Beyond DAPT Maximizing protection against ischaemic recurrence with potent antiplatelets

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Disclosure

Consultancy and lecture honoraria from Astrazeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Johnson & Johnson, Merck, Novartis, Novo Nordisk, Pfizer

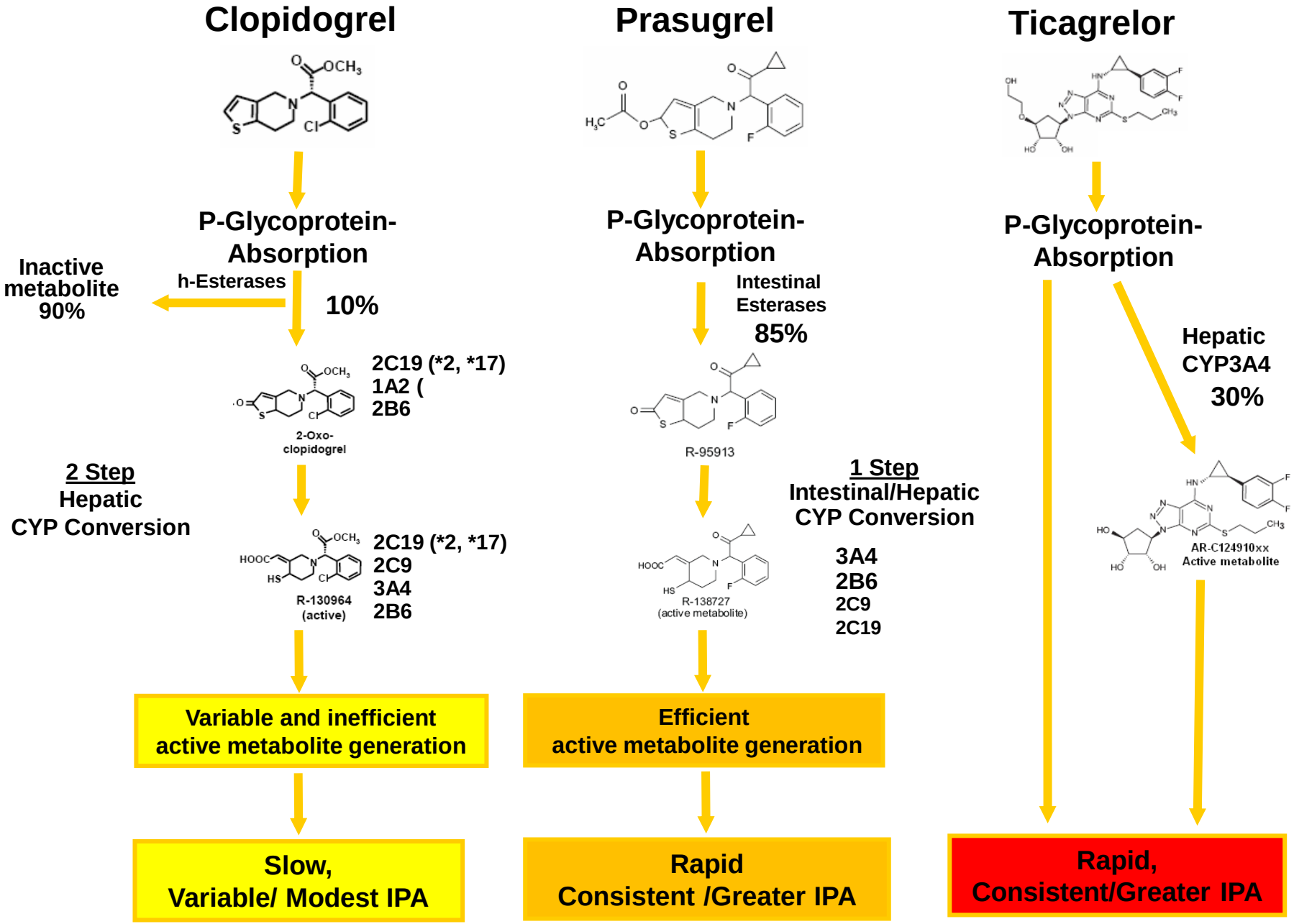
Pharmacologic properties of selected antiplatelet drugs

Drug	Binding	Activity	Route	Metabolism	Time to peak	Action offset
Clopidogrel	Irreversible	~30% ADP	Oral	Esterase inactivation & 2-step hepatic CYP-dependent activation	~4 hours	~5 days
Prasugrel	Irreversible	75%–80% ADP	Oral	Esterase activation & 1-step CYP-dependent activation (liver/gut)	1–2 hours	~5 days
Ticagrelor	Reversible	75%–80% ADP	Oral	None required	1–2 hours	1–2 days

ADP, adenosine diphosphate; CYP, cytochrome P450;

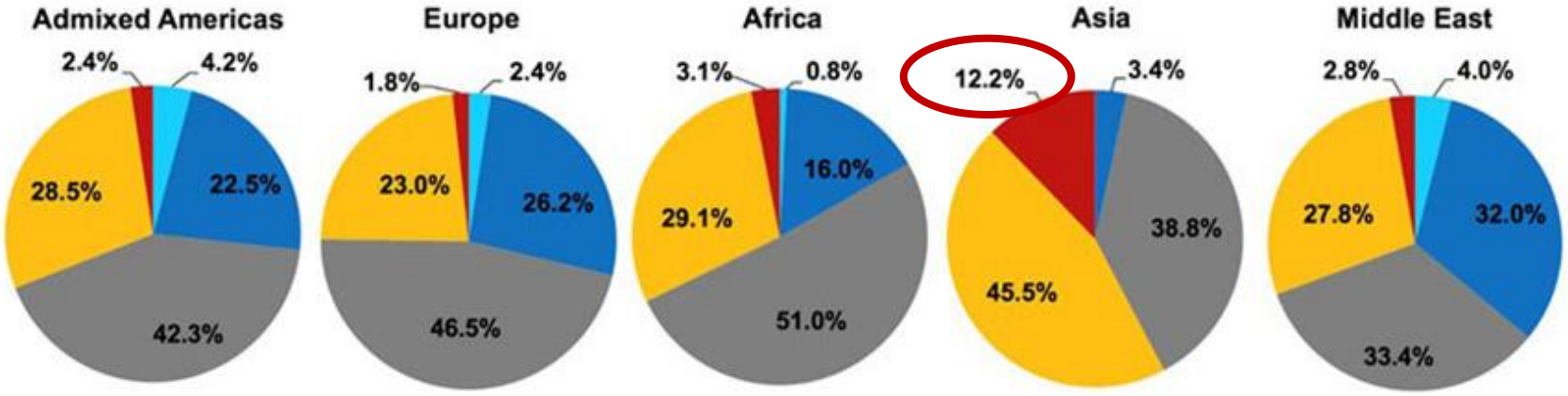
Vasc Health Risk Manag. 2010; 6: 419–429.

