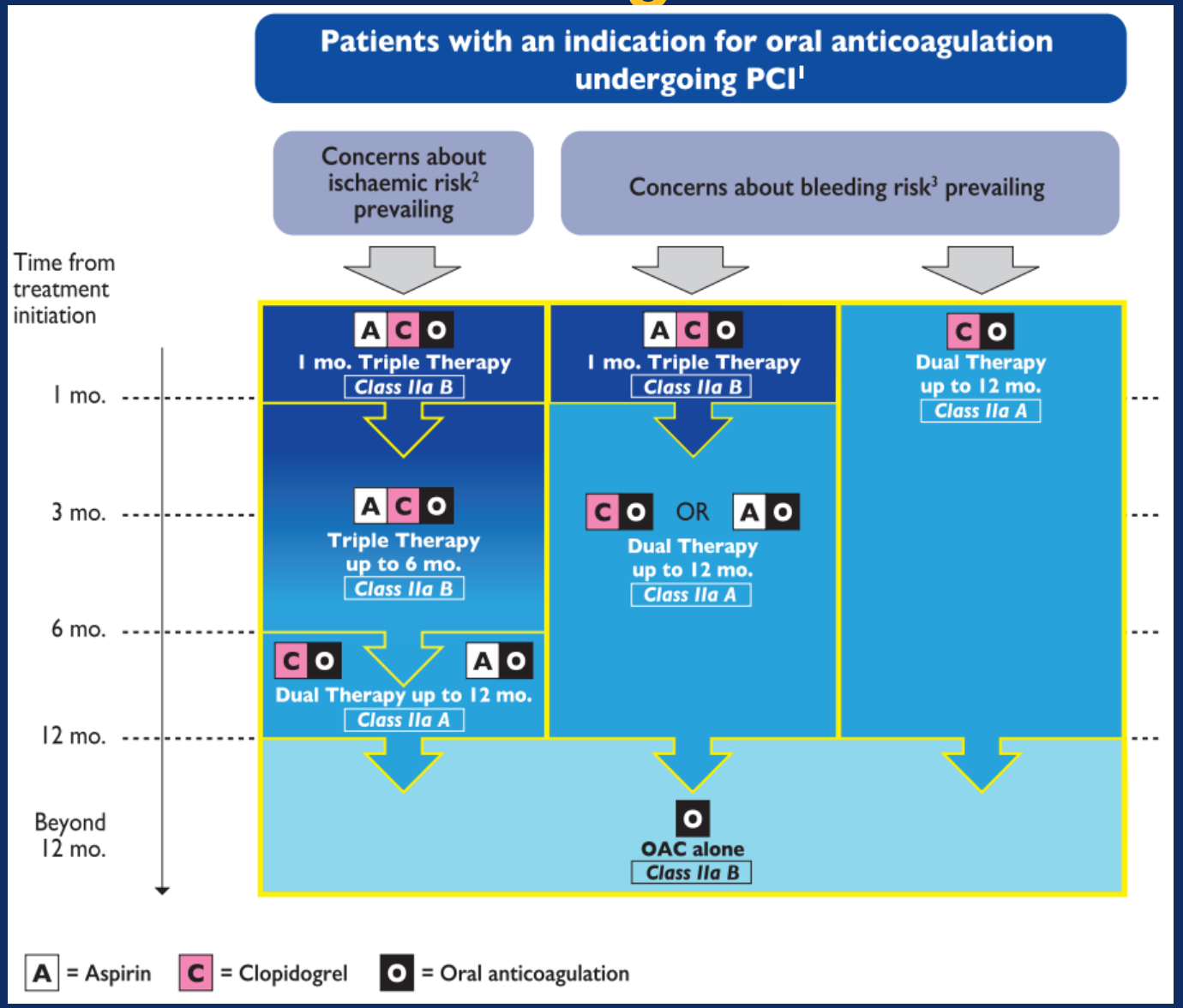
Antiplatelet Therapy in Patients with Anticoagulation

Antiplatelet Therapy in Patients with an Indication for Oral Anticoagulation Undergoing PCI

COR	LOE	RECOMMENDATIONS
1	B-R	1. In patients with atrial fibrillation who are undergoing PCI and are taking oral anticoagulant therapy, it is recommended to discontinue aspirin treatment after 1 to 4 weeks while maintaining P2Y12 inhibitors in addition to a non-vitamin K oral anticoagulant (rivaroxaban, dabigatran, apixaban, or edoxaban) or warfarin to reduce the risk of bleeding (1-7).
2a	B-R	2. In patients with atrial fibrillation who are undergoing PCI, are taking oral anticoagulant therapy, and are treated with DAPT or a P2Y12 inhibitor monotherapy, it is reasonable to choose a non-vitamin K oral anticoagulant over warfarin to reduce the risk of bleeding (1,3,4).

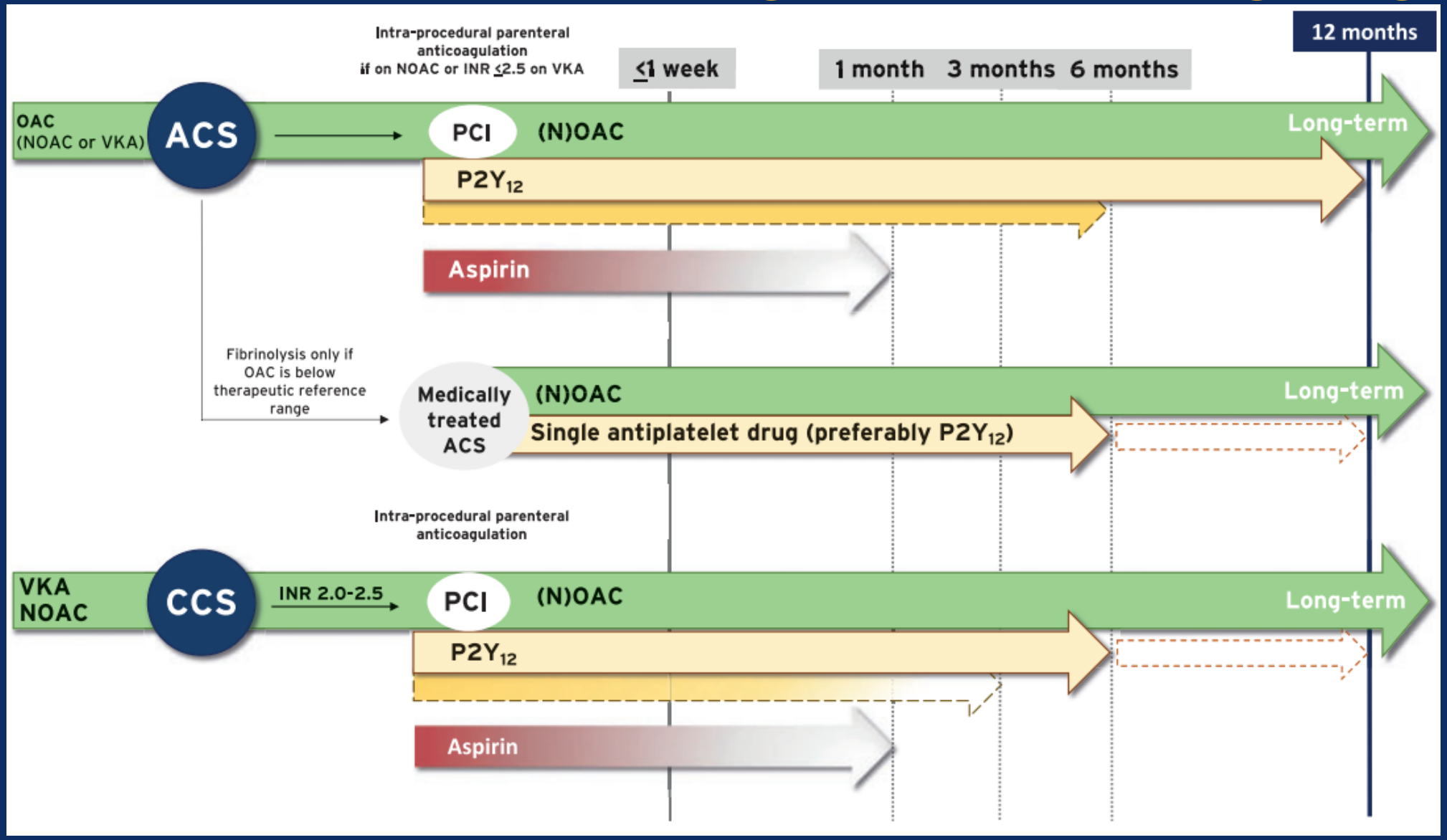
Lawton et al. 2021 ACC/AHA/SCAI Coronary Revascularization Guideline

Antiplatelet Therapy in Patients with an Indication for Oral Anticoagulation Undergoing PCI



Marco Valgimigli et al. 2017 ESC focused update on DAPT in coronary artery disease

Antiplatelet Therapy in Patients with an Indication for Oral Anticoagulation Undergoing PCI



Gerhard Hindricks et al. 2020 ESC Guidelines for atrial fibrillation

Antiplatelet Therapy in Patients with an Indication for Oral Anticoagulation Undergoing PCI

THROMBOTIC RISK FACTORS

- Diabetes mellitus requiring therapy
- Prior ACS/recurrent myocardial infarction
- Multivessel CAD
- Concomitant PAD
- Premature CAD (occurring at age of <45 y) or accelerated CAD (new lesion within 2 years)
- CKD (eGFR <60 mL/min)
- Clinical presentation (ACS)
- Multivessel stenting
- Complex revascularisation (left main stenting, bifurcation lesion stenting, chronic total occlusion intervention, last patent vessel stenting)
- Prior stent thrombosis on antiplatelet treatment
- Procedural factors (stent expansion, residual dissection, stent length, etc.)

BLEEDING RISK FACTORS

- Hypertension
- Abnormal renal or liver function
- Stroke or ICH history
- Bleeding history or bleeding diathesis (e.g., anaemia with haemoglobin <110 g/L)
- Labile INR (if on VKA)
- Elderly (>65 years)
- Drugs (concomitant OAC and antiplatelet therapy, NSAIDs), excessive alcohol consumption

