



PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE



**Azienda Ospedaliera
Ordine Mauriziano
di Torino**

IL FUTURO DELLA TERAPIA ANTITROMBOTICA

Acido acetilsalicilico: alleato insostituibile?

Giuseppe Musumeci

Azienda Ospedaliera Ordine Mauriziano

Torino



Aspirin at 120: Retiring, recombining, or repurposing?

Carlo Patrono MD | Bianca Rocca MD, PhD

Qualche cenno storico...

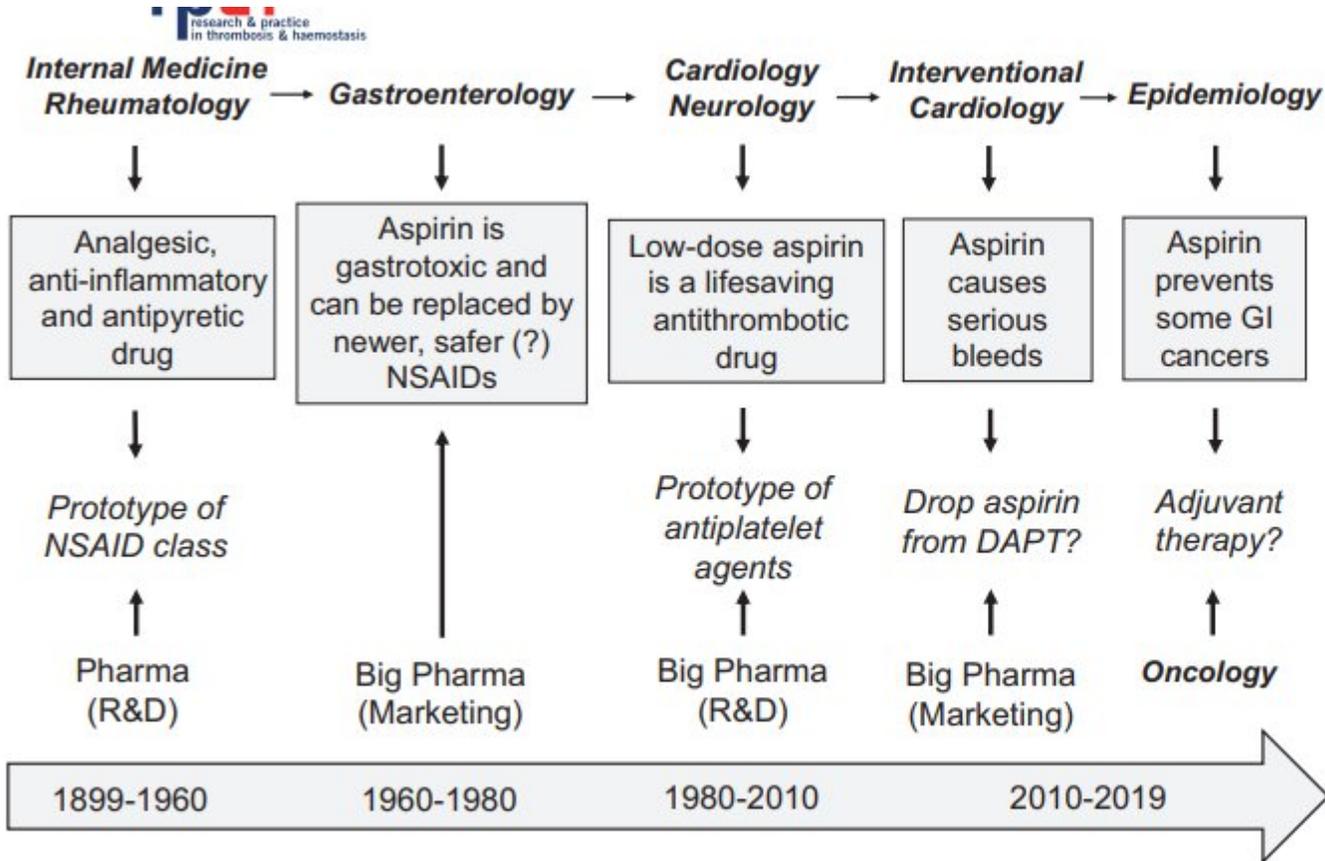


FIGURE 1 One hundred twenty years of aspirin-inspired research and development. The figure schematically summarizes the three phases of aspirin development: (A) as an analgesic, antipyretic, and anti-inflammatory agent; (B) as an antiplatelet drug; and (C) as a chemopreventive agent. Aspirin has inspired research throughout its 120-year life, by providing a tool for mechanistic understanding and a template for new drug development. DAPT, dual antiplatelet therapy; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; R&D, research and development



Qualche cenno storico...



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1970 Ticlopidine
in UA
Balsano F et al.
Circulation.
1990;82:17–26.

2007 Prasugrel
TRITON TIMI 38
Wiviott SD et al. N
Engl J Med.
2007;357:2001–15

2018 Ticagrelor
monotherapy
after 1-month
DAPT GLOBAL
LEADERS
Vranckx P. et al.
Lancet.
2018;392:940–949

2019 3-months
DAPT and
ticagrelor
monotherapy
TWILIGHT
Mehran R. et al. N
Engl J Med. 2019
Nov
21;381(21):2032-
2042.

2000
Clopidogrel
CLASSICS
Bertrand ME et al.
Circulation.
2000;102:624–9.

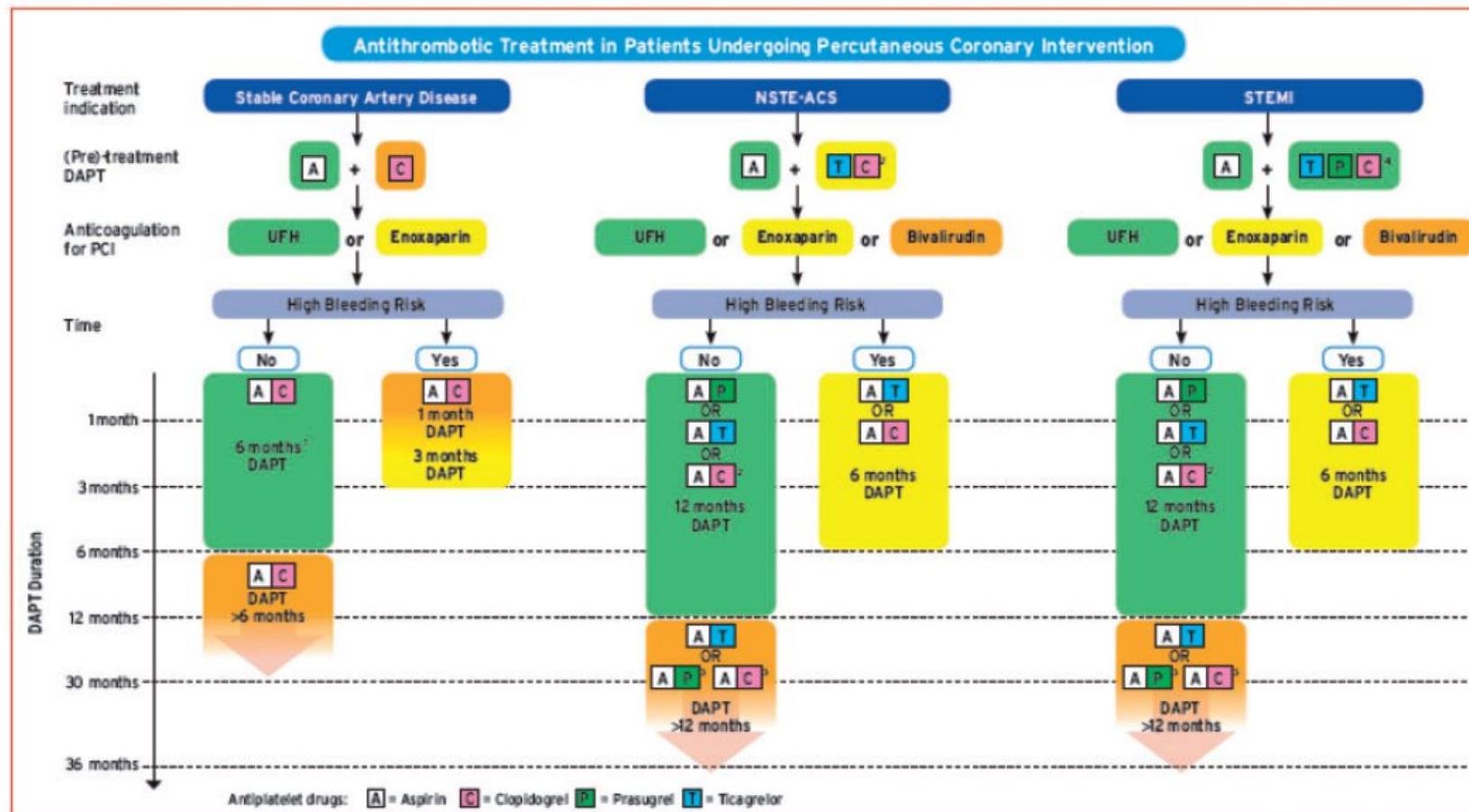
2009 Ticagrelor
PLATO
Wallentin L. et al.
N Engl J Med.
2009 Sep
10;361(11):1045-
57.

2019 Any P2Y12
inhibitor
monotherapy
after 3-months
DAPT
SMARTCHOICE
Hahn JY et al.
JAMA
2019;321:2428–
2437

2022 1 or 2-
months DAPT
and clopidogrel
monotherapy
STOPDAPT-2
ACS
Watanabe H. et al.
JAMA Cardiol.
2022 Apr
1;7(4):407-417



Quello che ci dicono le Linee Guida



DAPT = dual antiplatelet therapy; DCB = drug-coated balloon; NSTEMI-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting bleeding Complications in patients undergoing Stent Implantation and subsequent Dual Antiplatelet Therapy; STEMI = ST-elevation myocardial infarction; UFH = unfractionated heparin.

Colour-coding refers to the ESC classes of recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).

¹After PCI with DCB 6 months DAPT should be considered (class IIa) - ²Clopidogrel if patient is not eligible for a treatment with prasugrel or ticagrelor; or in a setting of DAPT de-escalation (Class IIb).