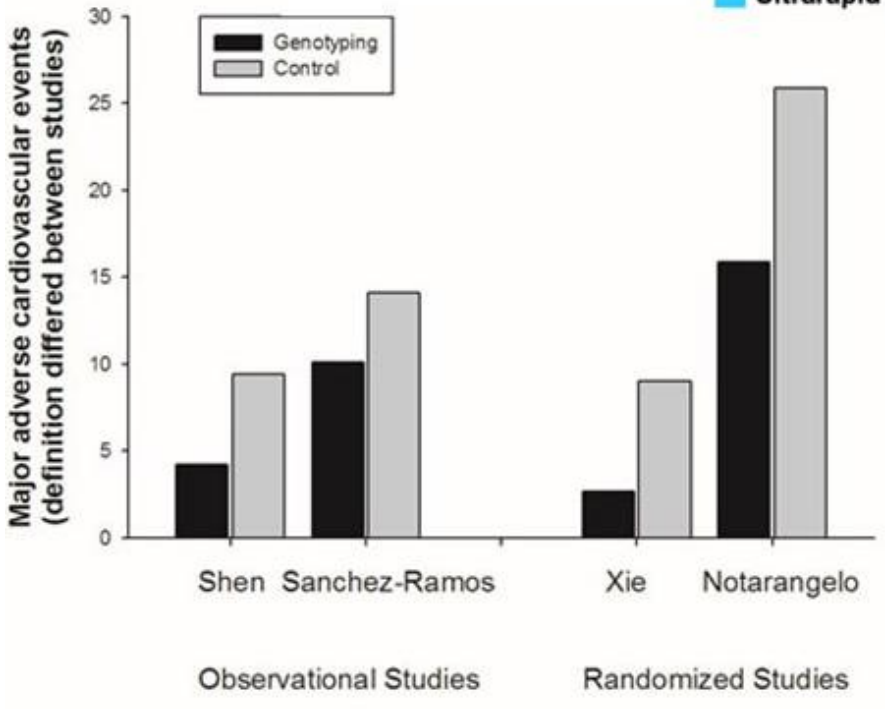
Metabolism of $P2Y_{12}$ Blockers



Farid NA, et al. J Clin Pharmacol. 2010;50:126-142; Bouman HJ, et al. Nat Med. 2011;17:110–116; Tantry US , Gurrbel PA, et al. Clin Inv. 2011;1:429–437.

Genotyping for clopidogrel responsiveness

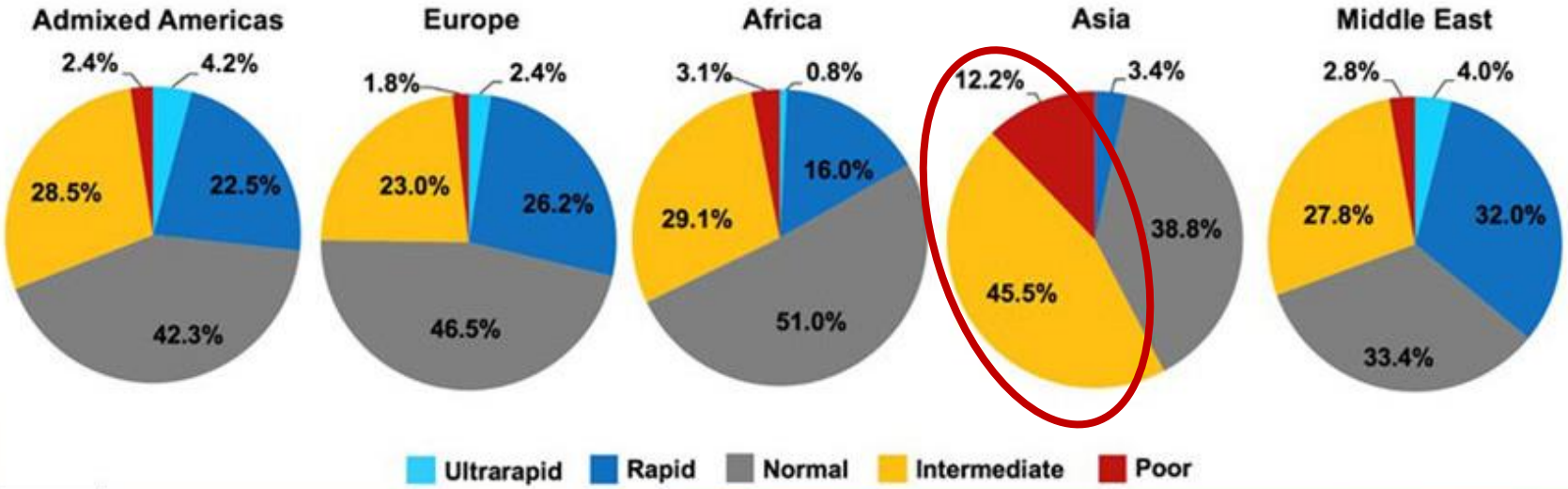


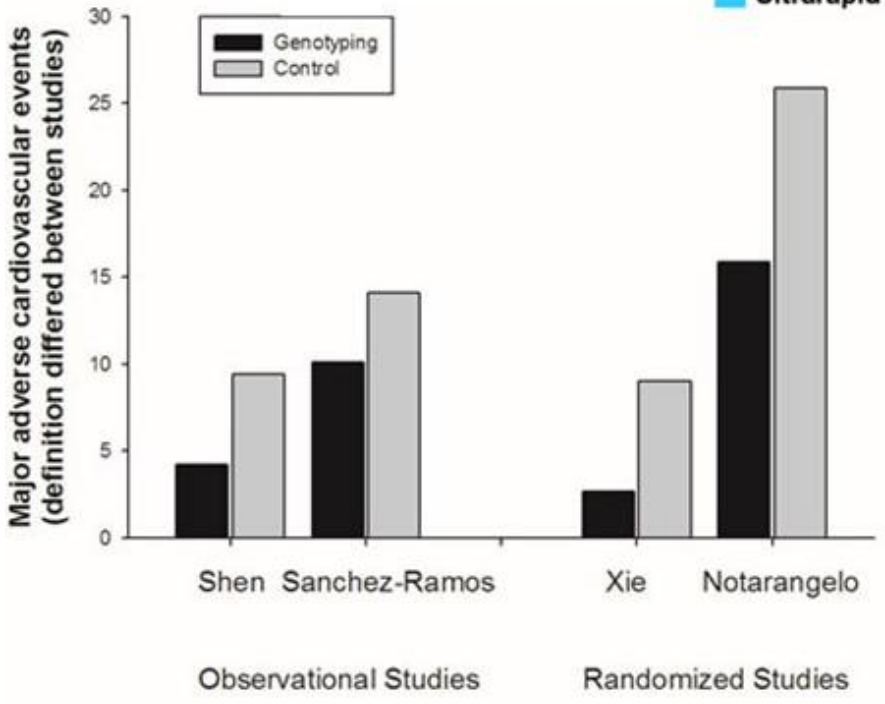


Metabolizer phenotype	Genotype	U.S. population	Response to clopidogrel
Ultra-rapid (UM)	2 increased function alleles (*17/*17)	1-5%	Normal or increased antiplatelet response to clopidogrel
Rapid (RM)	1 increased function and 1 normal function allele (*1/*17)	20-30%	Normal or increased antiplatelet response to clopidogrel
Normal (NM)	Absence of any tested increased function or LOF alleles (*1/*1)	35-50%	Normal antiplatelet response to clopidogrel
Intermediate (IM)	1 LOF allele (*1/*2, *1/3, *2/17, *3/*17)	20-30%	Reduced antiplatelet response to clopidogrel
Poor (PM)	2 LOF alleles (*2/*2, *2/3, *3/*3)	1-5%	Significantly reduced antiplatelet response to clopidogrel