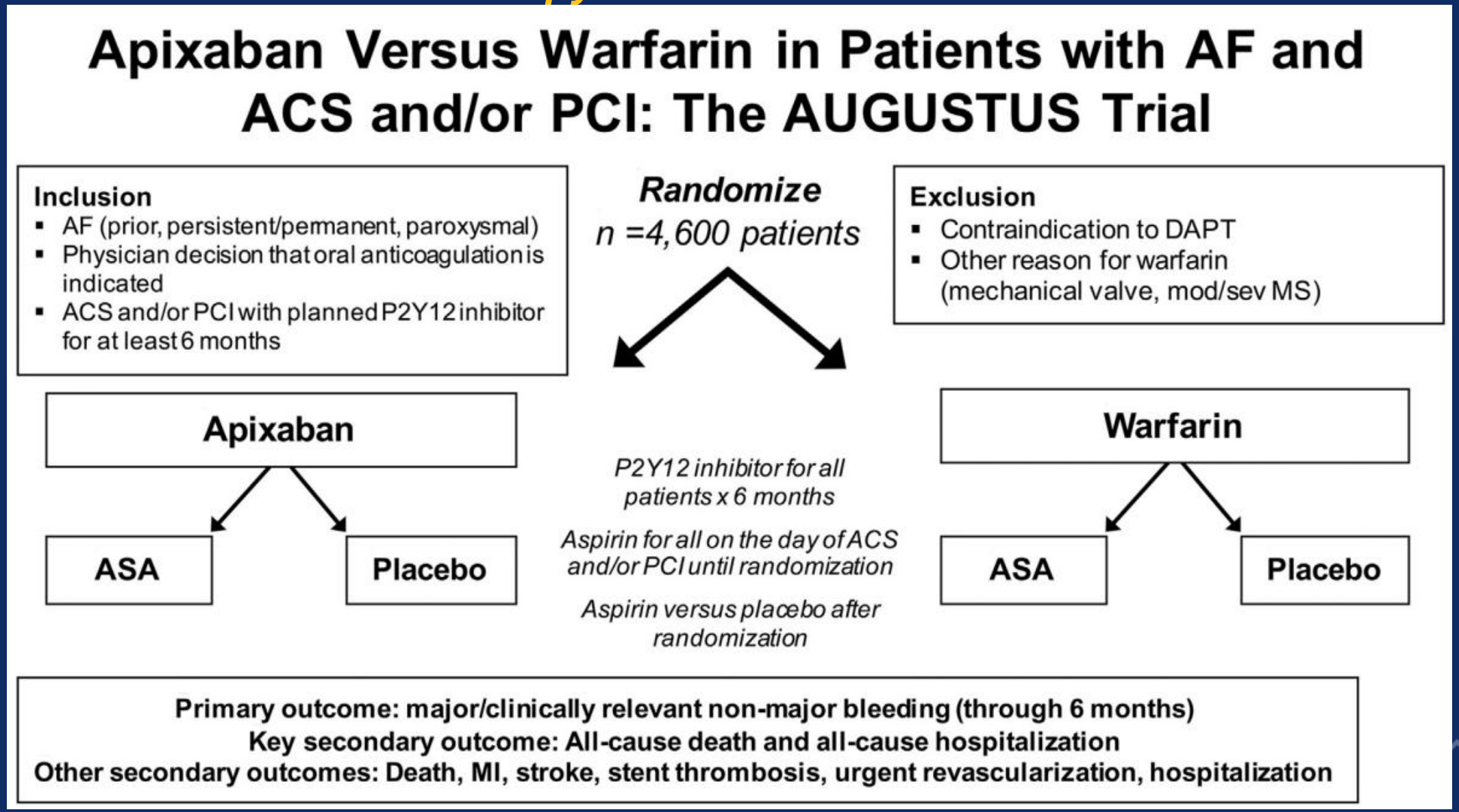
STRATEGIES TO REDUCE BLEEDING ASSOCIATED WITH PCI

- Radial artery access
- PPIs in patients taking DAPT who are at increased risk of bleeding (e.g., the elderly, dyspepsia, gastro-oesophageal reflux disease, Helicobacter pylori infection, chronic alcohol use)
- Non–administration of unfractionated heparin in patients on VKA with INR >2.5
- Pre-treatment with aspirin only, add a $P2Y_{12}$ inhibitor when coronary anatomy is known or if STEMI
- GP IIb/IIIa inhibitors only for bailout or periprocedural complications
- Shorter duration of combined antithrombotic therapy

Gerhard Hindricks et al. 2020 ESC Guidelines for atrial fibrillation

AUGUSTUS Trial

Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation

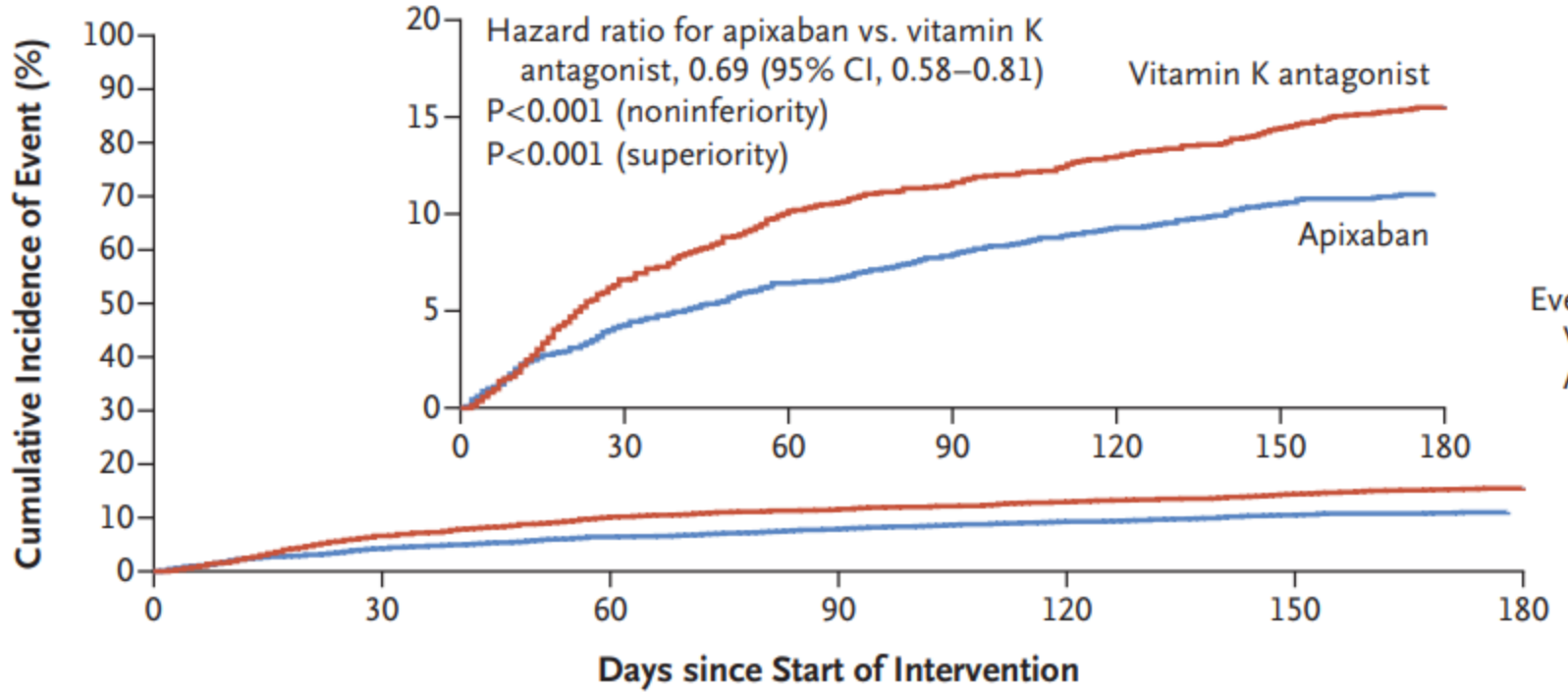


Renato D. Lopes et al. Am Heart J. 2018 Jun;200:17-23.

AUGUSTUS Trial

Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation

A Primary Outcome — Apixaban vs. Vitamin K Antagonist



Event rate per 100 patient-yr:
Vitamin K antagonist, 35.8
Apixaban, 24.7

No. at Risk

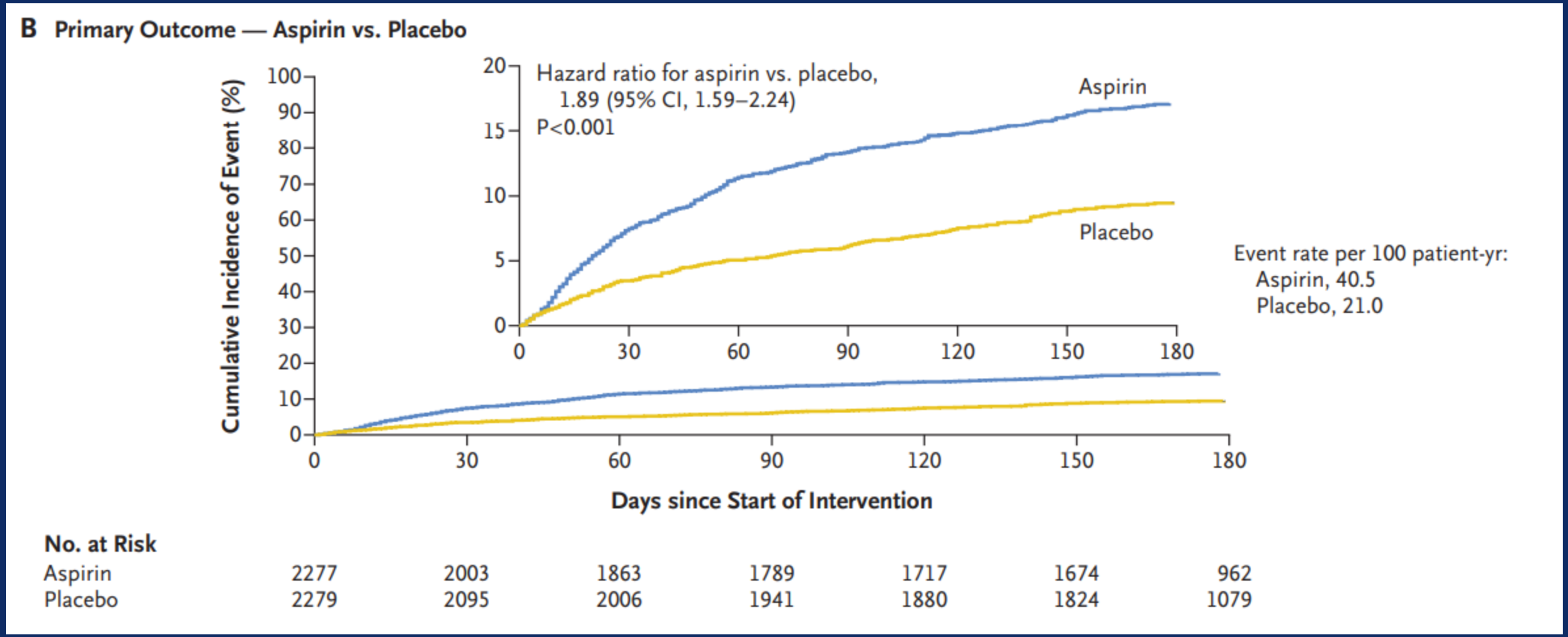
Vitamin K antagonist	2259	1984	1861	1795	1736	1686	1079
Apixaban	2290	2110	2019	1957	1902	1858	1037

- **Primary outcome was major or clinically relevant nonmajor bleeding defined by the International Society on Thrombosis and Haemostasis.**

Renato D. Lopes et al. N Engl J Med. 2019;380:1509-24.

AUGUSTUS Trial

Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation



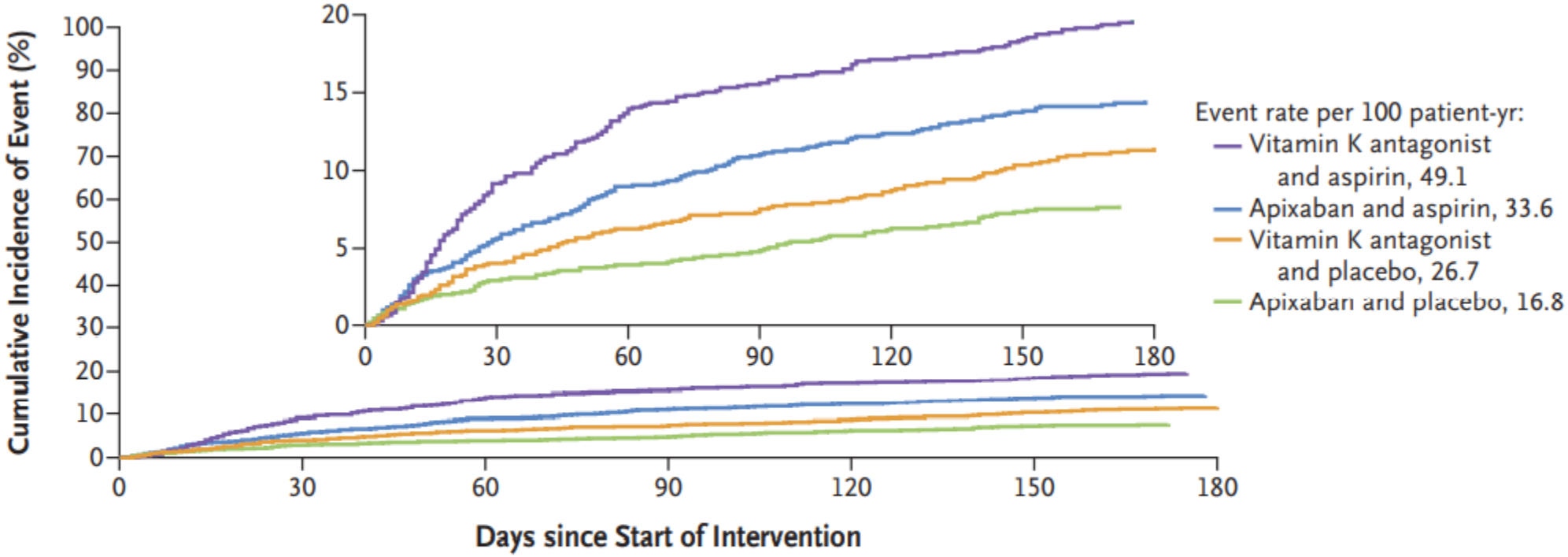
- **Primary outcome was major or clinically relevant nonmajor bleeding defined by the International Society on Thrombosis and Haemostasis.**

Renato D. Lopes et al. N Engl J Med. 2019;380:1509-24.