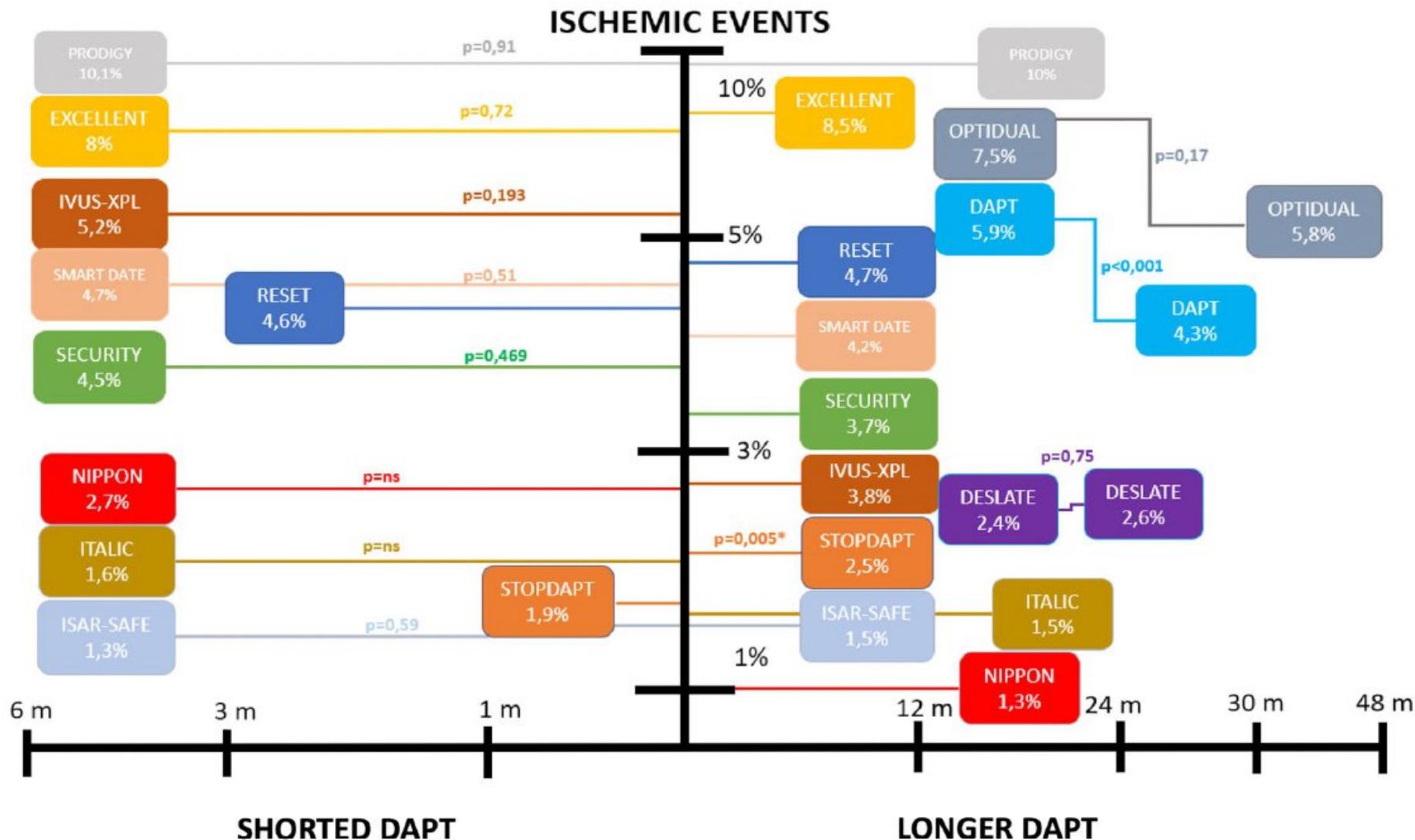
³Clopidogrel or prasugrel if patient is not eligible for a treatment with ticagrelor - ⁴Pretreatment before PCI (or at the latest at the time of PCI); clopidogrel if potent P2Y12 inhibitors are contraindicated or not available. (For scores see Supplementary Table 4.)

High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥ 25)

Figure 10 Algorithm for the use of antithrombotic drugs in patients undergoing percutaneous coronary intervention. High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥ 25). Colour-coding refers to the ESC classes of recommendations (green = class I; yellow = class IIa; and orange = class IIb).



Short vs Long DAPT

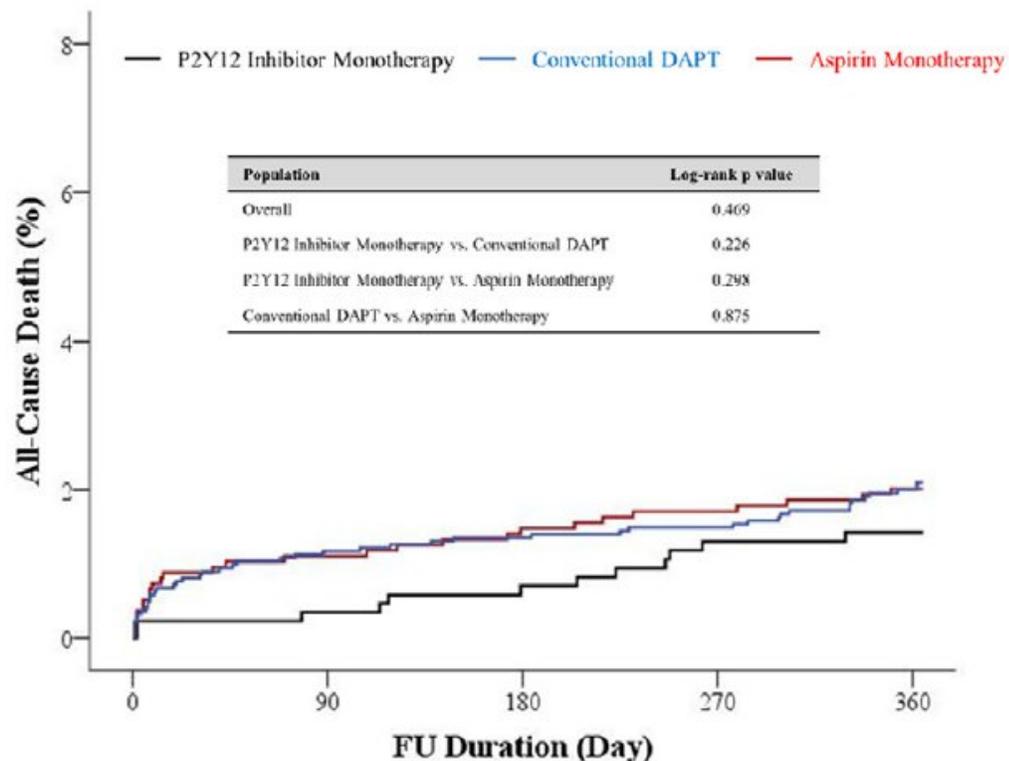




The SMART-DATE and SMART-CHOICE

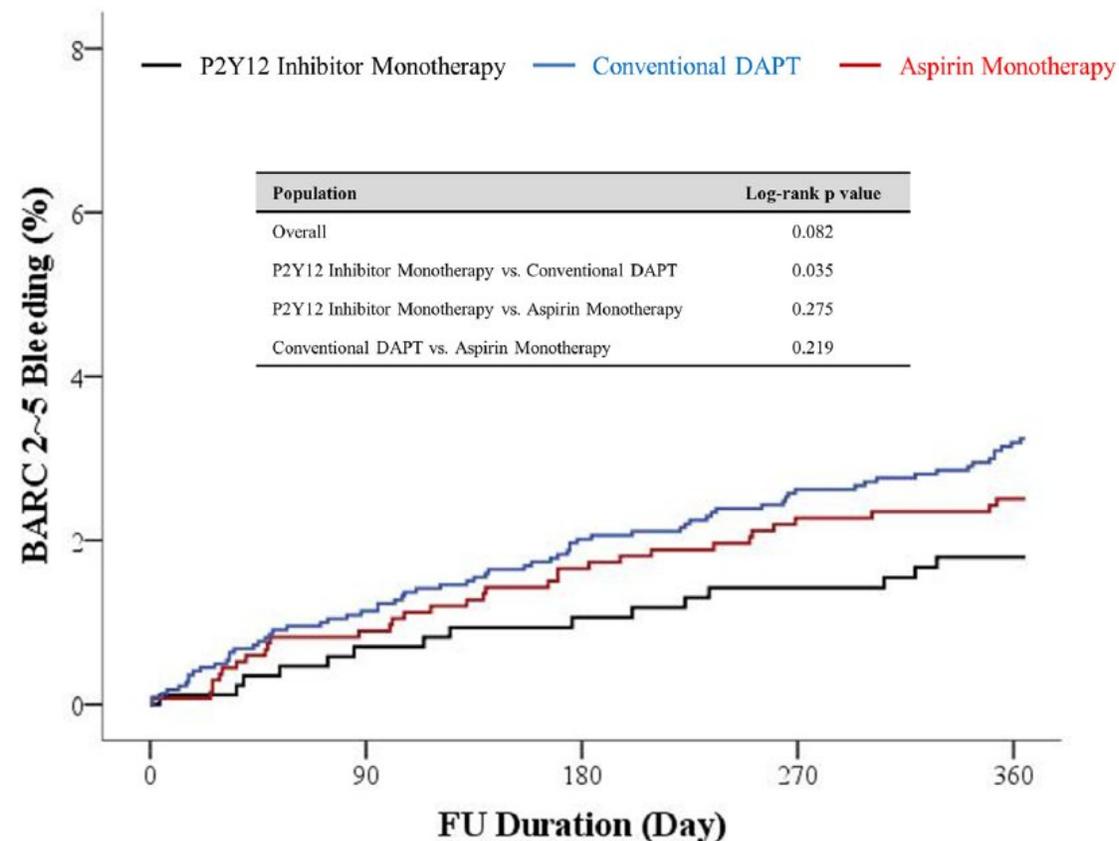


“..3-month DAPT followed by P2Y12 inhibitor monotherapy was comparable to conventional DAPT with regard to the prevention of ischemic events at 1 year after index PCI for ACS and it was associated with a lower risk of BARC type 2 to 5 bleeding



No. at risk

P2Y12 Inhibitor Monotherapy	870	847	831	821	709
Conventional DAPT	2,226	2,174	2,155	2,139	2,028
Aspirin Monotherapy	1,357	1,325	1,306	1,290	1,285