Melissa D. Klein. Arteriosclerosis, Thrombosis, and Vascular Biology. Clinical Utility of CYP2C19 Genotyping to Guide Antiplatelet Therapy in Patients With an Acute Coronary Syndrome or Undergoing Percutaneous Coronary Intervention, Volume: 39, Issue: 4, Pages: 647-652,

Genotyping for clopidogrel responsiveness





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PLoS Genet. 2021 Feb; 17(2): e1009323.
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PMCID: PMC7891783
PMID: 33600428

Actionable pharmacogenetic variants in Hong Kong Chinese exome sequencing data and projected prescription impact in the Hong Kong population

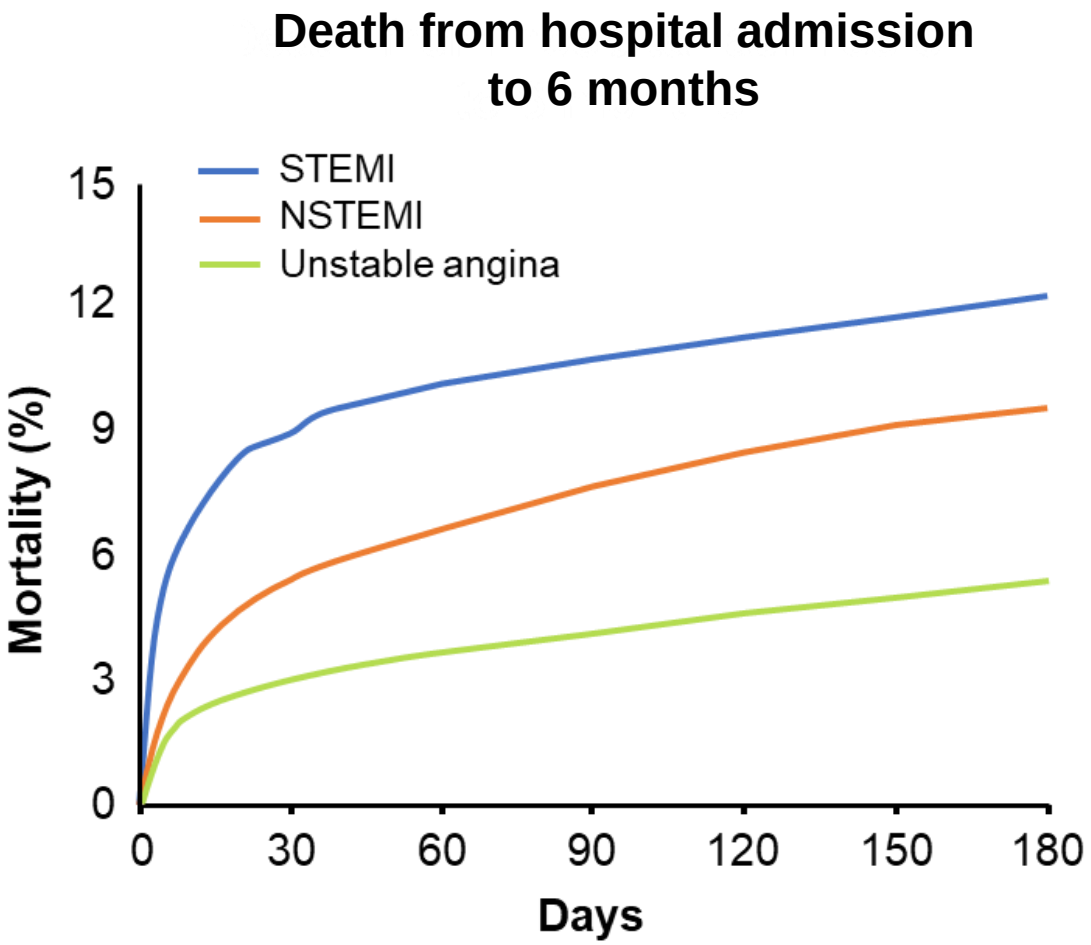
Table 1

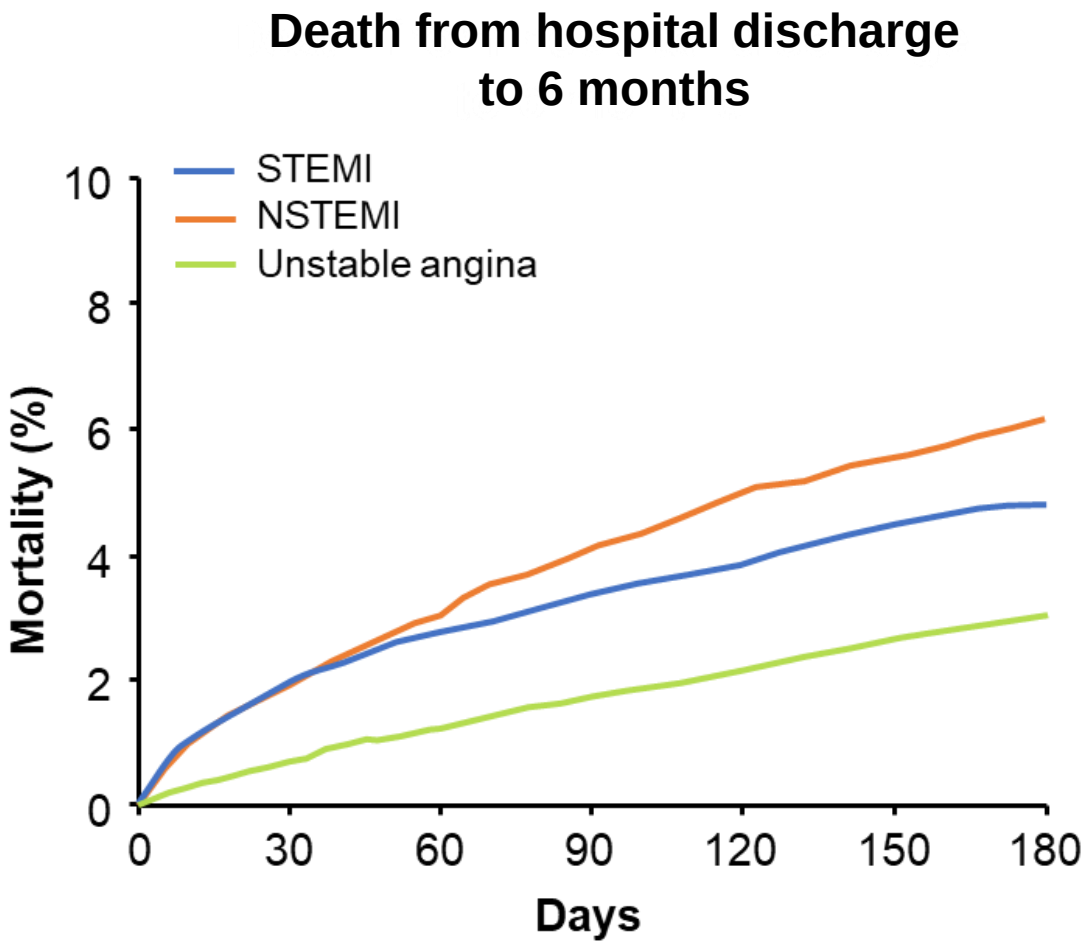
Frequency of actionable pharmacophenotypes in Hong Kong Chinese.