AUGUSTUS Trial

Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation

C Primary Outcome, According to Intervention Combination



No. at Risk							
Vitamin K antagonist and aspirin	1123	962	881	838	800	776	467
Apixaban and aspirin	1145	1036	975	937	903	880	485
Vitamin K antagonist and placebo	1126	1007	947	917	883	851	528
Apixaban and placebo	1143	1075	1044	1007	975	947	536

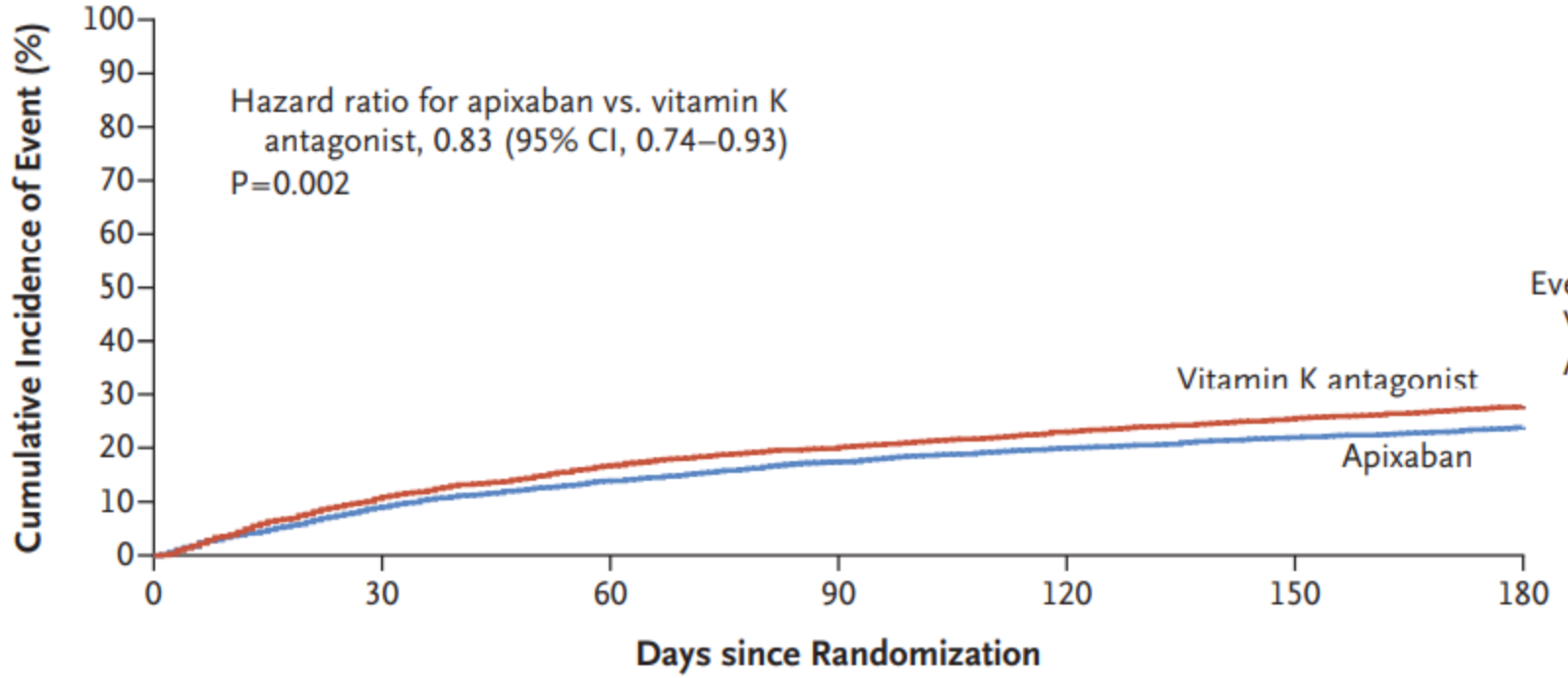
- **Primary outcome was major or clinically relevant nonmajor bleeding defined by the International Society on Thrombosis and Haemostasis.**

Renato D. Lopes et al. N Engl J Med. 2019;380:1509-24.

AUGUSTUS Trial

Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation

A Death or Hospitalization — Apixaban vs. Vitamin K Antagonist



No. at Risk

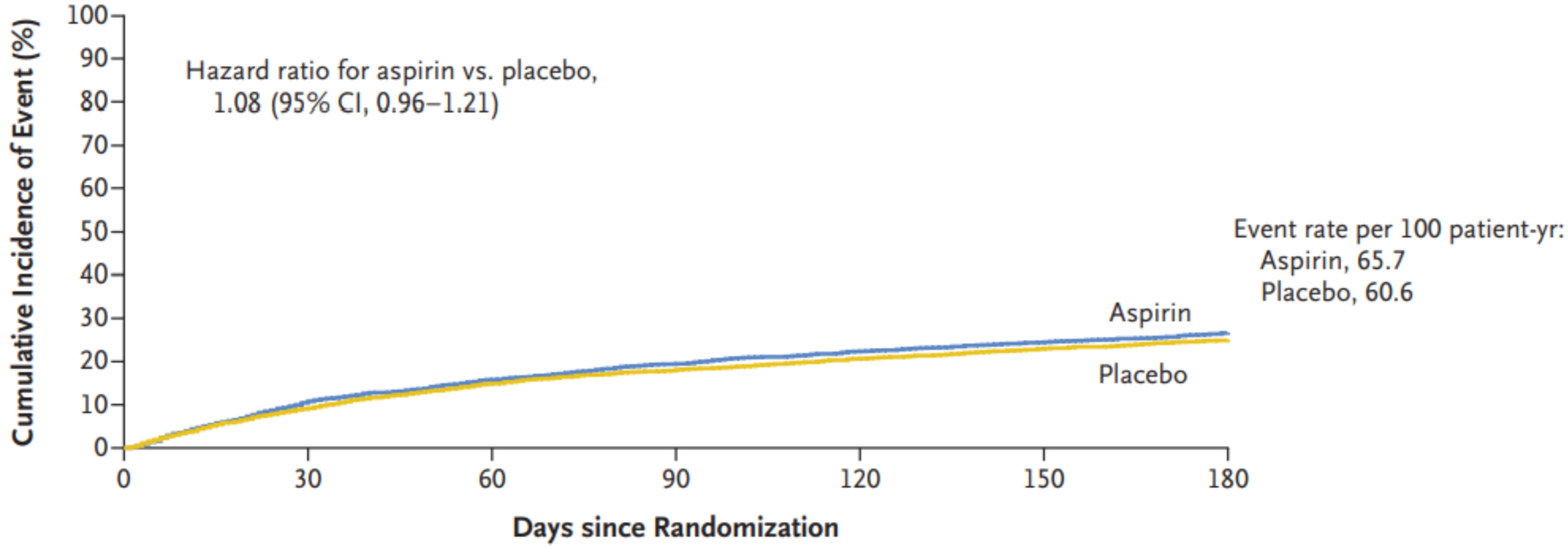
Vitamin K antagonist	2308	2035	1885	1805	1732	1673	1001
Apixaban	2306	2090	1965	1881	1821	1772	947

Renato D. Lopes et al. N Engl J Med. 2019;380:1509-24.

AUGUSTUS Trial

Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation

B **Death or Hospitalization — Aspirin vs. Placebo**



No. at Risk

Aspirin	2307	2042	1909	1822	1752	1699	951
Placebo	2307	2083	1941	1864	1801	1746	997

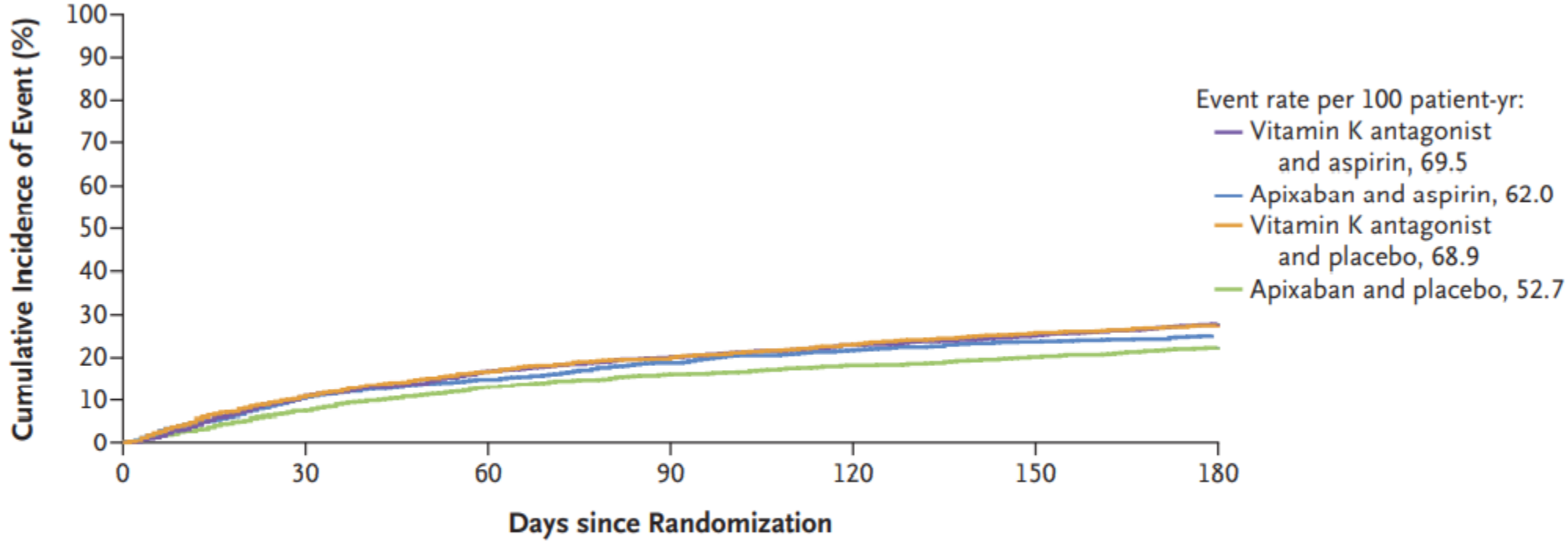
CVRF

Renato D. Lopes et al. N Engl J Med. 2019;380:1509-24.