The TICO trial

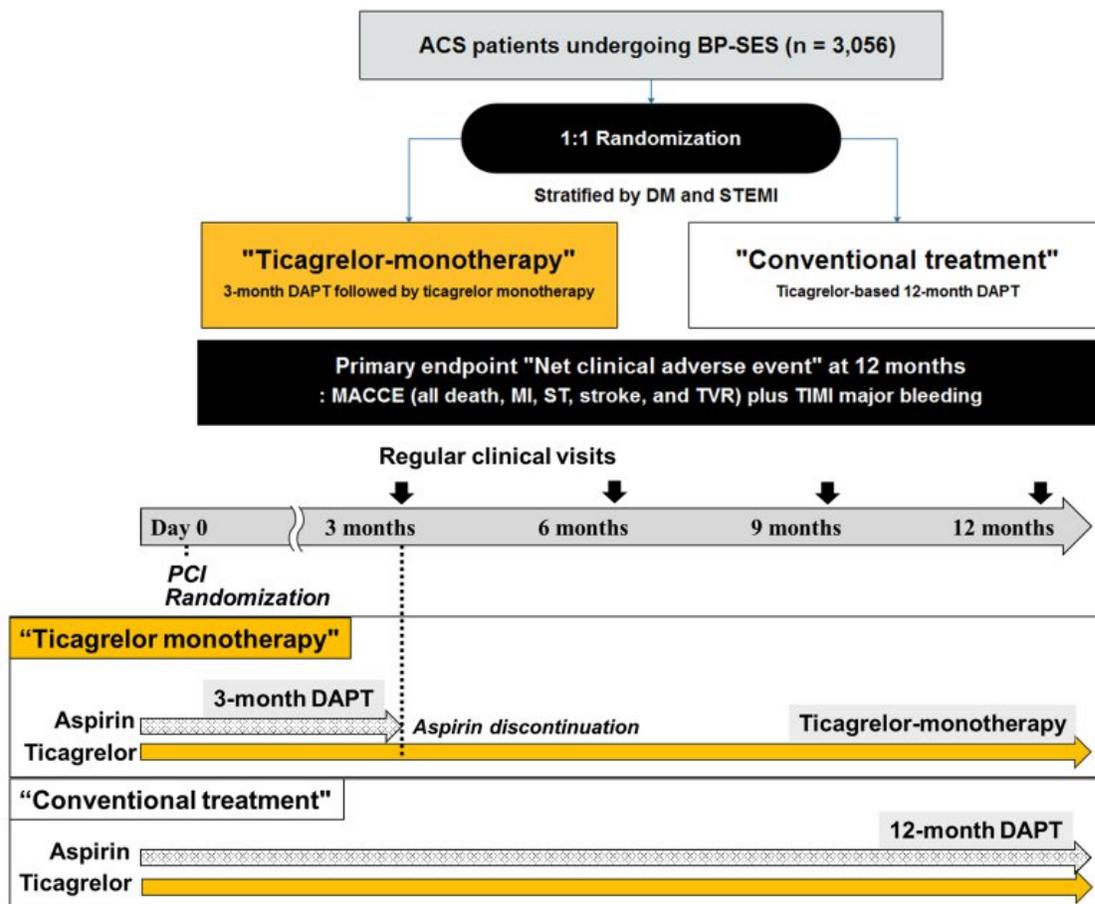
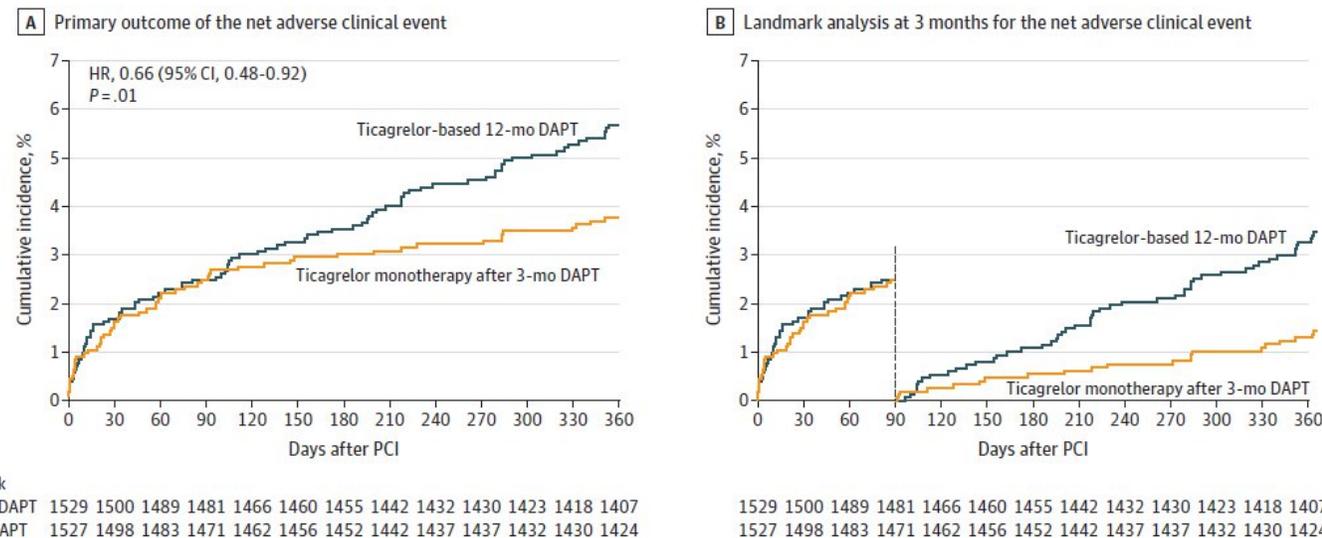
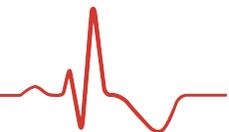


Figure 2. Time-to-Event Curves for the Primary Outcome and Landmark Analysis at 3 Months



Among patients with ACS treated with drug-eluting stents, ticagrelor monotherapy after 3-month DAPT, compared with ticagrelor-based 12-month DAPT, resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and cardiovascular events at 1 year. The study population and lower than expected event rates should be considered in interpreting the trial.





ARTICLES | [VOLUME 392, ISSUE 10151, P940-949, SEPTEMBER 15, 2018](#)

THE LANCET

Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial

[Pascal Vranckx, MD](#) [†] • [Prof Marco Valgimigli, MD](#) [†] • [Prof Peter Jüni, MD](#) [†] • [Prof Christian Hamm, MD](#)

[Prof Philippe Gabriel Steg, MD](#) • [Dik Heg, PhD](#) • et al. [Show all authors](#) • [Show footnotes](#)

The GLOBAL LEADERS trial, designed for superiority, failed to demonstrate a statistically significant reduction in the primary outcome of all-cause death or non-fatal, new Q-wave MI in post-PCI patients receiving a ticagrelor-based aspirin-free regimen as compared to standard therapy





Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial

Pascal Vranckx, MD [†] • Prof Marco Valgimigli, MD [†] • Prof Peter Jüni, MD [†] • Prof Christian Hamm, MD
Prof Philippe Gabriel Steg, MD • Dik Heg, PhD • et al. [Show all authors](#) • [Show footnotes](#)

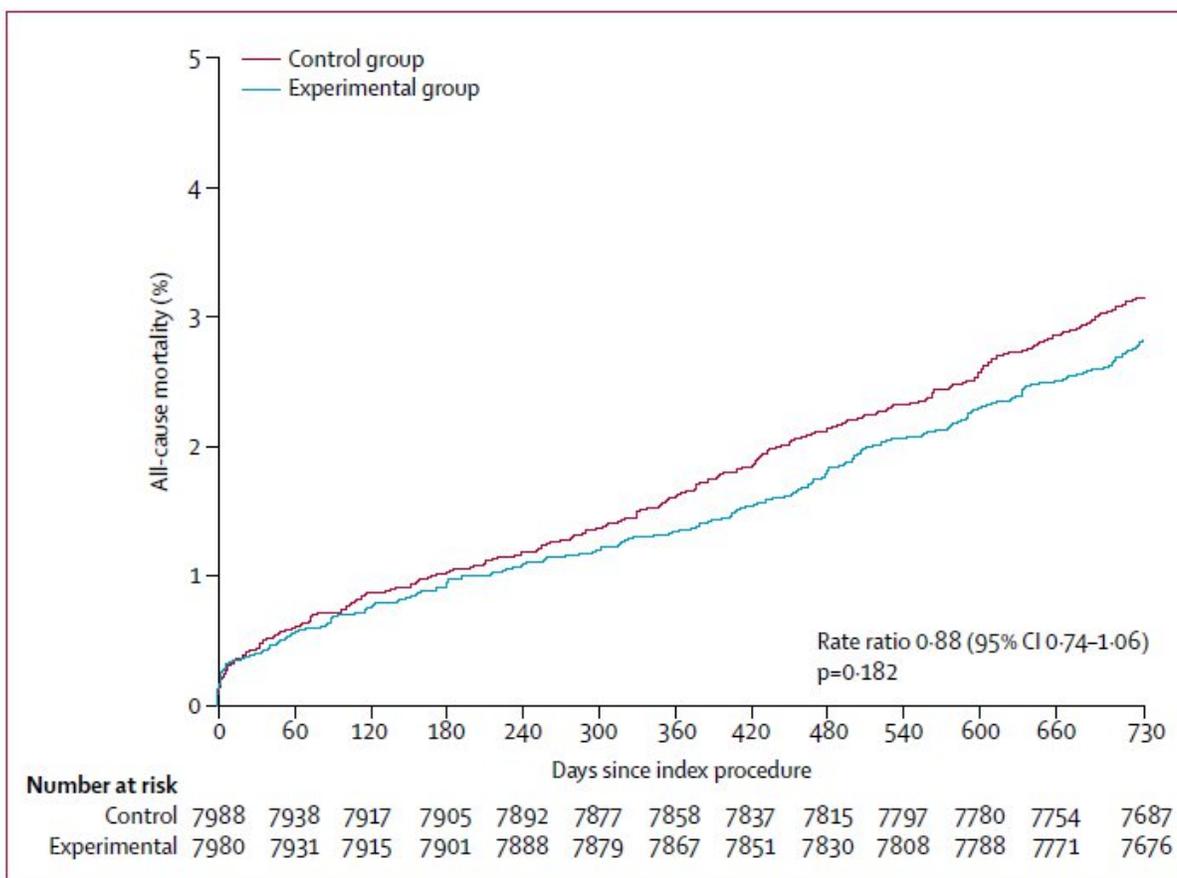


Figure 2: Cumulative incidence of all-cause mortality at 2 years

	Experimental treatment group (N=7980)	Control group (N=7988)	Rate ratio (95% CI)	p value
All-cause mortality or new Q-wave myocardial infarction	304 (3.81%)	349 (4.37%)	0.87 (0.75-1.01)	0.073
All-cause mortality	224 (2.81%)	253 (3.17%)	0.88 (0.74-1.06)	0.182
New Q-wave myocardial infarction*	83 (1.04%)	103 (1.29%)	0.80 (0.60-1.07)	0.14
Composite of all-cause mortality, stroke, or new Q-wave myocardial infarction	362 (4.54%)	416 (5.21%)	0.87 (0.76-1.00)	0.056
Myocardial infarction	248 (3.11%)	250 (3.13%)	1.00 (0.84-1.19)	0.98
Stroke				
Overall	80 (1.00%)	82 (1.03%)	0.98 (0.72-1.33)	0.90
Ischaemic	63 (0.79%)	68 (0.85%)	0.93 (0.66-1.31)	0.68
Haemorrhagic	13 (0.16%)	9 (0.11%)	1.45 (0.62-3.39)	0.39
Undetermined	6 (0.08%)	5 (0.06%)	1.21 (0.37-3.95)	0.76
Revascularisation	739 (9.26%)	793 (9.93%)	0.93 (0.84-1.03)	0.17
Target vessel revascularisation	389 (4.87%)	442 (5.54%)	0.88 (0.77-1.01)	0.068
Definite stent thrombosis	64 (0.80%)	64 (0.80%)	1.00 (0.71-1.42)	0.98
BARC				
BARC 3 or 5 bleeding	163 (2.04%)	169 (2.12%)	0.97 (0.78-1.20)	0.77
BARC 5 bleeding				
Any	22 (0.28%)	24 (0.30%)	0.92 (0.52-1.64)	0.78
5b bleeding	15 (0.19%)	18 (0.23%)	0.84 (0.42-1.66)	0.61
5a bleeding	7 (0.09%)	6 (0.08%)	1.17 (0.39-3.49)	0.78
BARC 3 bleeding				
Any	150 (1.88%)	159 (1.99%)	0.95 (0.76-1.18)	0.63
3c bleeding	35 (0.44%)	25 (0.31%)	1.41 (0.84-2.35)	0.19
3b bleeding	53 (0.66%)	74 (0.93%)	0.72 (0.51-1.02)	0.065
3a bleeding	77 (0.96%)	70 (0.88%)	1.10 (0.80-1.53)	0.55