Gene	Allele	Actionable phenotype	Genotype definition	Frequency (%) by phenotype	Frequency (%) by gene
CYP2C19	No function: *2, *3, *6	Intermediate metabolizer	One normal function allele and one no function allele	45.25	57.21
		Poor metabolizer	Two no function alleles	11.96	

Six-month mortality rate following an ACS event is high

Global Registry of Acute Coronary Events, 43,810 patients with ACS, 1999–2005





Fox *et al. BMJ* 2006;333:1091.

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

6.1.Coronary artery disease

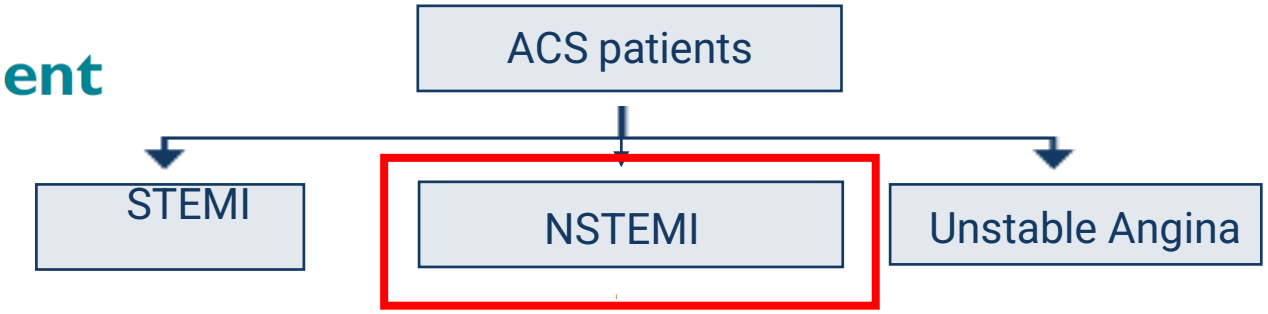
Disease-specific acute management of coronary syndromes is covered in detail in recent guidelines.[677–680]

As for antithrombotic therapy, dual antiplatelet therapy (DAPT) for 12 months, preferably with prasugrel or ticagrelor, is the standard antithrombotic treatment after ACS.[681–683] There are conflicting data as to whether prasugrel is preferable to ticagrelor.[684,685] A 6-month duration of DAPT after ACS is generally too short,[686] but may be considered in selected patients at high bleeding risk.

Recommendations	Class[a]	Level[b]
Aspirin 75 - 100 mg daily is recommended for patients with a previous myocardial infarction or revascularization.[619]	I	A
Aspirin 75 - 100 mg daily may be considered in patients without a history of myocardial infarction or revascularization, but with definitive evidence of CAD on imaging.[622]	IIb	C
In ACS, DAPT with a $P2Y_{12}$ inhibitor in addition to aspirin is recommended for 12 months, unless there are contraindications such as excessive risk of bleeding.[681–683]	I	A

European Heart Journal (2021) 00, 1111, ESC GUIDELINES, doi:10.1093/eurheartj/ehab484

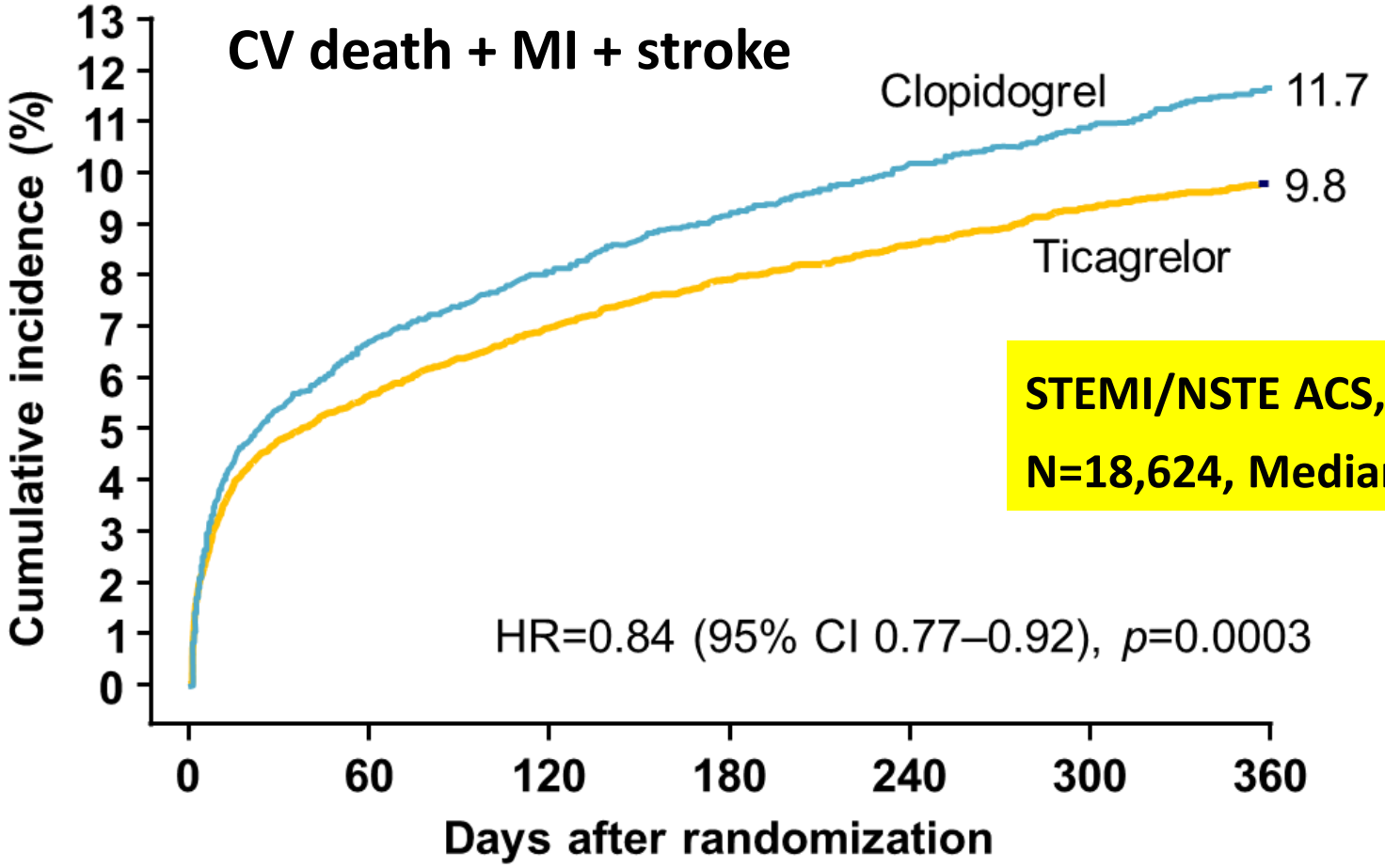
2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation



Recommendations	Class[a]	Level[b]
Antiplatelet treatment		
Aspirin is recommended for all patients without contraindications at an initial oral LD of 150–300 mg (or 75–250 mg i.v.), and at a MD of 75–100 mg o.d. for long-term treatment.[179–181]	I	A
A $P2Y_{12}$ receptor inhibitor is recommended in addition to aspirin, and maintained over 12 months unless there are contraindications or an excessive risk of bleeding.[170,171,182] Options are:	I	A
• Prasugrel in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI (60 mg LD, 10 mg/d as standard dose, 5 mg/d for patients aged ≥75 years or with a body weight <60 kg).[171]	I	B
• Ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d.).[170]	I	B
• Clopidogrel (300–600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.[182,183]	I	C

European Heart Journal 2021;42:2298.

PLATO Primary efficacy endpoint



STEMI/NSTE ACS, with and without PCI

N=18,624, Median duration of Rx 9 months

No at risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6743	5096	4047

Wallentin *et al, N Engl J Med* 2009

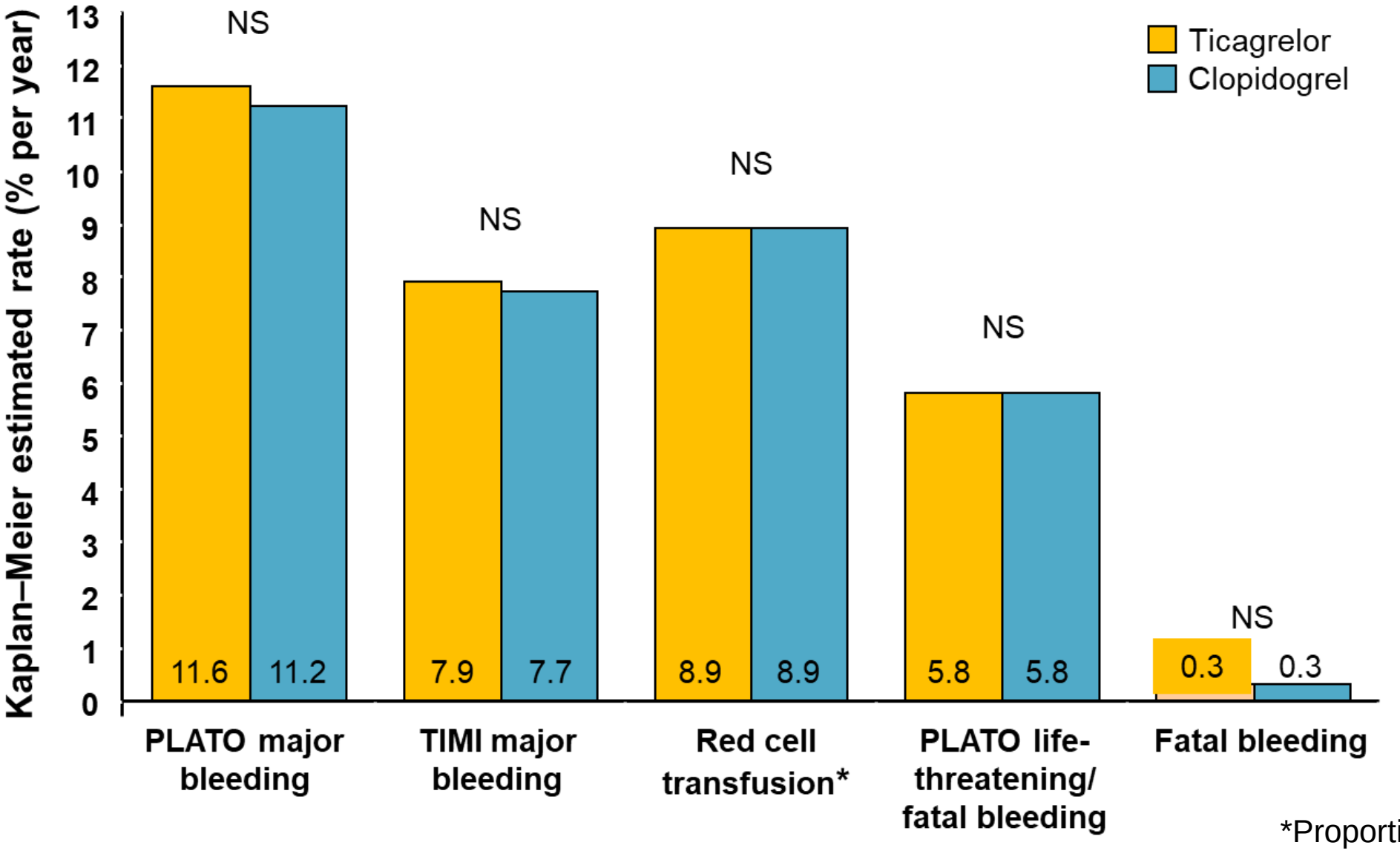
All-cause mortality data from key dual antiplatelet studies

Study	Study duration	Rate of all-cause mortality (%)		p-value
CURE[1]	12 months	ASA alone group = 6.2	Clopidogrel + ASA group = 5.7	NA
TRITON TIMI-38[2]	15 months	Clopidogrel + ASA group = 3.2	Prasugrel + ASA group = 3.0	0.64
PLATO[3]	12 months	Clopidogrel + ASA group = 5.9	Ticagrelor + ASA group = 4.5	<0.001

NA, not available

1. Yusuf *et al. N Engl J Med* 2001;345:494–502; 2. Wiviott *et al. N Engl J Med* 2007;357:2001–15;
3. Wallentin *et al. N Engl J Med* 2009;361:1045–57.