AUGUSTUS Trial

Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation

C Death or Hospitalization, According to Intervention Combination

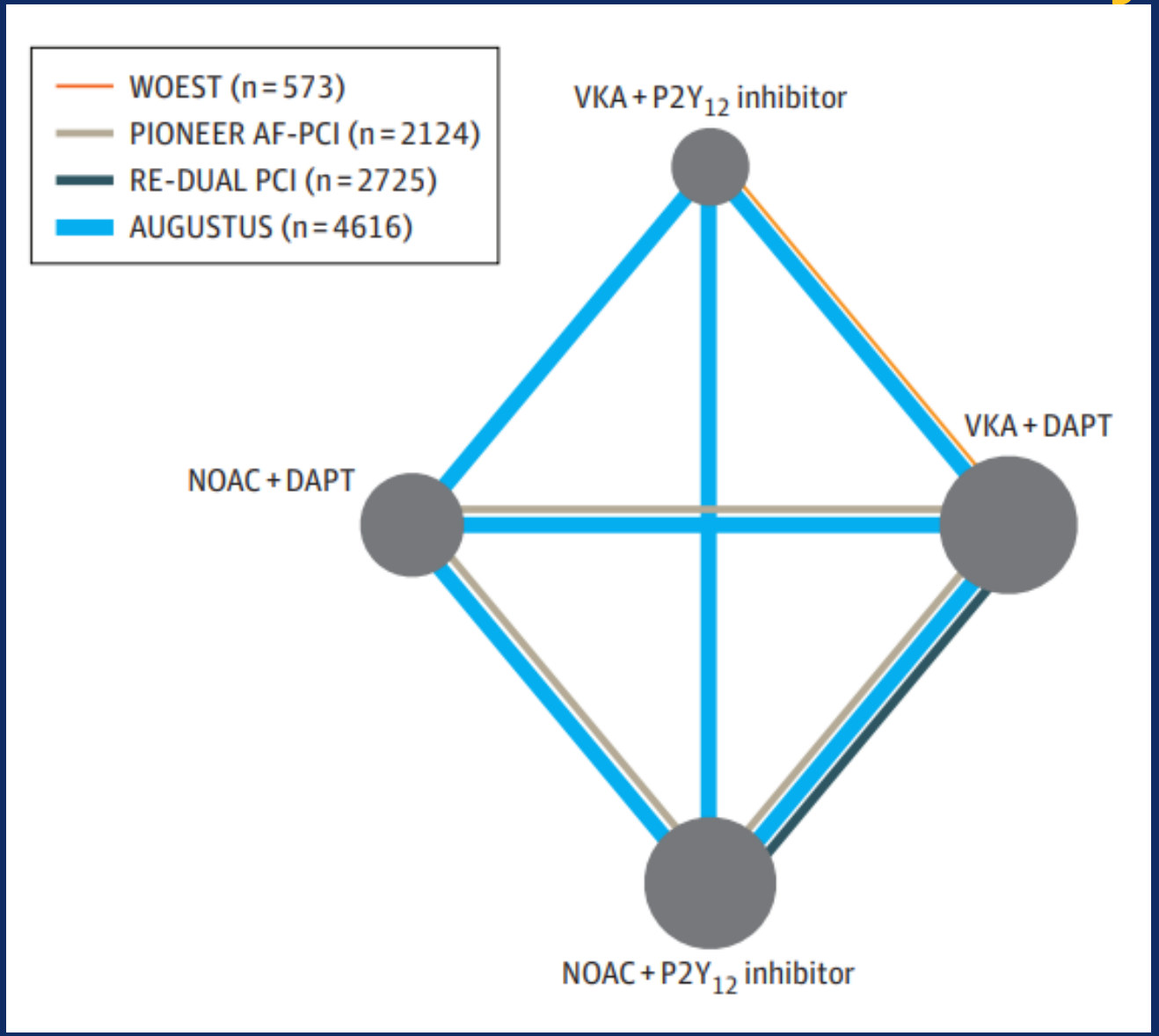


No. at Risk

Vitamin K antagonist and aspirin	1154	1016	939	899	864	836	492
Apixaban and aspirin	1153	1026	970	923	888	863	459
Vitamin K antagonist and placebo	1154	1019	946	906	868	837	509
Apixaban and placebo	1153	1064	995	958	933	909	488

Renato D. Lopes et al. N Engl J Med. 2019;380:1509-24.

Safety and Efficacy of Antithrombotic Strategies in Patients with AF after PCI: Meta-analysis of RCTs

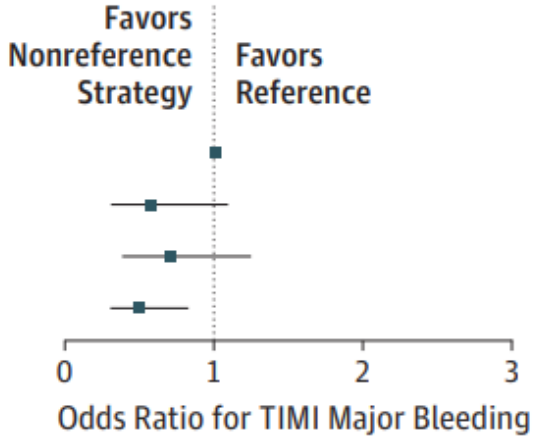


Renato D. Lopes et al. JAMA Cardiol. 2019;4(8):747-755.

Safety and Efficacy of Antithrombotic Strategies in Patients with AF after PCI: Meta-analysis of RCTs

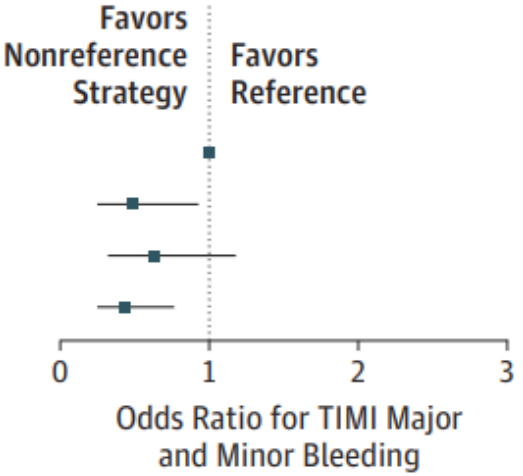
A TIMI major bleeding

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.58 (0.31-1.08)
NOAC + DAPT	0.70 (0.38-1.23)
NOAC + $P2Y_{12}$ inhibitor	0.49 (0.30-0.82)



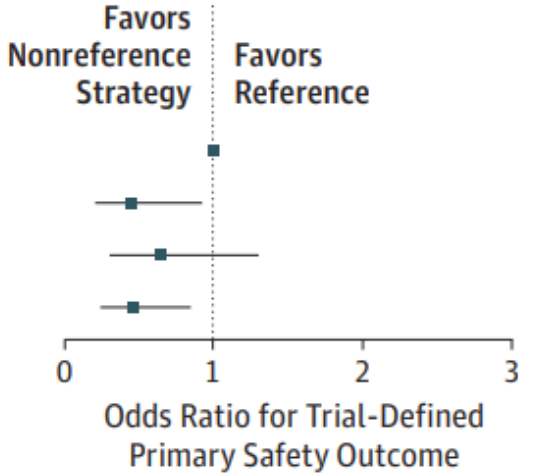
B TIMI major and minor bleeding

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.49 (0.26-0.92)
NOAC + DAPT	0.63 (0.33-1.17)
NOAC + $P2Y_{12}$ inhibitor	0.43 (0.25-0.76)



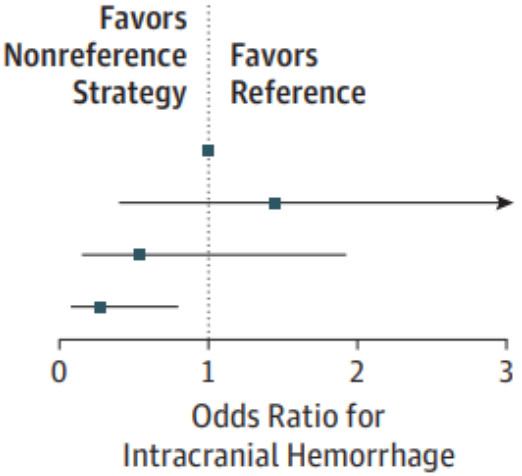
C Trial-defined primary safety outcome

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.45 (0.21-0.92)
NOAC + DAPT	0.64 (0.31-1.31)
NOAC + $P2Y_{12}$ inhibitor	0.47 (0.25-0.85)



D Intracranial hemorrhage

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	1.44 (0.40-5.22)
NOAC + DAPT	0.54 (0.15-1.92)
NOAC + $P2Y_{12}$ inhibitor	0.26 (0.08-0.79)

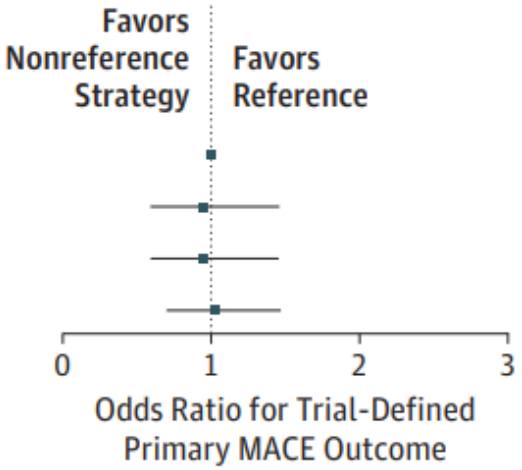


Renato D. Lopes et al. JAMA Cardiol. 2019;4(8):747-755.

Safety and Efficacy of Antithrombotic Strategies in Patients with AF after PCI: Meta-analysis of RCTs

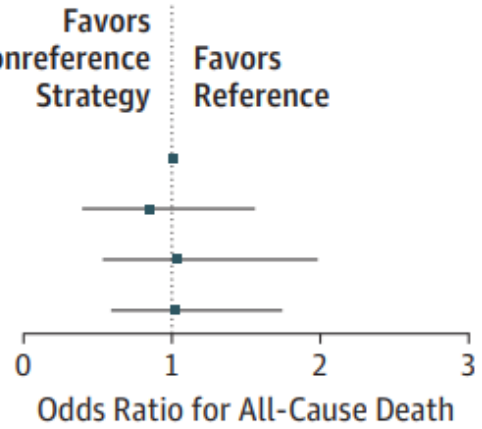
A Trial-defined primary MACE

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.96 (0.60-1.46)
NOAC + DAPT	0.94 (0.60-1.15)
NOAC + $P2Y_{12}$ inhibitor	1.02 (0.71-1.97)



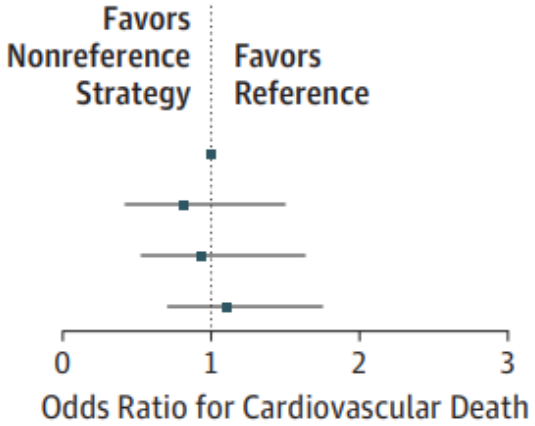
B All-cause death

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.84 (0.40-1.56)
NOAC + DAPT	1.04 (0.54-1.98)
NOAC + $P2Y_{12}$ inhibitor	1.02 (0.59-1.74)



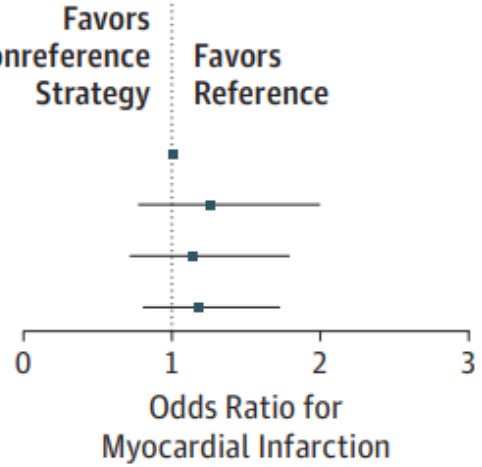
C Cardiovascular death

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.82 (0.42-1.49)
NOAC + DAPT	0.94 (0.53-1.63)
NOAC + $P2Y_{12}$ inhibitor	1.11 (0.70-1.75)



D Myocardial infarction

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	1.25 (0.77-1.99)
NOAC + DAPT	1.13 (0.72-1.78)
NOAC + $P2Y_{12}$ inhibitor	1.18 (0.81-1.72)

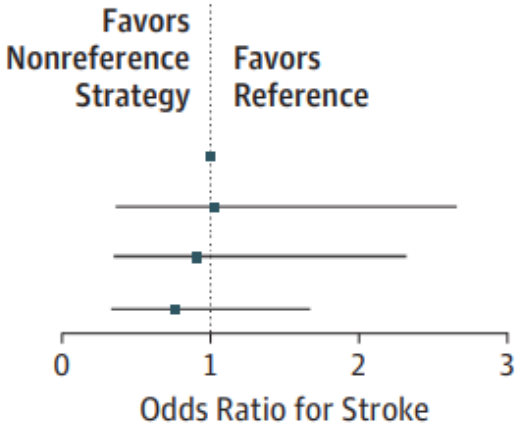


Renato D. Lopes et al. JAMA Cardiol. 2019;4(8):747-755.