Shown are the first event per event type for each patient only. Multiple events of the same type within the same patient are disregarded. Data were censored 730 days after index percutaneous coronary intervention. BARC=Bleeding Academic Research Consortium.³¹ *New Q-wave or equivalent left bundle branch block (n=3) as adjudicated by the core laboratory.

Table 3: Primary and prespecified secondary outcomes



The TWILIGHT trial



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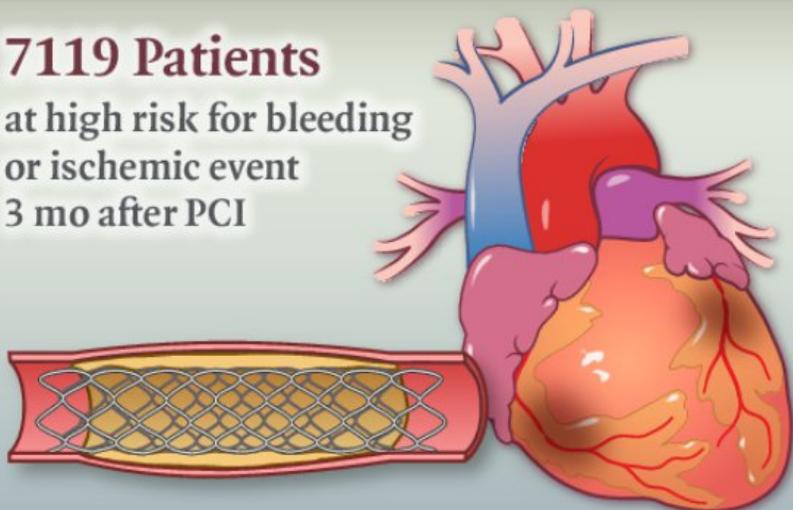
The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor with or without Aspirin after PCI

MULTICENTER, DOUBLE-BLIND, RANDOMIZED TRIAL

7119 Patients

at high risk for bleeding
or ischemic event
3 mo after PCI



Ticagrelor
(90 mg twice daily)
+
Placebo



(N=3555)

Ticagrelor
(90 mg twice daily)
+
Aspirin
(81–100 mg daily)



(N=3564)

**Clinically relevant
bleeding in 12 mo**

4.0%

7.1%

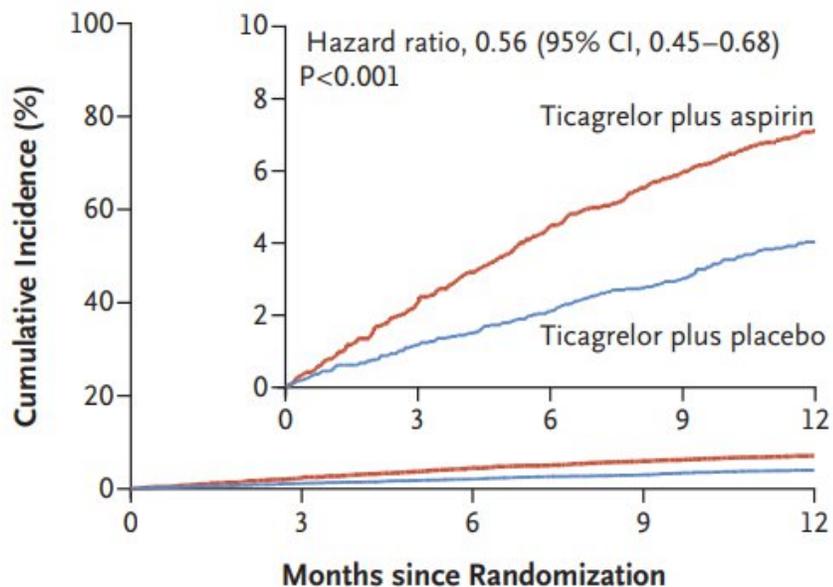
HR, 0.56; 95% CI, 0.45–0.68; P<0.001

Ticagrelor monotherapy also noninferior in preventing
a composite of death from any cause, MI, or stroke





The TWILIGHT trial

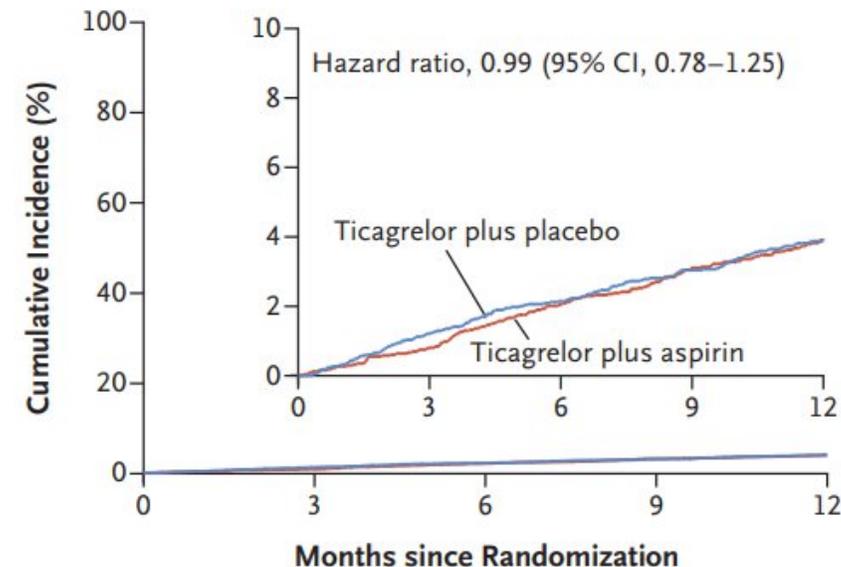


No. at Risk

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

Figure 2. Kaplan–Meier Estimates of the Incidence of BARC Type 2, 3, or 5 Bleeding 1 Year after Randomization (Intention-to-Treat Population).

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). The inset shows the same data on an expanded y axis. CI denotes confidence interval.



No. at Risk

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

Figure 3. Kaplan–Meier Estimates of the Incidence of Death from Any Cause, Nonfatal Myocardial Infarction, or Nonfatal Stroke 1 Year after Randomization (Per-Protocol Population).

The per-protocol population included patients who underwent randomization and had no major deviations from the protocol. The hazard ratio shown is for ticagrelor plus placebo versus ticagrelor plus aspirin. The inset shows the same data on an expanded y axis.



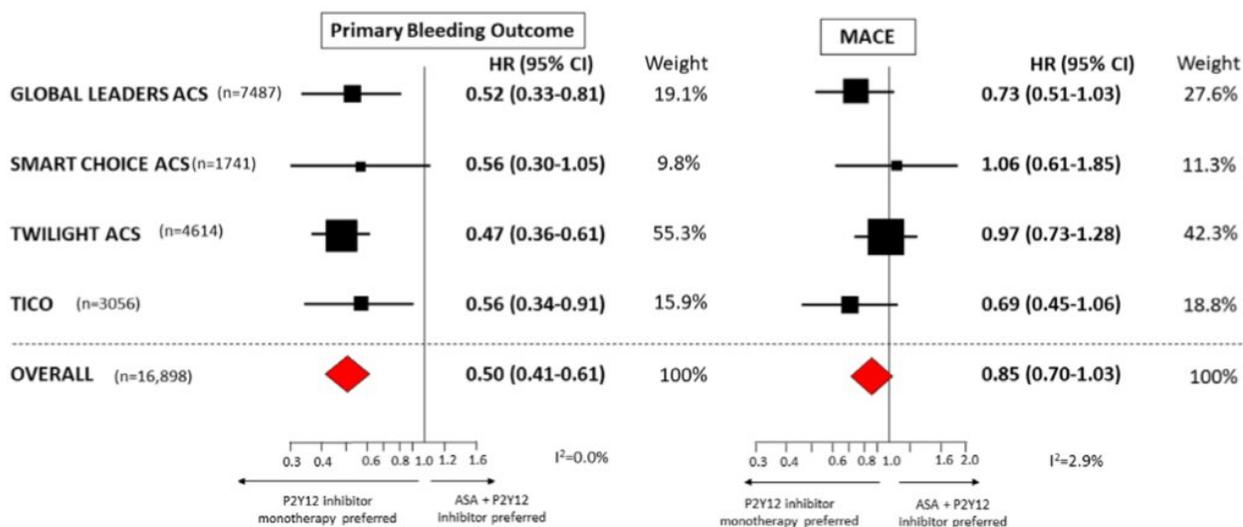
ORIGINAL RESEARCH ARTICLE

The Safety and Efficacy of Aspirin Discontinuation on a Background of a P2Y₁₂ Inhibitor in Patients After Percutaneous Coronary Intervention

A Systematic Review and Meta-Analysis

BACKGROUND: Dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor has been shown to reduce the risk of major adverse cardiovascular events (MACE) compared with aspirin alone after percutaneous coronary intervention (PCI) or acute coronary syndrome but with increased risk of bleeding. The safety of discontinuing aspirin in favor of P2Y₁₂ inhibitor monotherapy remains disputed.