PLATO Primary and other safety endpoints



*Proportion of patients (%)

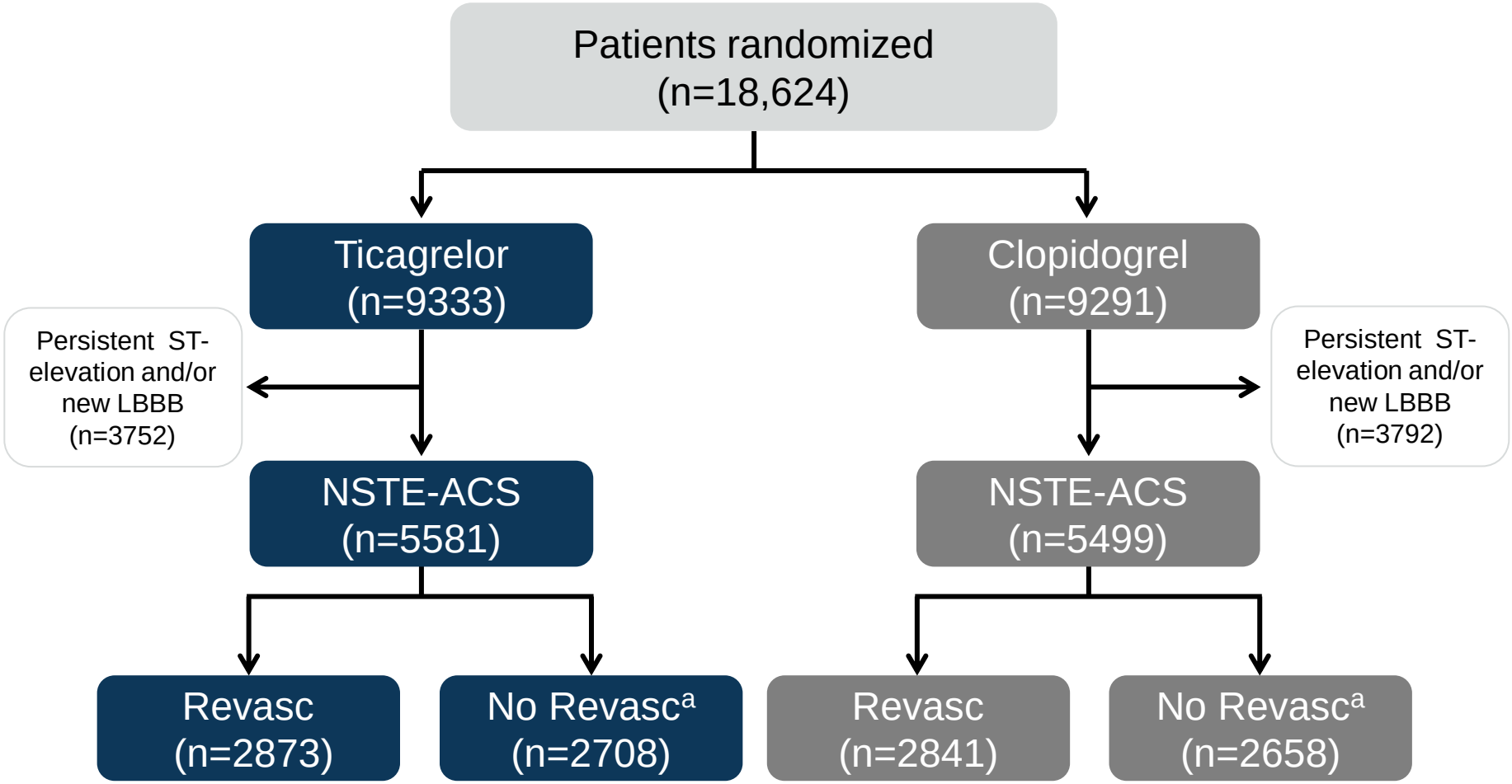
Wallentin *et al, N Engl J Med* 2009

PLATO Subgroup Analyses Primary Efficacy Endpoint by Subgroup

Subgroup	Total Patients	K-M% at Month 12 Tic	K-M% at Month 12 Clop	HR (95% CI)	p-value (interaction)
Overall Treatment Effect	18,624	9.8	11.7	0.84 (0.77, 0.92)	
Region					0.05
Asia/Australia	1714	11.4	14.8	0.80 (0.65, 1.04)	
Central/South America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Europe/Middle East/Africa	13,859	8.8	11.0	0.80 (0.72, 0.90)	
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	
Antiplatelet Therapy Prior to Index Event					0.43
Clopidogrel ± ASA	1397	15.8	17.8	0.95 (0.73, 1.24)	
ASA	5024	11.8	14.0	0.84 (0.71, 0.98)	
None	12,147	8.2	10.0	0.82 (0.73, 0.93)	
ASA on Day of Randomization					0.86
No	927	11.6	13.8	0.87 (0.60, 1.27)	
Yes	17,697	9.7	11.6	0.84 (0.77, 0.93)	
GPIIb/IIIa (IE to End of Index Hosp.)					0.41
No	13,562	9.7	11.9	0.82 (0.74, 0.92)	
Yes	5062	10.0	11.1	0.90 (0.76, 1.07)	
Final Diagnosis					0.41
Unstable angina	3112	8.6	9.1	0.96 (0.75, 1.22)	
NSTEMI	7955	11.4	13.9	0.83 (0.73, 0.94)	
STEMI	7026	8.5	10.1	0.84 (0.72, 0.98)	
Other	489	9.1	14.7	0.58 (0.34, 1.00)	

Wallentin L et al. Supplementary appendix. *N Engl J Med*. 2009;361:1045-1057.