Safety and Efficacy of Antithrombotic Strategies in Patients with AF after PCI: Meta-analysis of RCTs

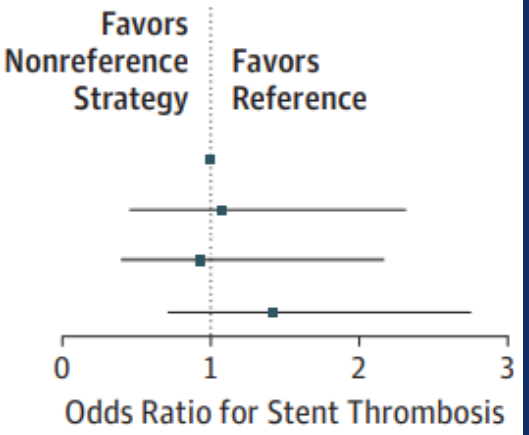
E Stroke

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	1.02 (0.36-2.65)
NOAC + DAPT	0.91 (0.35-2.32)
NOAC + $P2Y_{12}$ inhibitor	0.77 (0.34-1.67)



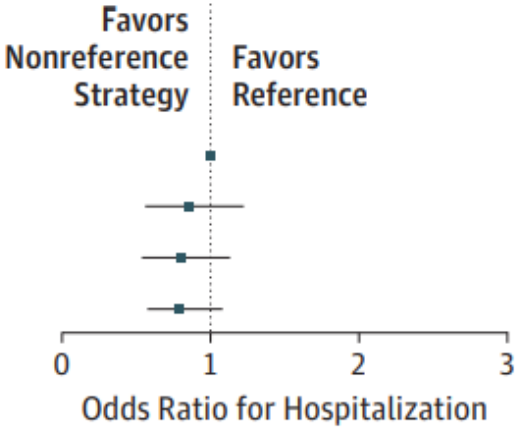
F Stent thrombosis

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	1.08 (0.46-2.31)
NOAC + DAPT	0.93 (0.40-2.17)
NOAC + $P2Y_{12}$ inhibitor	1.41 (0.71-2.76)



G Hospitalization

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.86 (0.57-1.23)
NOAC + DAPT	0.80 (0.55-1.13)
NOAC + $P2Y_{12}$ inhibitor	0.80 (0.59-1.08)



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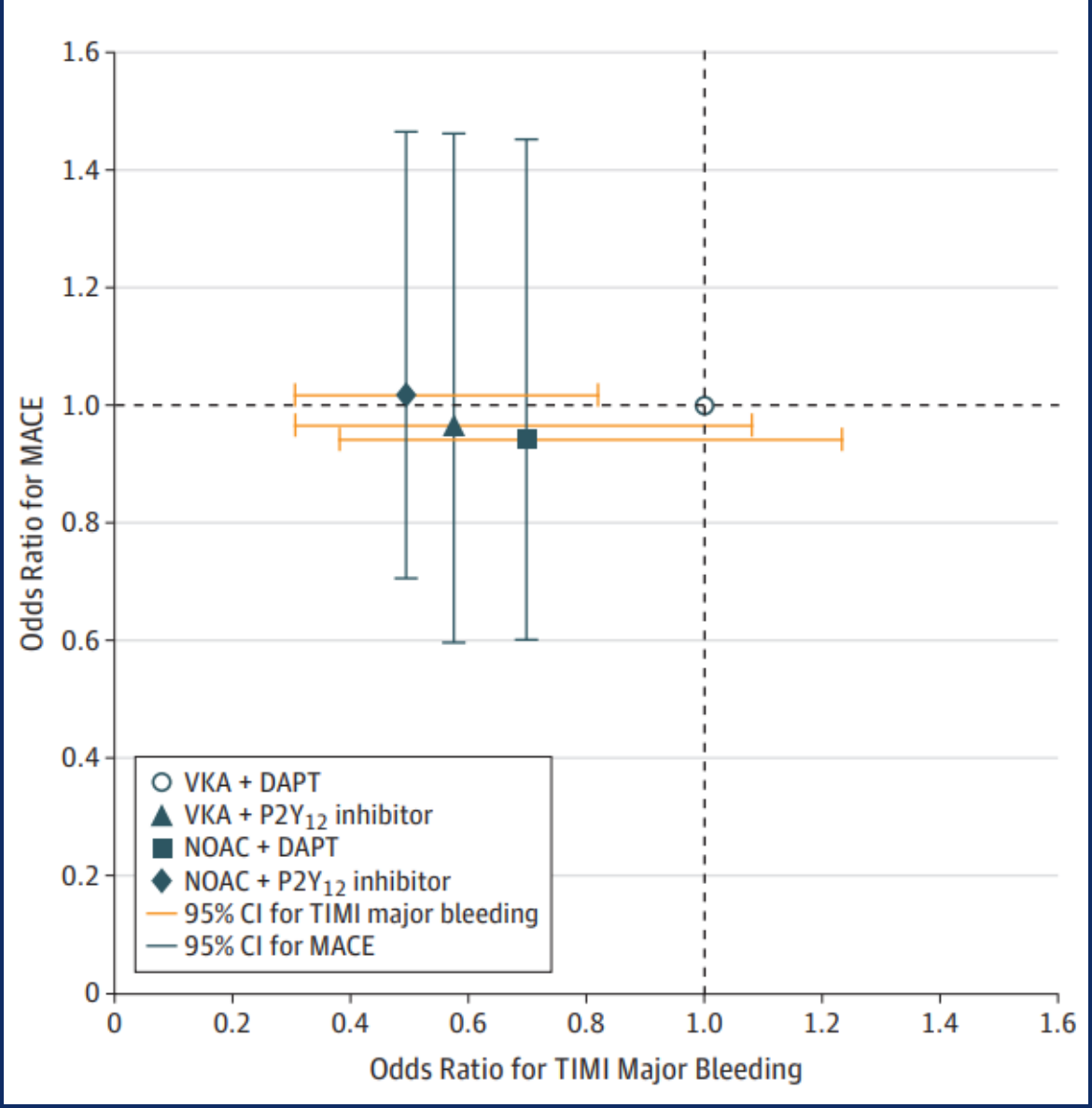
Safety and Efficacy of Antithrombotic Strategies in Patients with AF after PCI: Meta-analysis of RCTs



- A regimen of NOACs plus P2Y12 inhibitor was associated with less bleeding compared with VKAs plus DAPT.
- Strategies omitting aspirin caused less bleeding, including intracranial bleeding, without significant difference in MACE, compared with strategies including aspirin.
- Our results support the us of NOAC plus P2Y12 inhibitor as the preferred regimen post-percutaneous coronary intervention for these high-risk patients with AF.
- A regimen of VKA plus DAPT should generally be avoided.

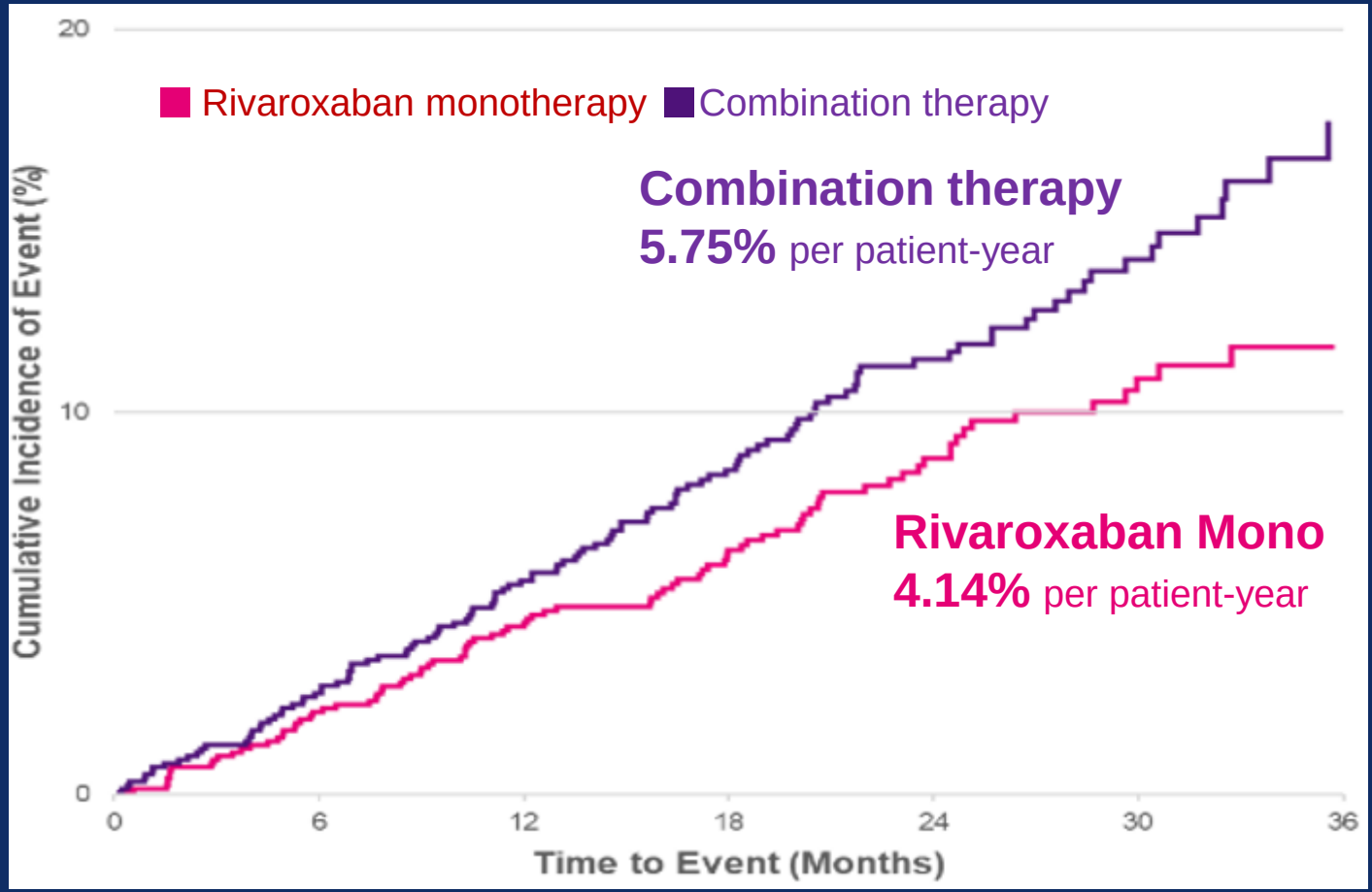
Renato D. Lopes et al. JAMA Cardiol. 2019;4(8):747-755.