Michelle L. O'Donoghue, MD, MPH
Sabina A. Murphy, MPH
Marc S. Sabatine, MD, MPH



Trial Name	Blind	Study Population	Intervention	Control	Sample Size	Primary Bleeding End Point	Primary Cardiovascular End Point	Follow-Up Time
GLOBAL LEADERS ^{11,14}	Open label	ACS (47%) or stable CAD after DES	Ticagrelor monotherapy after month 1	Clopidogrel (stable CAD) or ticagrelor (ACS) + ASA 75 to 100 mg daily	15 968	BARC 3 or 5 bleeding (site-reported)	All-cause death or MI (adjudicated new Q wave)	12 months*
SMART CHOICE ¹⁵	Open label	ACS (58%) or stable CAD after DES	Any P2Y ₁₂ inhibitor monotherapy after month 3	Any P2Y ₁₂ inhibitor + ASA 100 mg daily	2993	BARC 2 to 5 bleeding	All-cause death, MI, or stroke	12 months
STOPDAPT-2 ¹⁶	Open label	ACS (38%) or stable CAD after DES	Clopidogrel monotherapy after month 1	Clopidogrel + ASA 81 to 200 mg daily after month 1	3045 (3009 in ITT)	TIMI major or minor bleeding	Cardiovascular death, MI, stroke, or definite stent thrombosis ¹	12 months
TWILIGHT ¹⁷	Double blind	NSTE-ACS or stable CAD after DES	Ticagrelor monotherapy after month 3	Ticagrelor + ASA 81 to 100 mg daily	7119	BARC 2, 3, or 5 bleeding	All-cause death, MI, or stroke	Month 15 (randomized at month 3)
TICO ¹⁸	Open label	ACS (STEMI or NSTE-ACS) after DES	Ticagrelor monotherapy after month 3	Ticagrelor + ASA 100 mg daily	3056	TIMI major bleeding	All-cause death, MI, stroke, stent thrombosis, or target vessel revascularization	12 months



The STOPDAPT-2 ACS trial



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This Issue Views **12,816** | Citations **0** | Altmetric **116**

Original Investigation

March 2, 2022

Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome

The STOPDAPT-2 ACS Randomized Clinical Trial

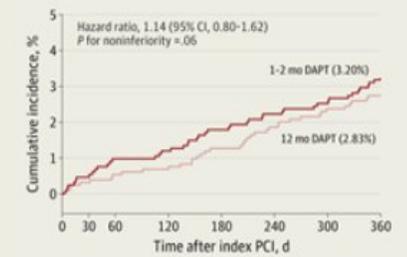
Hirotohi Watanabe, MD¹; Takeshi Morimoto, MD²; Masahiro Natsuaki, MD³; et al

» Author Affiliations

JAMA Cardiol. 2022;7(4):407-417. doi:10.1001/jamacardio.2021.5244

JAMA Cardiology

RCT: Comparison of Clopidogrel Monotherapy After 1 to 2 Months of DAPT With 12 Months of DAPT in Patients With Acute Coronary Syndrome

<p>POPULATION 3280 Men, 856 Women</p>  <p>Patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) with everolimus eluting stents Mean age, 66.8 y</p>	<p>INTERVENTION 4169 Patients randomized</p>   <p>2078 DAPT group, 1-2 mo Dual antiplatelet therapy (DAPT) for 1-2 mo followed by clopidogrel monotherapy</p> <p>2091 DAPT group, 12 mo DAPT with aspirin and clopidogrel for 12 mo</p>	<p>FINDINGS</p> <p>Clopidogrel monotherapy after 1-2 mo of DAPT failed to attest noninferiority compared with 12 mo of DAPT with aspirin and clopidogrel</p>  <p>Composite cardiovascular or bleeding events: 1-2 mo DAPT: 65 patients (3.20%) 12-mo DAPT: 58 patients (2.83%) Hazard ratio, 1.14 (95% CI, 0.80-1.62); P for noninferiority = .06</p>
<p>SETTINGS / LOCATIONS</p>  <p>96 PCI centers in Japan</p>	<p>PRIMARY OUTCOME</p> <p>A composite of cardiovascular events (death, myocardial infarction, definite stent thrombosis, ischemic/hemorrhagic stroke) or bleeding defined by Thrombolysis in Myocardial Infarction (TIMI) major/minor criteria at 12 mo</p>	

Watanabe H, Morimoto T, Natsuaki M, et al; STOPDAPT-2 ACS Investigators. Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: the STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol.* Published online March 2, 2022. doi:10.1001/jamacardio.2021.5244

Conclusions and Relevance In patients with ACS with successful PCI, clopidogrel monotherapy after 1 to 2 months of DAPT failed to attest noninferiority to standard 12 months of DAPT for the net clinical benefit with a numerical increase in cardiovascular events despite reduction in bleeding events. The directionally different efficacy and safety outcomes indicate the need for further clinical trials.

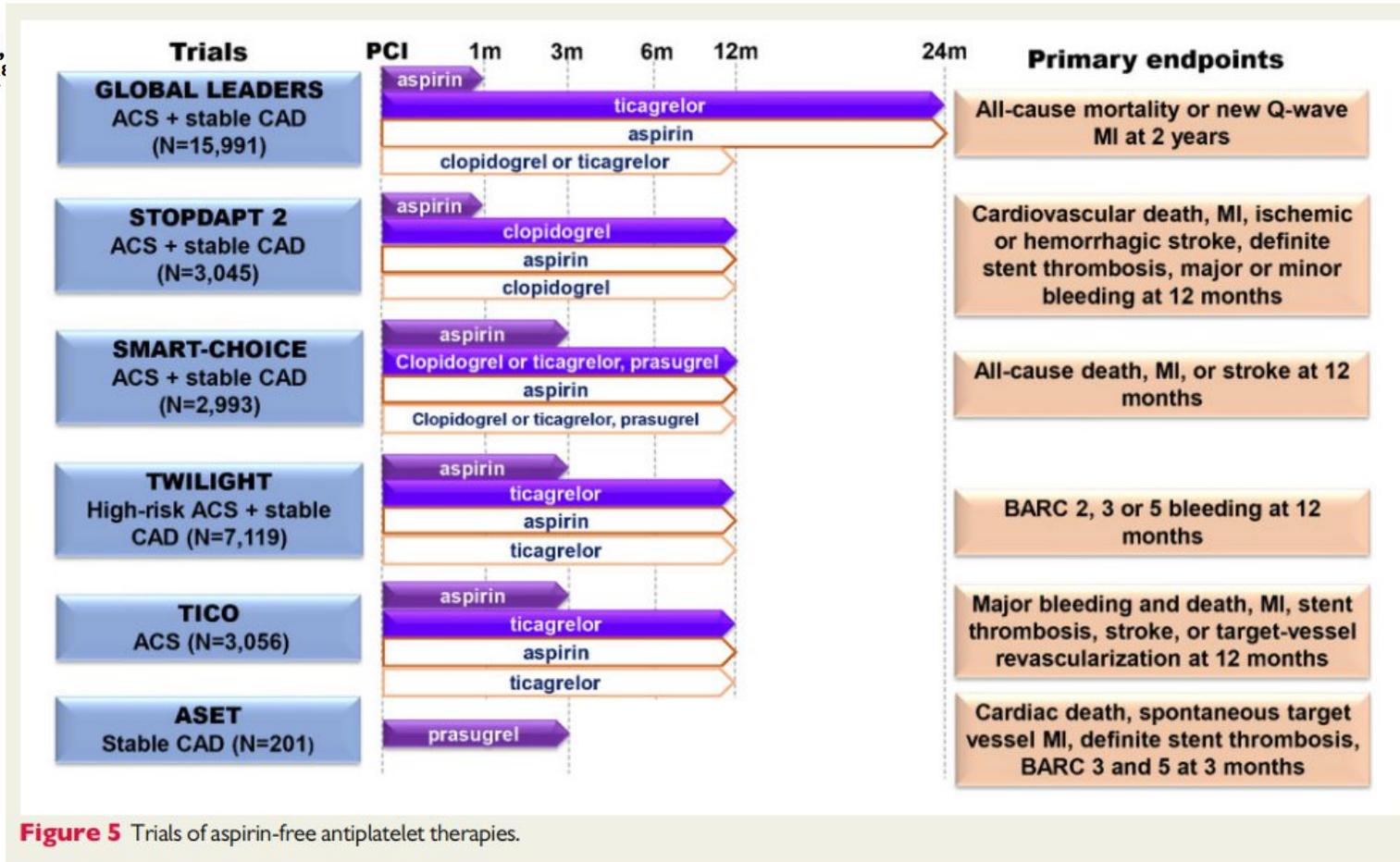
Trial Registration ClinicalTrials.gov Identifiers: [NCT02619760](https://clinicaltrials.gov/ct2/show/study/NCT02619760) and [NCT03462498](https://clinicaltrials.gov/ct2/show/study/NCT03462498)





Aspirin-free antiplatelet regimens after PCI: insights from the GLOBAL LEADERS trial and beyond

Rutao Wang^{1,2,3†}, Sijing Wu^{2,4,5†}, Amr Gamal^{2,6,7}, Chao Gao^{1,2,3}, Hironori Hara^{2,5}, Hideyuki Kawashima^{2,5}, Masafumi Ono^{2,5}, Robert-Jan van Geuns³, Pascal Vranckx⁴, Stephan Windecker¹⁰, Yoshinobu Onuma², Patrick W. Serruys^{2,11*}, and Scot Garg¹²



Wang R. et al. Eur Heart J Cardiovasc Pharmacother. 2021 Nov 3;7(6):547-556.



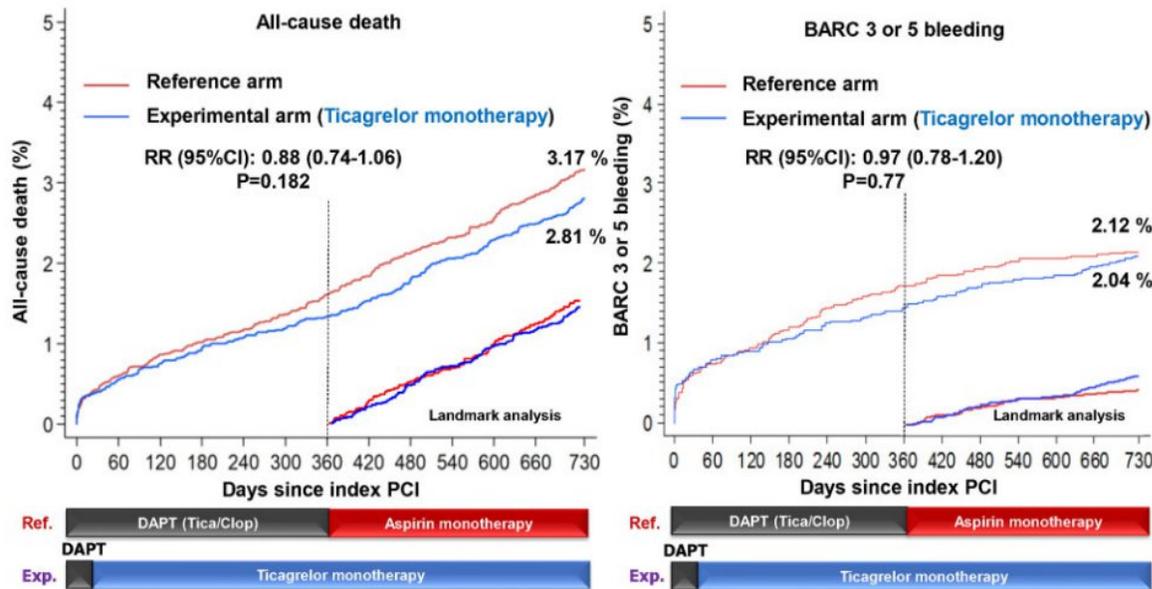


Figure 3 Kaplan-Meier estimate of mortality and safety outcome at 2 years of GLOBAL LEADERS trial.