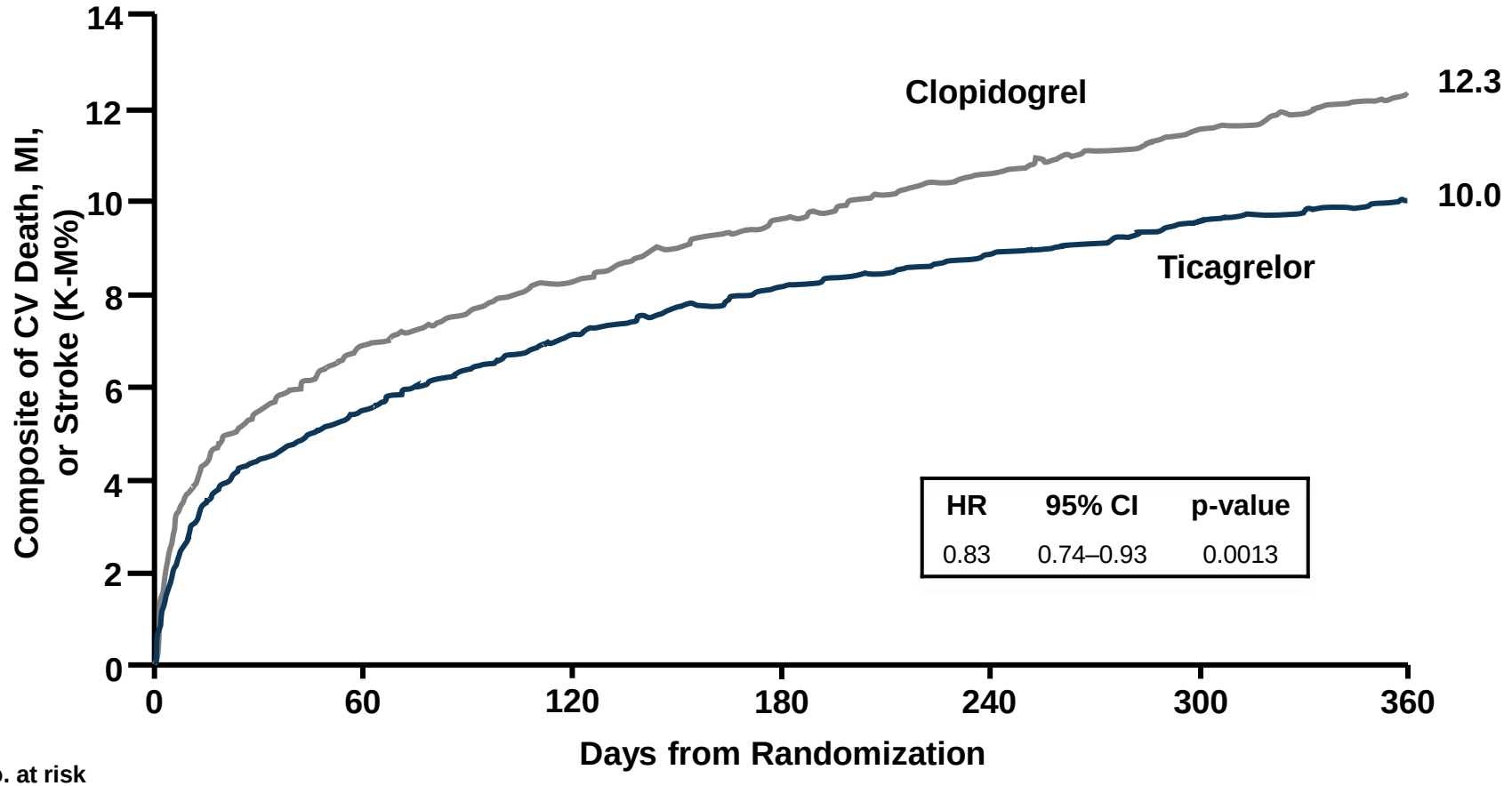
PLATO NSTE-ACS Subgroup Analysis Patient Disposition



[a]No revascularization within first 10 days after randomization.

Lindholm D et al. *Eur Heart J*. 2014;35:2083-2093.

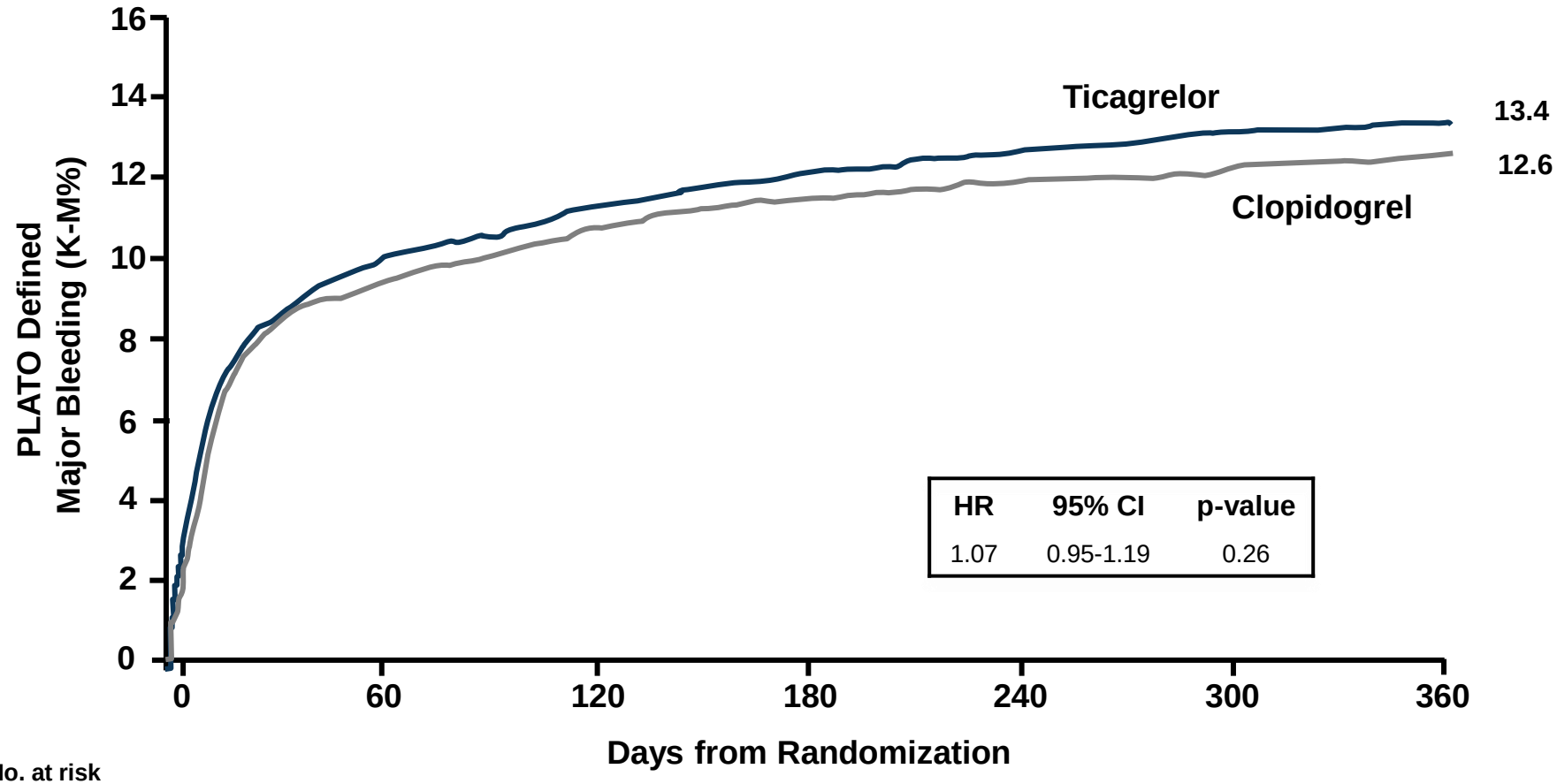
PLATO NSTE-ACS Subgroup Analysis Primary Efficacy Endpoint



No. at risk							
Clopidogrel	5499	5019	4924	4768	3924	2999	2395
Ticagrelor	5581	5152	5036	4888	4056	3112	2471

Lindholm D et al. *Eur Heart J*. 2014;35:2083-2093.