AFIRE
Early Termination of the Trial

- The evaluation of the patients was planned to continue until September 2018.
- Because of a **higher risk of death from any cause** in the **combination-therapy group**, the independent data and safety monitoring committee recommended early termination of the trial in July 2018.
- The median treatment duration was 23.0 months (interquartile range, 15.8 to 31.0)
- The median follow-up period was 24.1 months (interquartile range, 17.3 to 31.5)

ESC Congress Paris 2019 N Engl J Med 2019;381:1103-13

Primary Efficacy Endpoint* (CV Events or Death)



HR, 0.72 (0.55 - 0.95)
P<0.001 (noninferiority)

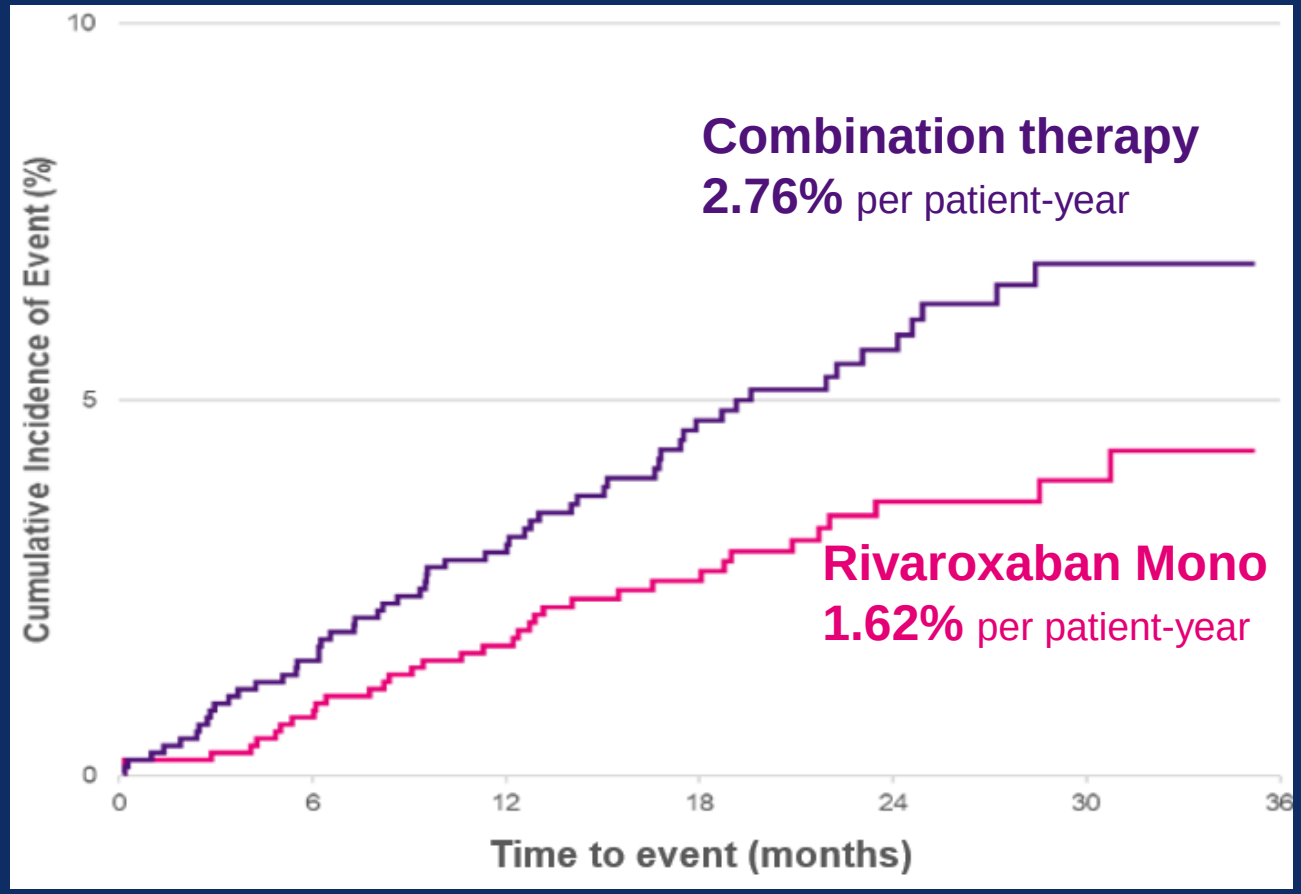
Number of patients at risk							
Rivaroxaban monotherapy	1107	1071	984	774	518	309	89
Combination therapy	1108	1057	962	754	499	292	80

Bayer does not recommend off-label use of products. Before prescribing any products, please consult the relevant local prescribing information.

*The composite endpoint included stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization and all-cause mortality

Yasuda S *et al*, *N Engl J Med* 2019;381:1103–1113

Primary Safety Endpoint (Major Bleeding)*



HR 0.59 (0.39 - 0.89)
P<0.001 (superiority)

Number of patients at risk							
Rivaroxaban monotherapy	1099	1074	994	786	526	312	89
Combination therapy	1099	1055	962	750	506	294	80

Bayer does not recommend off-label use of products. Before prescribing any products, please consult the relevant local prescribing information.

*As defined according to the criteria of the International Society on Thrombosis and Haemostasis

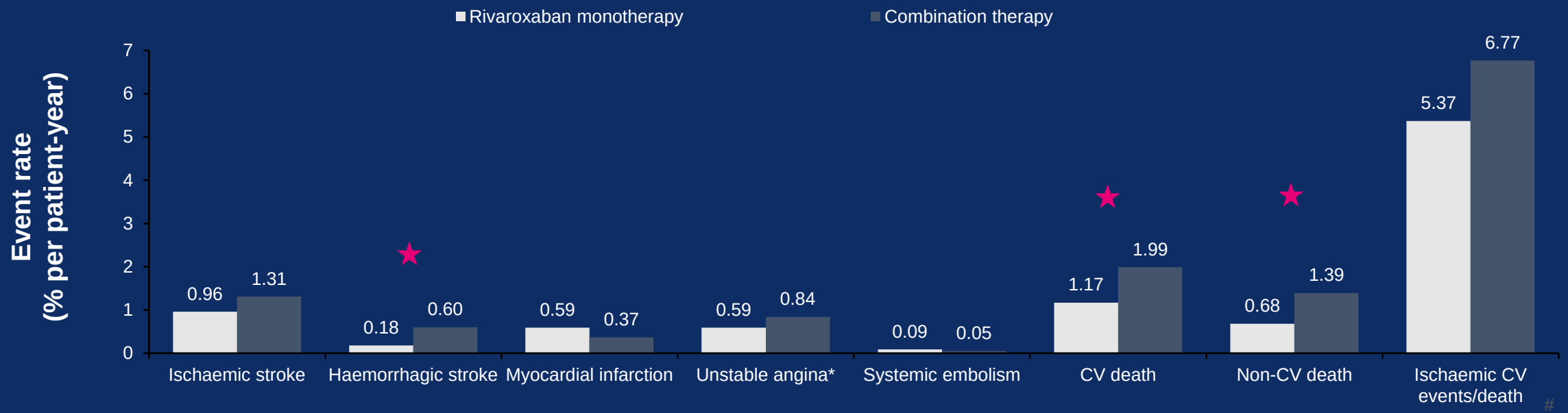
Yasuda S *et al*, *N Engl J Med* 2019;381:1103–1113

Secondary Efficacy Endpoints

Lower rate of all-cause mortality for rivaroxaban monotherapy versus combination therapy (HR=0.55; 95% CI 0.38–0.81), due to lower incidences of both CV and non-CV death

Trial terminated early because of higher risk of death in the combination therapy group

The most common causes of death were heart failure, stroke and cancer



Bayer does not recommend off-label use of products. Before prescribing any products, please consult the relevant local prescribing information.

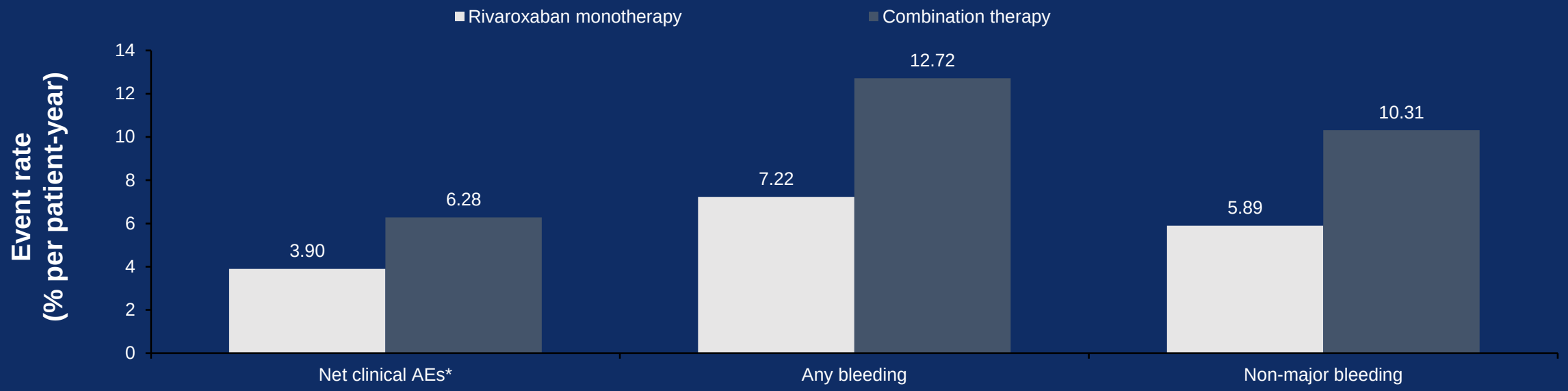
*Unstable angina requiring revascularization; #composite of death from any cause, myocardial infarction, unstable angina requiring revascularization, stroke, transient ischaemic attack, systemic arterial embolism, venous thromboembolism, revascularization or stent thrombosis

Yasuda S *et al*, *N Engl J Med* 2019;381:1103–1113

Other Secondary Endpoints

Lower rate of net clinical AEs* for rivaroxaban monotherapy versus combination therapy (HR=0.62; 95% CI 0.47–0.82)