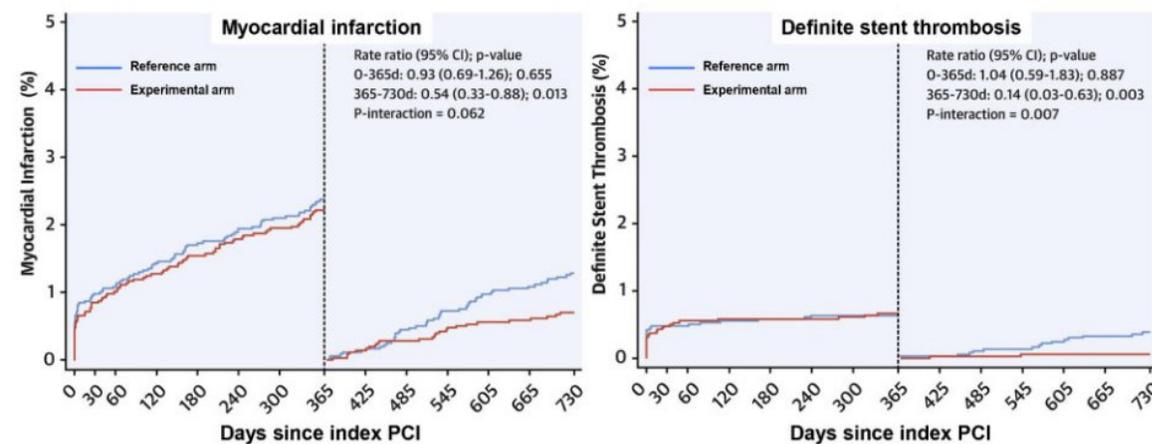


Figure 4 Kaplan-Meier graphs by landmark analysis for MI and definite ST in GLASSY study.

Early discontinuation of aspirin therapy reduced the risk of major bleeding (using heterogeneous outcome definitions as used in each trial) by 40% compared with DAPT (2.0% vs 3.1%; hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.45-0.79)

There was no apparent increase in the risk of major adverse cardiovascular events (MACEs) (2.7% vs 3.1%; HR, 0.88; 95% CI, 0.77-1.02)

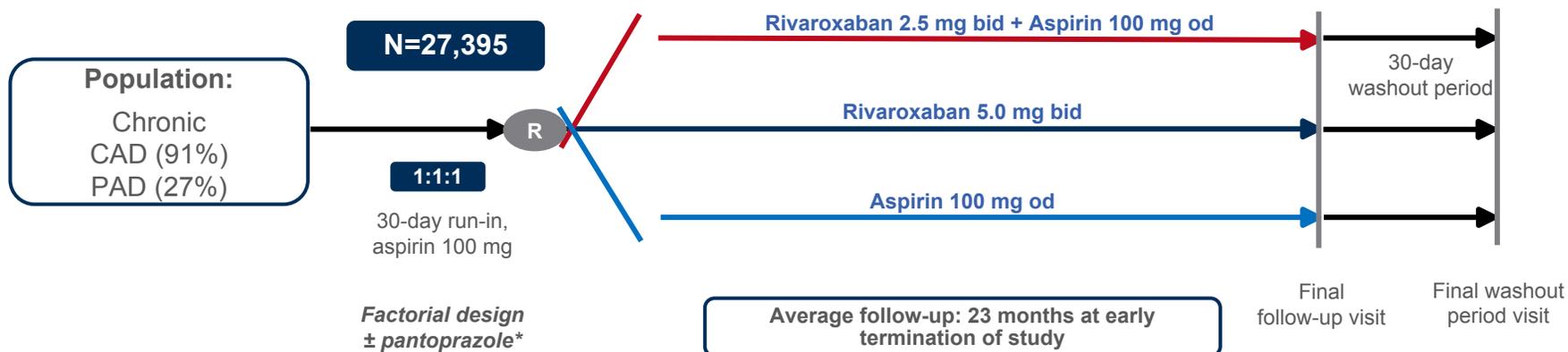


COMPASS Trial



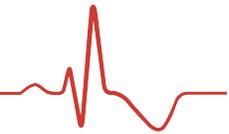
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Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design);

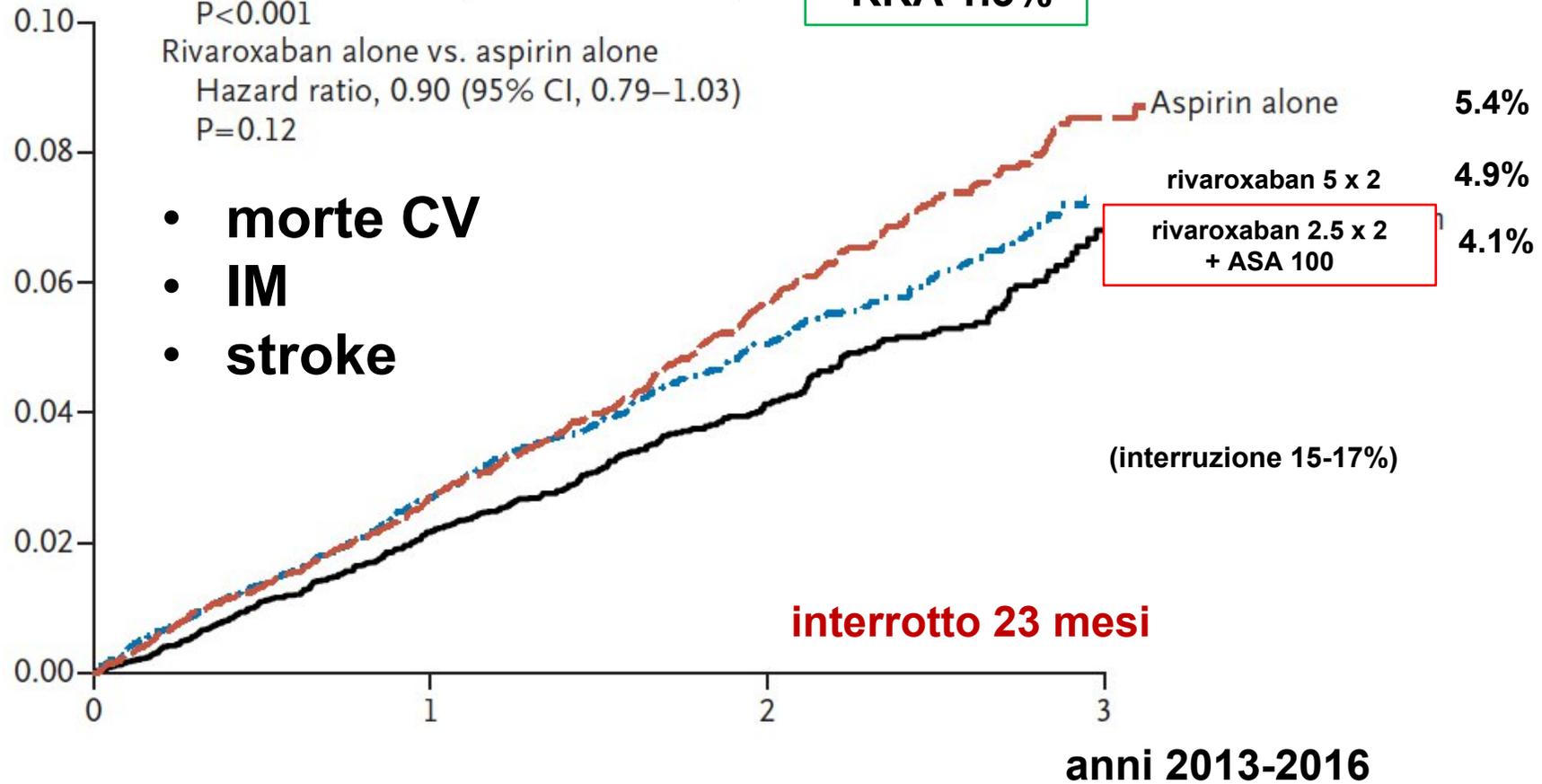




Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Rivaroxaban+aspirin vs. aspirin alone
Hazard ratio, 0.76 (95% CI, 0.66–0.86)
P<0.001
Rivaroxaban alone vs. aspirin alone
Hazard ratio, 0.90 (95% CI, 0.79–1.03)
P=0.12

RRR 24%
RRA 1.3%





Secondary outcomes



Outcome	R + A N=9,152	Riva N=9,117	Aspirin N=9,126	Riva + aspirin vs. aspirin		Rivaroxaban vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	p	HR (95% CI)	p
CHD death, Isch. stroke, MI, ALL	329 (3.6)	397 (4.4)	450 (4.9)	0.72 (0.63-0.83)	<0.0001	0.88 (0.77-1.01)	0.06
CV death, Isch. stroke, MI, ALL	389 (4.3)	453 (5.0)	516 (5.7)	0.74 (0.65-0.85)	<0.0001	0.88 (0.77-0.99)	0.04
Death	313 (3.4)	366 (4.0)	378 (4.1)	0.82 (0.71-0.96)	0.01	0.97 (0.84-1.12)	0.66



AUGUSTUS: Study Design

A Phase IV, Open-label, 2 x 2 Factorial, Randomized Controlled Study

Key Inclusion Criteria

- Aged ≥ 18 years.
- AF (prior, persistent/permanent, paroxysmal) or flutter with planned or existing use of OAC.
- ACS and/or PCI within the prior 14 days.
- Planned use of P2Y₁₂ inhibitor for at least 6 months.

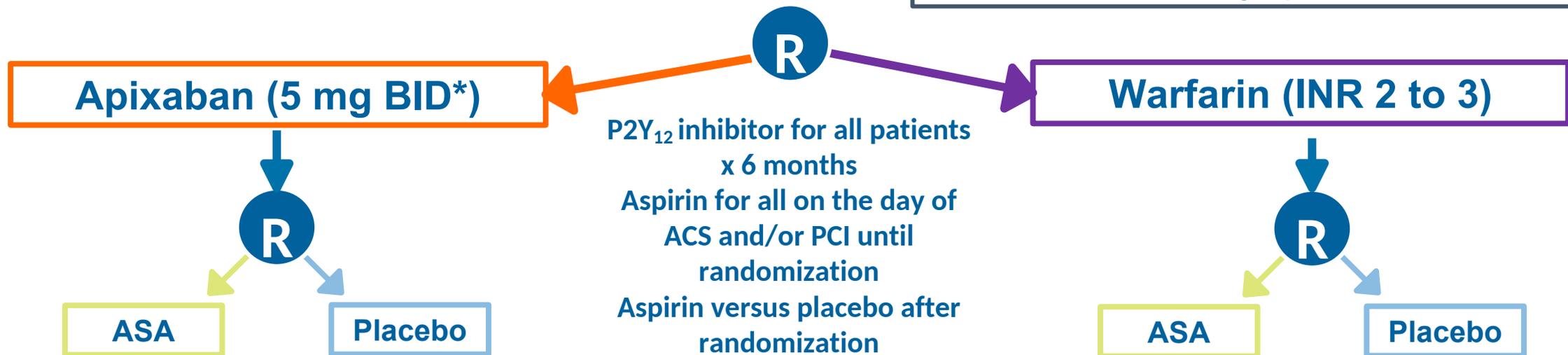
Key Exclusion Criteria

- Other conditions that require anticoagulation eg, mechanical heart valve, moderate/severe mitral stenosis, DVT, or PE.
- Serum creatinine > 2.5 [$221 \mu\text{mol/L}$] or CrCl < 30 mL/min.
- History of intracranial hemorrhage.
- Contraindications to VKA, apixaban, intended P2Y₁₂ or ASA.
- Recent/planned CABG surgery for index ACS event.
- Patients with known ongoing bleeding.
- Patients with known coagulopathies.

N = 4600

Approximately 500 sites in 34 countries

Randomization stratified by indication (ACS vs PCI)



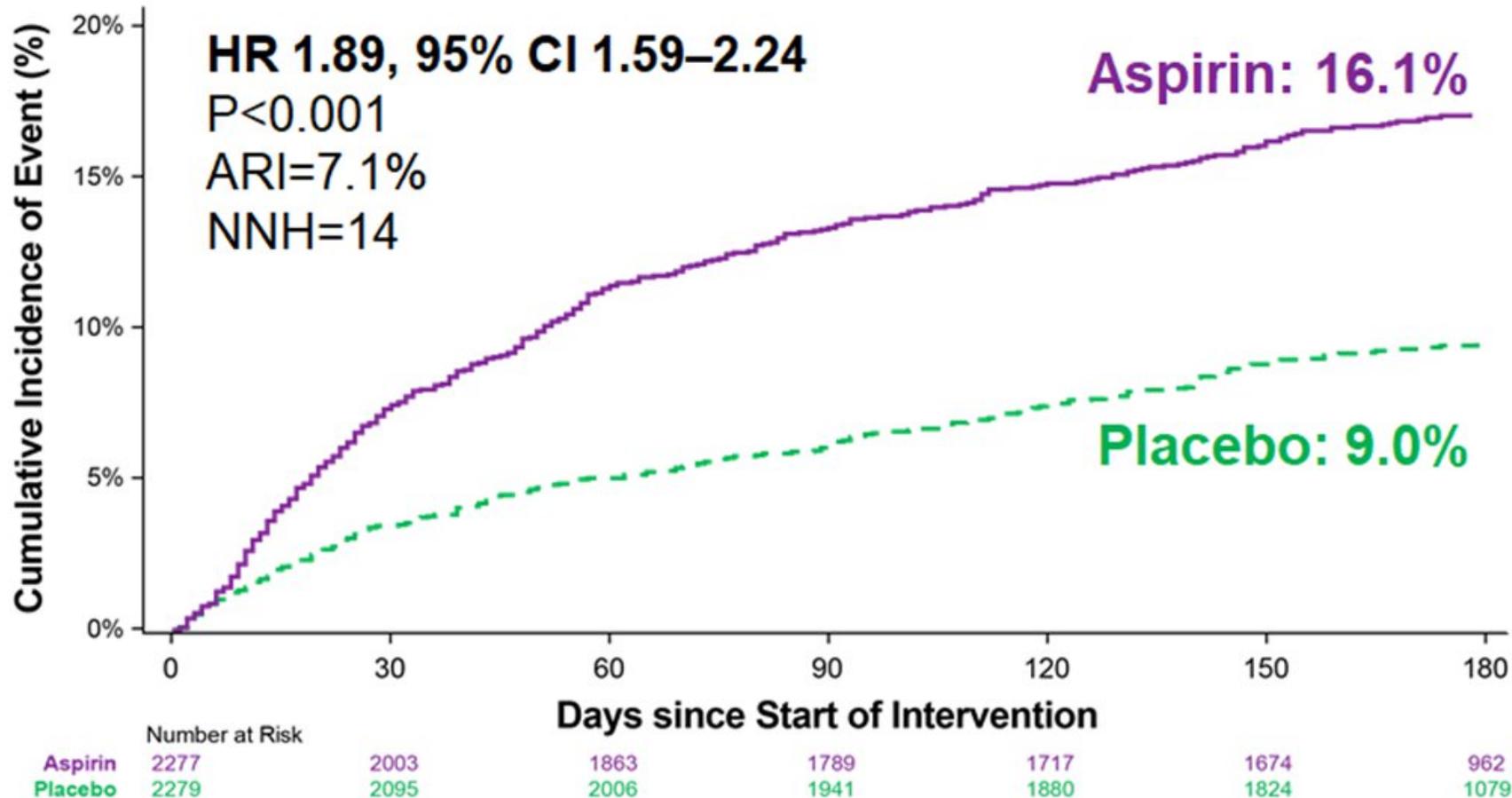
*Dose reduced to 2.5 mg BID if patients meet 2 or more of the following criteria: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL ($133 \mu\text{mol/L}$)

Adapted from Lopes RD et al. Am Heart J. March 2018 doi:10.1016/j.ahj.2018.03.001 [Epub ahead of print]

Primary Outcome: Aspirin versus Placebo ISTH major or CRNM bleeding



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ARI: absolute risk increase
NNH: number needed to harm

Secondary Endpoint: Aspirin vs Aspirin Placebo Ischemic Outcomes



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Endpoint	Aspirin (N=2307)	placebo (N=2307)	Hazard Ratio (95%CI)
Death / Ischemic Events (%)	6.5	7.3	0.89 (0.71-1.11)
Death (%)	3.1	3.4	0.91 (0.66-1.26)
CV Death (%)	2.3	2.5	0.92 (0.63-1.33)
Stroke (%)	0.9	0.8	1.06 (0.56-1.98)
Myocardial Infarction (%)	2.9	3.6	0.81 (0.59-1.12)
Definite or Probable Stent Thrombosis (%)	0.5	0.9	0.52 (0.25-1.08)
Urgent Revascularization (%)	1.6	2.0	0.79 (0.51-1.21)
Hospitalization (%)	25.4	23.4	1.10 (0.98-1.24)

All patients were concomitantly receiving P2Y₁₂ therapy

P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials

Valgimigli et al PROSPERO trial BMJ 2021 Jun 16;373:n1332

Weekly Journal Scan

Aspirin-free antiplatelet strategies: is the evidence supporting a paradigm shift?

Giovanna Liuzzo  ^{1*} and Carlo Patrono  ²

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The results of P2Y12 Inhibitor Monotherapy or Dual Antiplatelet Therapy after Coronary Revascularisation: Individual Patient Level Meta-Analysis of Randomised Controlled Trials have been published in *Br Med J*. doi:10.1136/bmj.n1332.

The authors conclude that their results support a paradigm shift in antithrombotic management and question the central role of DAPT beyond one to three months after PCI.¹ We believe that a paradigm shift requires a pragmatic, randomized comparison of aspirin monotherapy vs. P2Y₁₂i monotherapy, after 1–3-month DAPT following PCI, with stratification according to the gender and type of P2Y₁₂i, to assess long-term tolerability and safety of the two monotherapy options, because the relevant medical question is not what happens over the next few months but over the next years.





PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE



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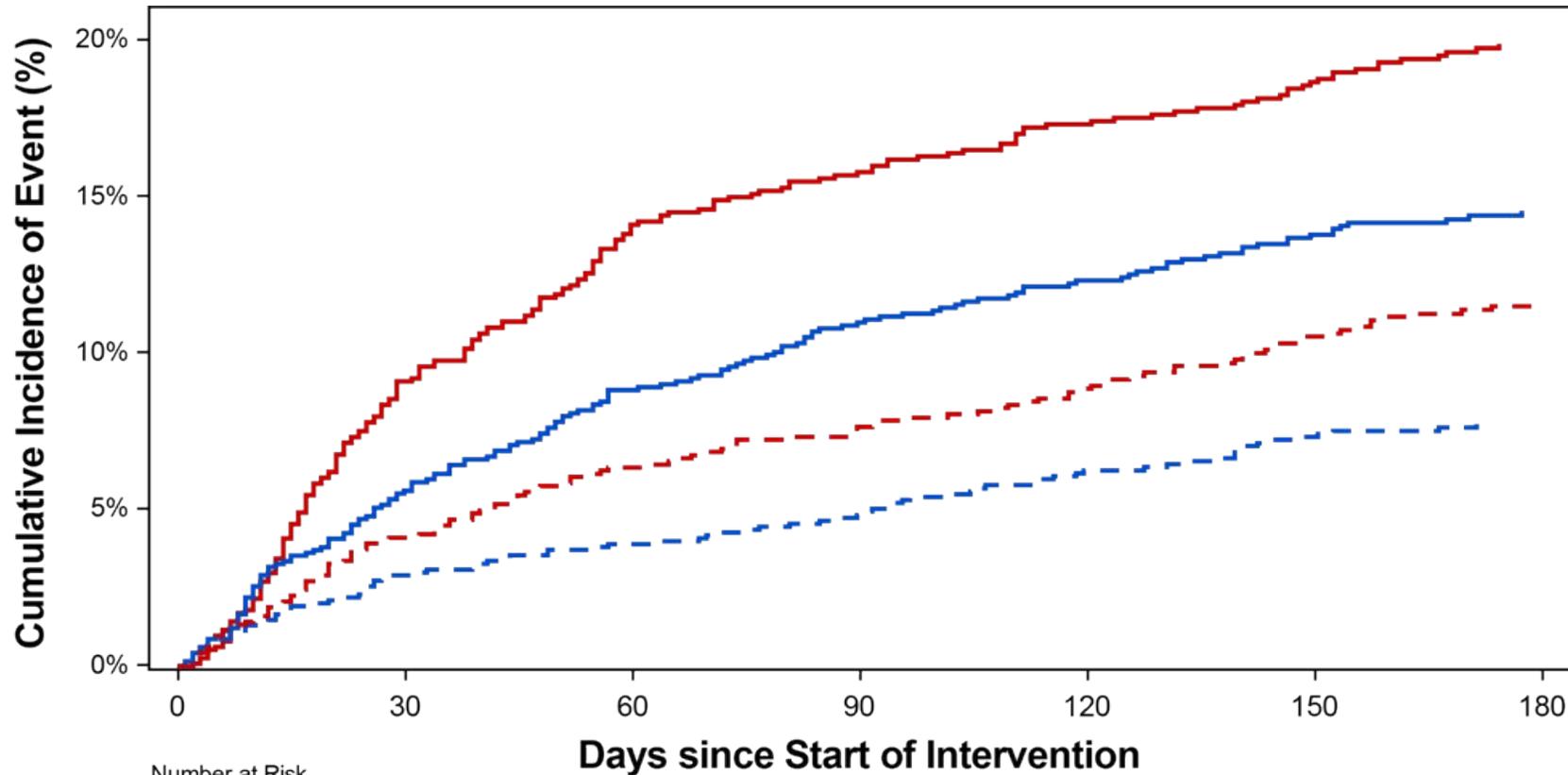
TERAPIA