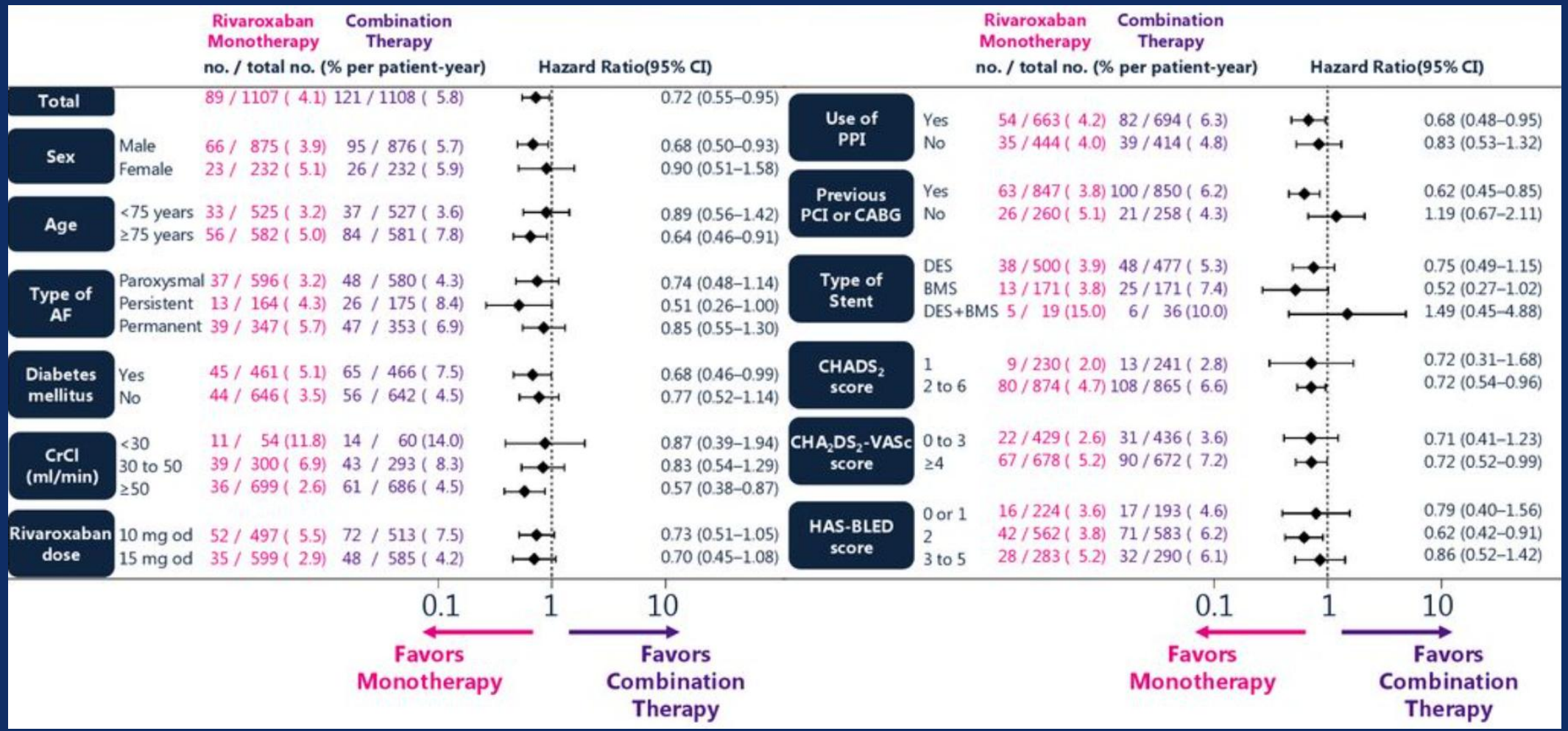
Lower rate of non-major bleeding events for rivaroxaban monotherapy versus combination therapy (HR=0.58; 95% CI 0.46–0.72)



*Composite of death from any cause, myocardial infarction, stroke or major bleeding, transient ischaemic attack, systemic arterial embolism, venous thromboembolism, revascularization or stent thrombosis

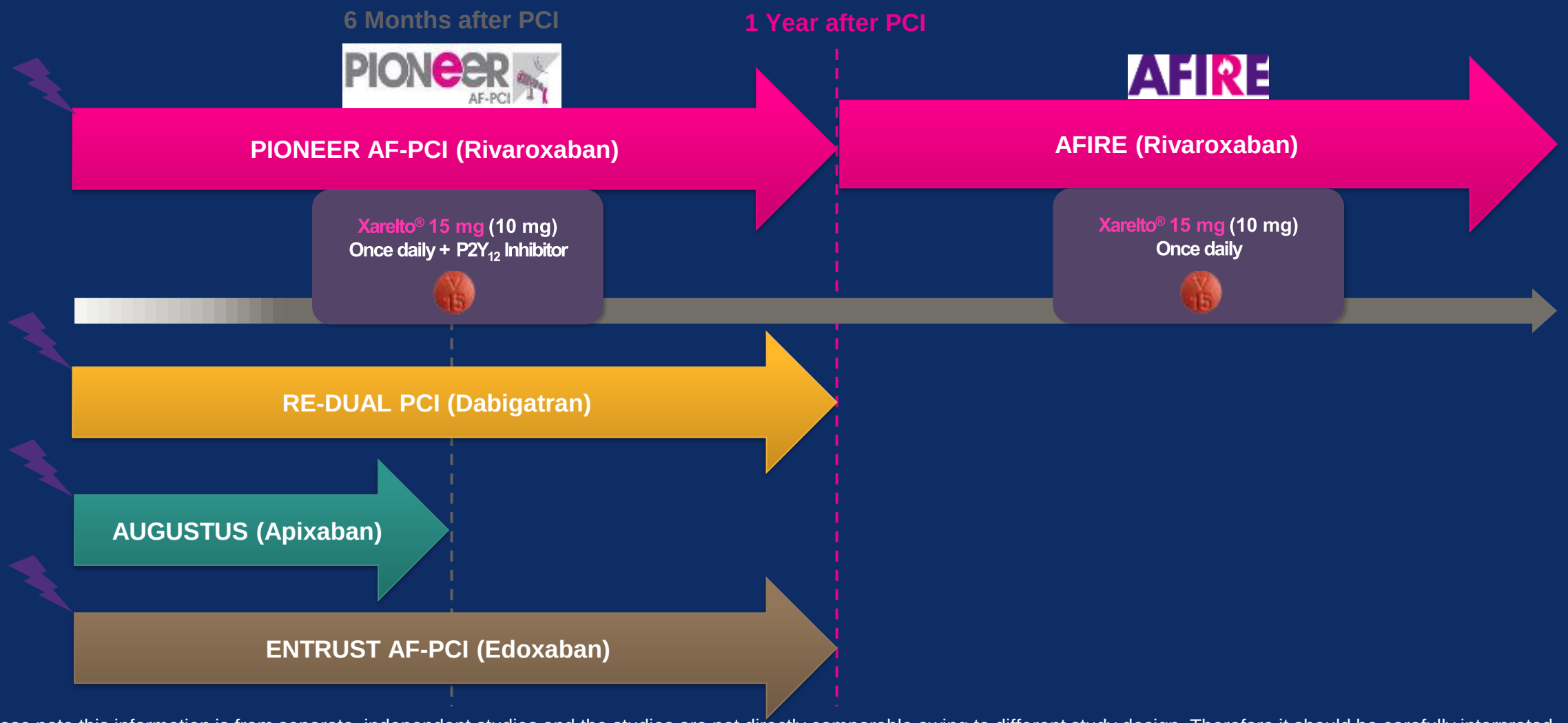
Yasuda S *et al*, *N Engl J Med* 2019;381:1103–1113

Subgroup Analysis for Primary Efficacy Endpoint



Yasuda S *et al*, *N Engl J Med* 2019;381:1103–1113

AF-PCI Trials among NOACs

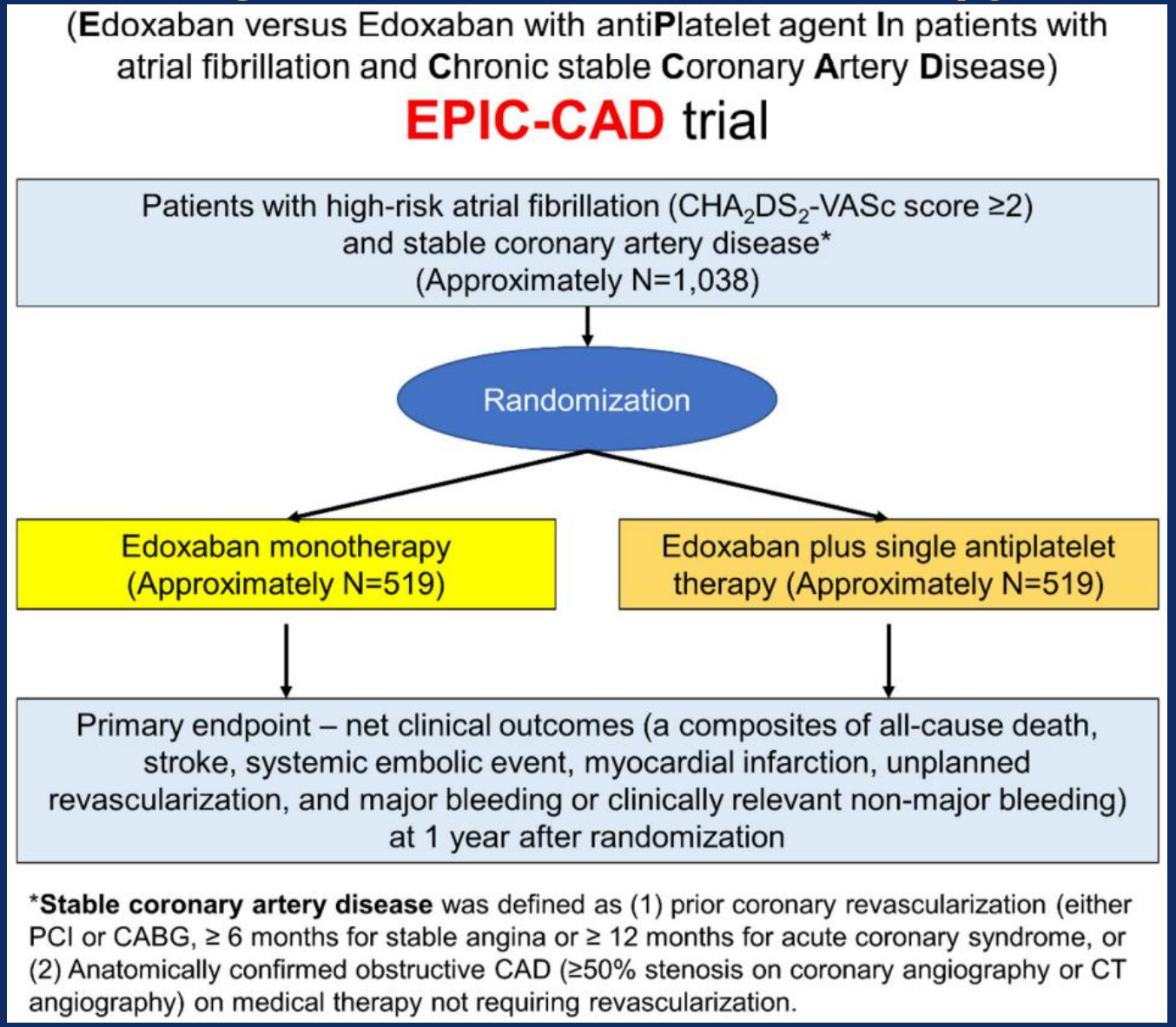


Please note this information is from separate, independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

1. Gibson CM et al, New Engl J Med 2016; doi: 10.1056/NEJMoa1611594
2. Christopher PC et al, New Engl J Med 2017; 377:1513-1524
3. Lopes RD et al, New Engl J Med 2019; DOI: 10.1056/NEJMoa1817083
4. Vranckx P et al, American Heart Journal. 2018;196:105-112

EPIC-CAD Trial

Edoxaban-based long-term antithrombotic therapy with AF and CAD



Min Soo Cho et al. Am Heart J. 2022;247:123-131.

EPIC-CAD Trial

Edoxaban-based long-term antithrombotic therapy with AF and CAD

Inclusion criteria

- 1. Patients aged ≥18 y
- 2. Patients with AF with high embolic risk (CHA2DS2-VASc score ≥ 2)
- 3. Patients with stable CAD

• Coronary revascularization (either PCI or CABG) at least 6 mo for stable angina or at least 1 y for ACS before study enrollment

• Anatomically confirmed (with ≥50% stenosis of major coronary artery by CAG or coronary CTA on optimal medical therapy not requiring revascularization

Min Soo Cho et al. Am Heart J. 2022;247:123-131.

EPIC-CAD Trial

Edoxaban-based long-term antithrombotic therapy with AF and CAD

Exclusion criteria

- 1. Patients with thrombocytopenia (<50,000/uL)
- 2. High risk of bleeding prohibiting anticoagulant use according to the attending physician's discretion (ie, baseline comorbidities, hyper- or hypocoagulable state, increased prothrombin time, or activated partial thromboplastin time)
- 3. Prior history of intracranial hemorrhage
- 4. Mechanical prosthetic valve or moderate-to-severe mitral stenosis
- 5. Patients contraindicated for edoxaban or antiplatelets
- 6. Planned PCI or CABG within 1 y after randomization
- 7. Liver cirrhosis or liver dysfunction (AST or ALT > ×3 of normal range or coagulation abnormality)
- 8. Creatinine clearance <30 mL/min
- 9. Life expectancy <12 mo
- 10. Patients unable to provide written informed consent or participate in long-term follow-up
- 11. Pregnant or lactating women
- 12. Patients actively participating in another drug or device investigational study

Min Soo Cho et al. Am Heart J. 2022;247:123-131.

EPIC-CAD Trial

Edoxaban-based long-term antithrombotic therapy with AF and CAD

Primary endpoint

- Net clinical outcomes – composites of all-cause death, stroke, systemic embolic event, myocardial infarction, unplanned revascularization of the major coronary artery, and major bleeding or clinically relevant nonmajor bleeding event

Secondary endpoints

- Efficacy outcomes

1) All-cause death
2) Cardiovascular death
3) Myocardial infarction
4) Ischemic stroke
5) Systemic embolism
6) Unplanned revascularization
7) Composite of hard clinical endpoints (all-cause death, myocardial infarction, ischemic stroke, and systemic embolism)
8) Stent thrombosis (in patients who under went coronary stenting)

Min Soo Cho et al. Am Heart J. 2022;247:123-131.

EPIC-CAD Trial

Edoxaban-based long-term antithrombotic therapy with AF and CAD

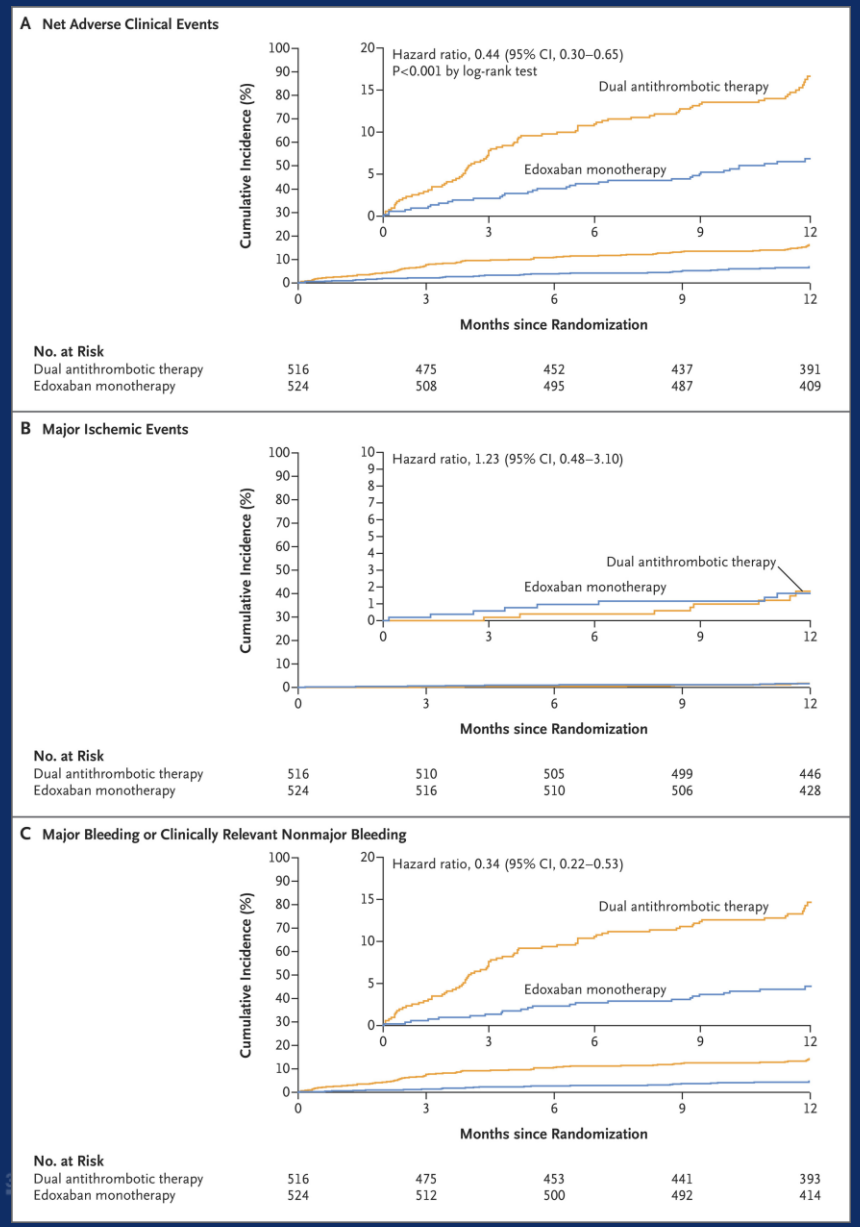
Secondary endpoints

- **Safety outcomes**

1) Composite of major or clinically relevant nonmajor bleeding during follow-up as defined by the International Society on Thrombosis and Hemostasis (ISTH)
2) Fatal bleeding (ISTH, BARC 5)
3) Major bleeding (ISTH, BARC 3, TIMI major bleeding)
4) Clinically relevant nonmajor bleeding (ISTH, BARC, and TIMI criteria)
5) Any bleeding (ISTH, BARC, and TIMI criteria)
6) Intracranial hemorrhage
7) Gastrointestinal hemorrhage

Min Soo Cho et al. Am Heart J. 2022;247:123-131.

EPIC-CAD Trial



Subgroup	Patients	Edoxaban Monotherapy	Dual Antithrombotic Therapy	Hazard Ratio (95% CI)
	%	*estimated %*		
Overall	100	6.8	16.2	0.44 (0.30–0.65)
Age				
≥75 yr	42.2	5.3	18.7	0.31 (0.17–0.59)
<75 yr	57.8	7.8	14.2	0.56 (0.35–0.92)
Sex				
Male	77.1	6.0	17.4	0.37 (0.23–0.58)
Female	22.9	9.4	12.1	0.81 (0.39–1.72)
Creatinine clearance				
≥50 ml/min	75.8	5.2	14.5	0.41 (0.25–0.66)
<50 ml/min	24.2	12.1	21.7	0.53 (0.28–0.99)
Type of most recent revascularization				
Percutaneous coronary intervention	59.1	6.4	17.1	0.43 (0.26–0.70)
CABG	6.5	7.4	20.6	0.46 (0.13–1.67)
Medical treatment alone	34.3	7.1	13.7	0.50 (0.26–0.99)
Edoxaban dose				
60 mg/day	57.5	6.5	16.4	0.46 (0.28–0.75)
30 mg/day	42.5	7.5	16.1	0.44 (0.24–0.79)
CHA_2DS_2-VASc score				
≥4	67.3	6.1	16.2	0.39 (0.24–0.63)
<4	32.7	8.2	16.3	0.57 (0.31–1.05)
HAS-BLED score				
≥3	31.8	7.7	15.1	0.48 (0.25–0.93)
<3	68.2	6.5	16.9	0.43 (0.27–0.69)

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TABLE 2 Functional Test Results of Patients Who Underwent Routine Functional Testing

Test Result	Timing of Functional Test	
	6 Wks	6 Mon*
No. of METs achieved (mean ± SD)	9 ± 3%	9 ± 3%
Mean maximum predicted heart rate achieved	91 ± 19%	89 ± 18%
Maximum predicted heart rate ≥85%	66%	65%
Electrically or clinically positive	23%	30%
Electrically, clinically, or imaging positive†	–	38%
Electrically and clinically negative	60%	57%

TABLE 3 Functional Test Results at Nine Months*

Test Result	Functional Testing Strategy		
	Routine	Selective	p Value
No. of METs achieved (mean ± SD)	10 ± 3%	9 ± 3%	0.09
Mean maximum predicted heart rate achieved	90 ± 21%	91 ± 16%	0.87
Maximum predicted heart rate ≥85%	68%	69%	0.89
Electrically or clinically positive	20%	22%	0.76
Electrically and clinically negative	69%	70%	0.89

Mark J. Eisenberg et al. Am J Cardiol. 2004;93:744-747.

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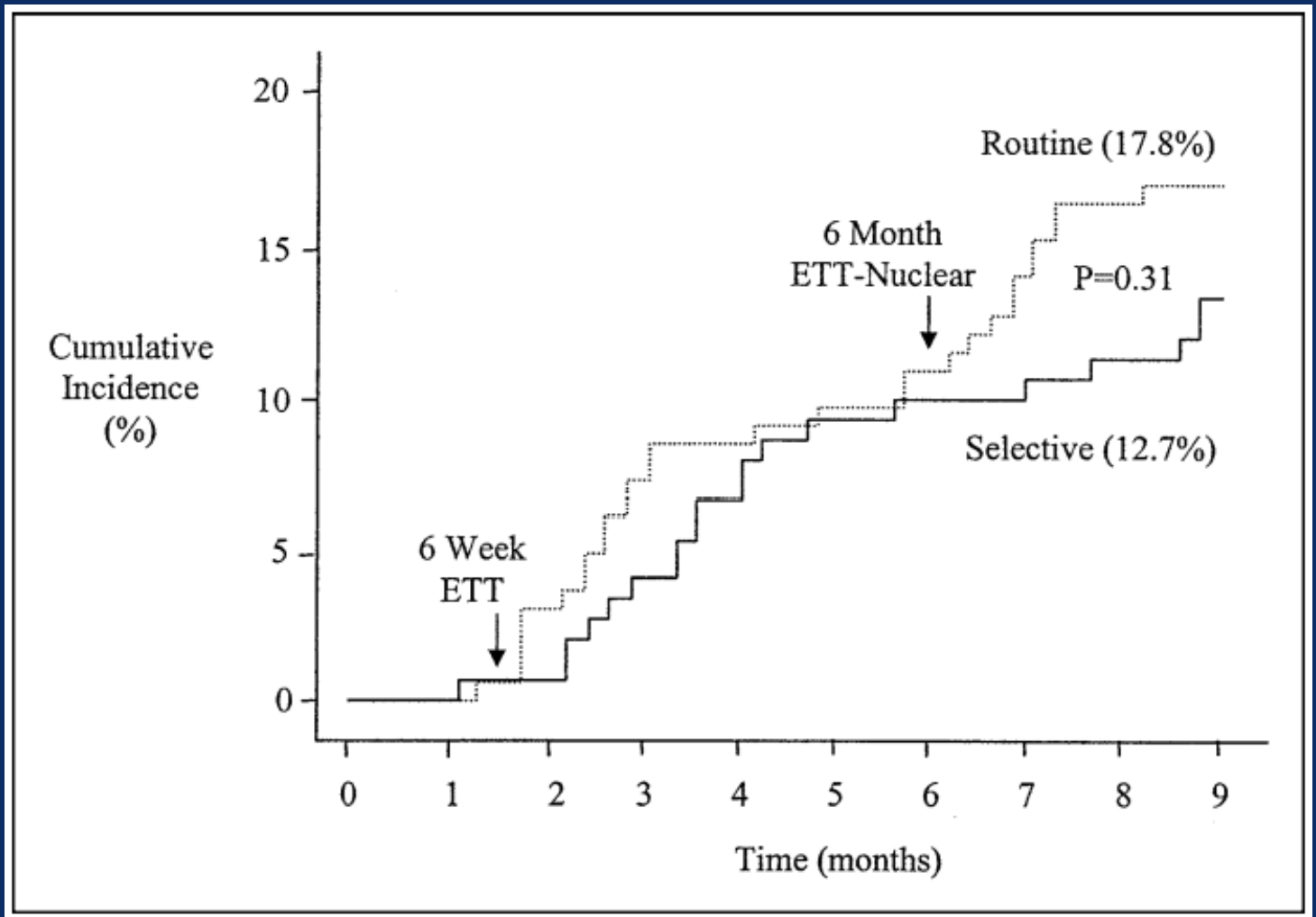

FIGURE 1. Cardiac procedure use during the 9-month follow-up period. ETT = exercise treadmill test.

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Thank you for your attention!