ANTITROMBOTICA

Acido acetilsalicilico: alleato insostituibile?

Per ora.....SI

ISTH or CRNM Bleeding, According to Intervention Combination



VKA + Aspirin (18.7%)

Apixaban + Aspirin (13.8%)

VKA + Placebo (10.9%)

Apixaban + Placebo (7.3%)

**Apixaban + Placebo vs. VKA + Aspirin:
11.4% absolute risk reduction (NNT=9)**

	0	30	60	90	120	150	180
Apixaban and Aspirin	1145	1036	975	937	903	880	485
Apixaban and Placebo	1143	1075	1044	1007	975	947	536
VKA and Aspirin	1123	962	881	838	800	776	467
VKA and Placebo	1126	1007	947	917	883	851	528



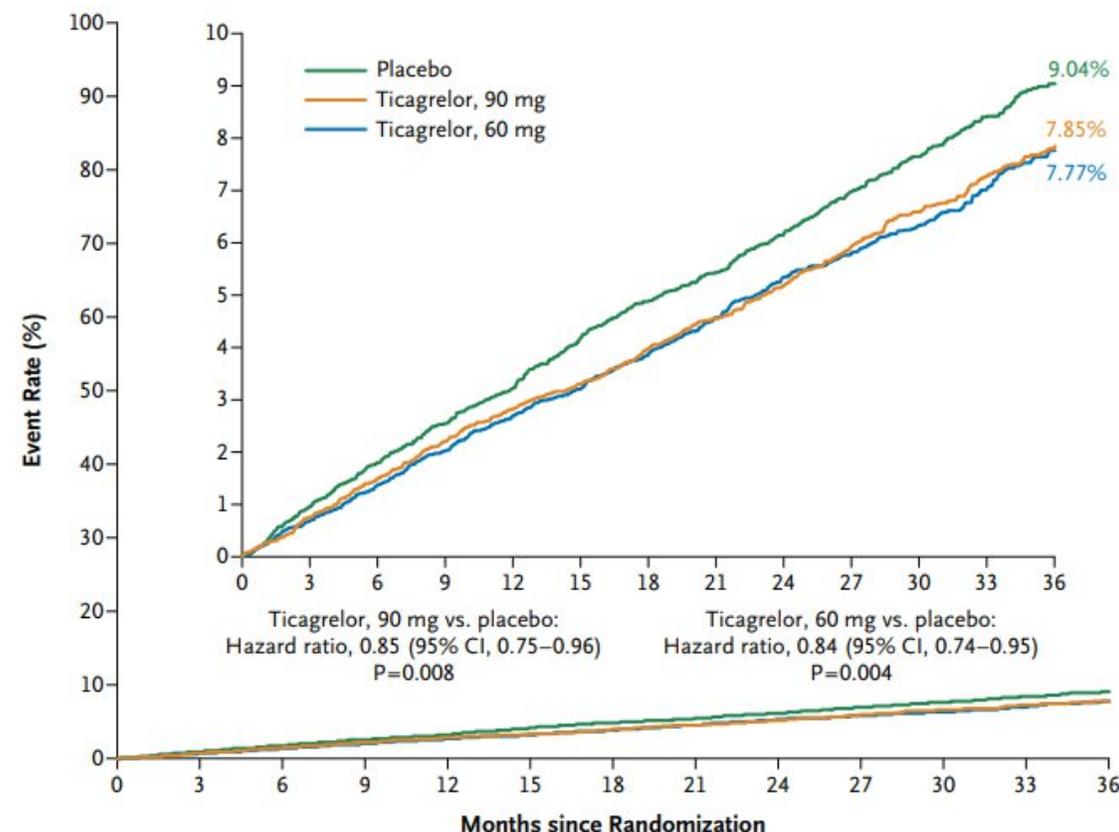
The PEGASUS TIMI 54 trial



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The lower dose of ticagrelor reduced the 3-year SVE rate by 16%, from 9.04% in the placebo group to 7.77% (HR, 0.84; 95% CI, 0.74-0.95; P = .004; NNT = 79) with no statistically significant reduction in mortality.

Rates of TIMI major bleeding were significantly higher with ticagrelor (2.30% with 60 mg) than with placebo (1.06%) (HR, 2.32; 95% CI, 1.68-3.21; P < .001; NNH = 81), but the rates of fatal bleeding or nonfatal intracranial hemorrhage did not differ significantly between either ticagrelor dose and placebo



No. at Risk

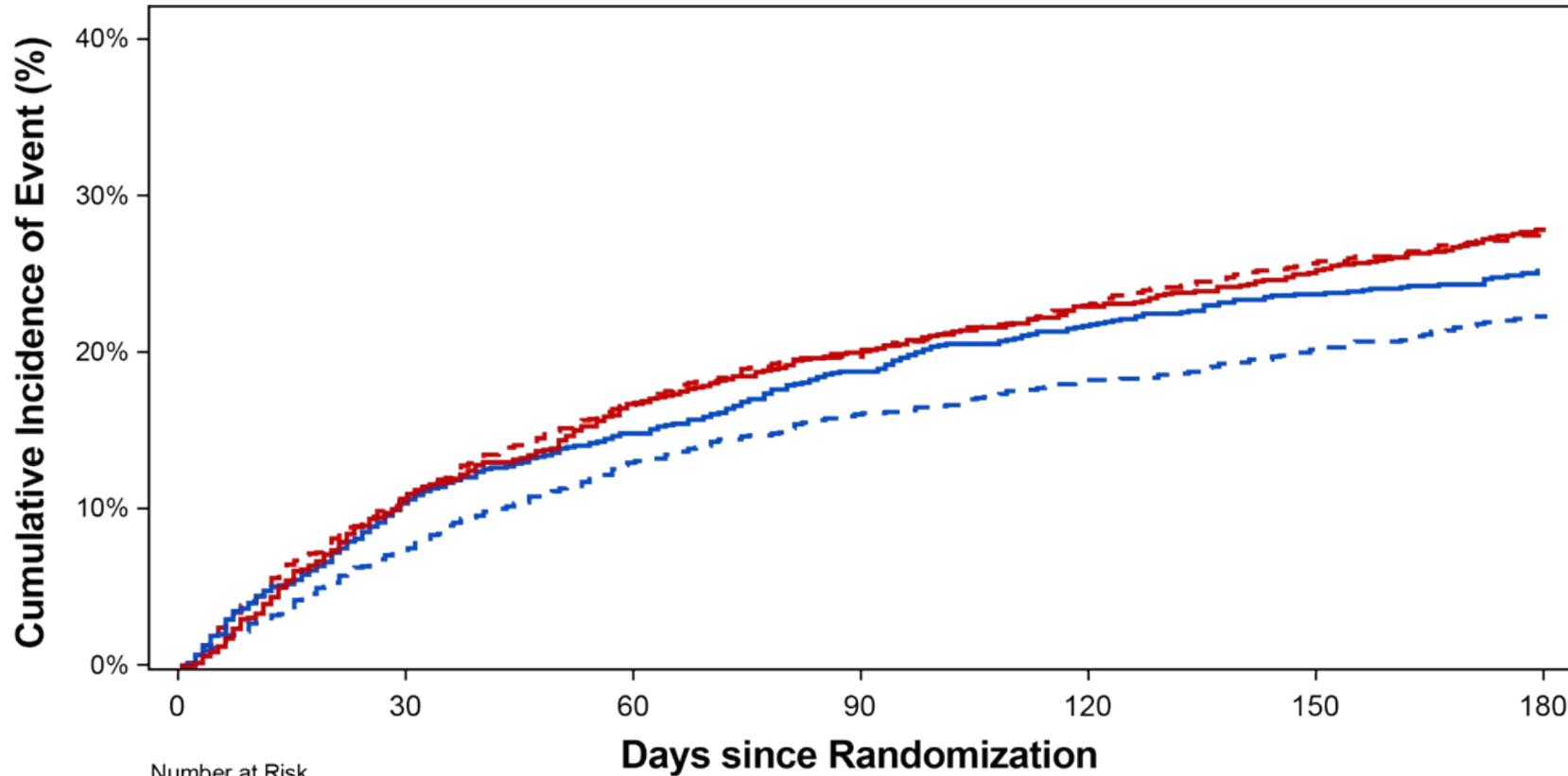
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

Figure 1. Kaplan–Meier Rates of Cardiovascular Death, Myocardial Infarction, and Stroke through 3 Years, According to Study Group.

Study drugs were administered twice daily. The inset shows the same data on an enlarged y axis.



Death or Hospitalization, According to Intervention Combination



VKA + Aspirin (27.5%)
VKA + Placebo (27.3%)
Apixaban + Aspirin (24.9%)
Apixaban + Placebo (22.0%)

Apixaban + Placebo
vs. VKA + Aspirin:
5.5% absolute risk
reduction (NNT=18)

	Number at Risk						
	0	30	60	90	120	150	180
Apixaban and Aspirin	1153	1026	970	923	888	863	459
Apixaban and Placebo	1153	1064	995	958	933	909	488
VKA and Aspirin	1154	1016	939	899	864	836	492
VKA and Placebo	1154	1019	946	906	868	837	509

All patients were concomitantly receiving P2Y₁₂ therapy