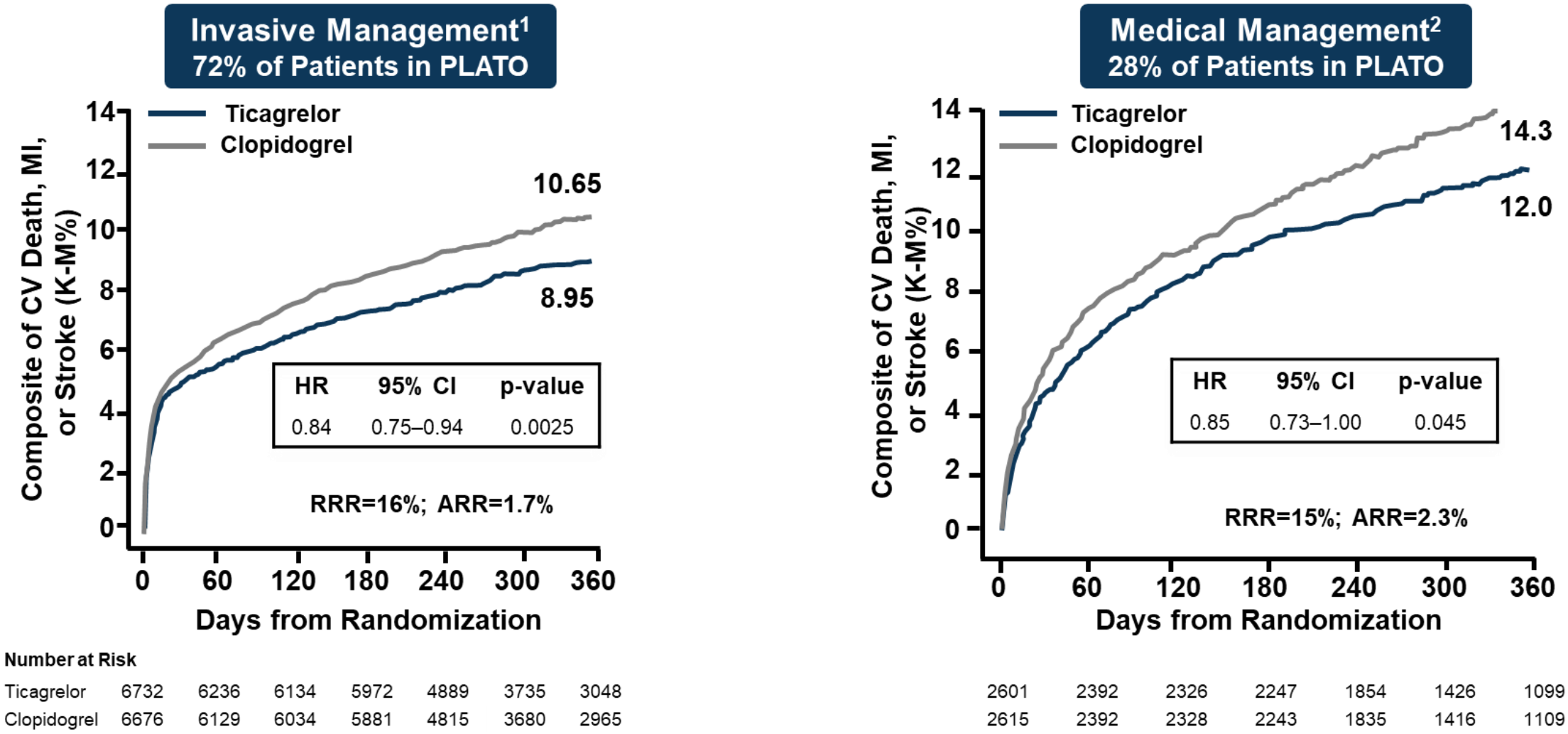
PLATO NSTE-ACS Subgroup Analysis Primary Safety Endpoint



No. at risk							
Clopidogrel	5434	4211	3956	3811	3006	2212	2000
Ticagrelor	5516	4166	3904	3725	2943	2183	1965

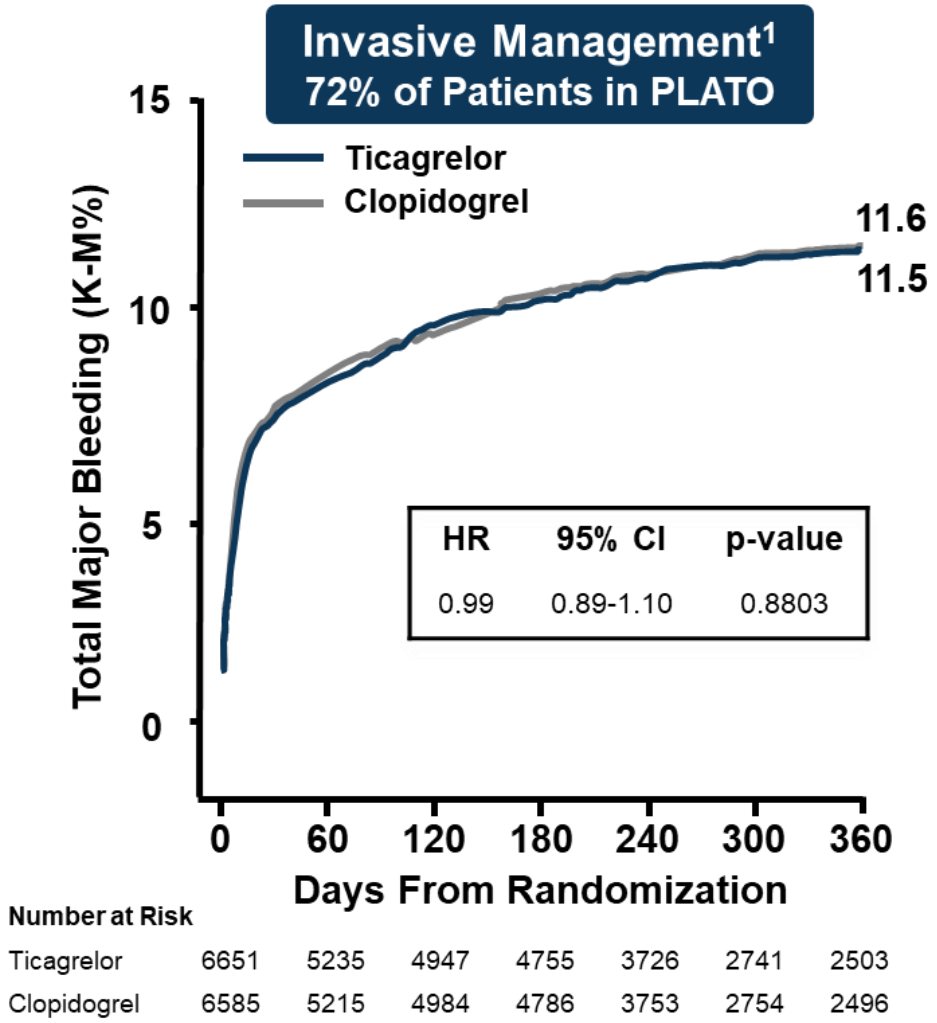
Lindholm D et al. Article and online supplementary data. *Eur Heart J*. 2014;35:2083-2093.

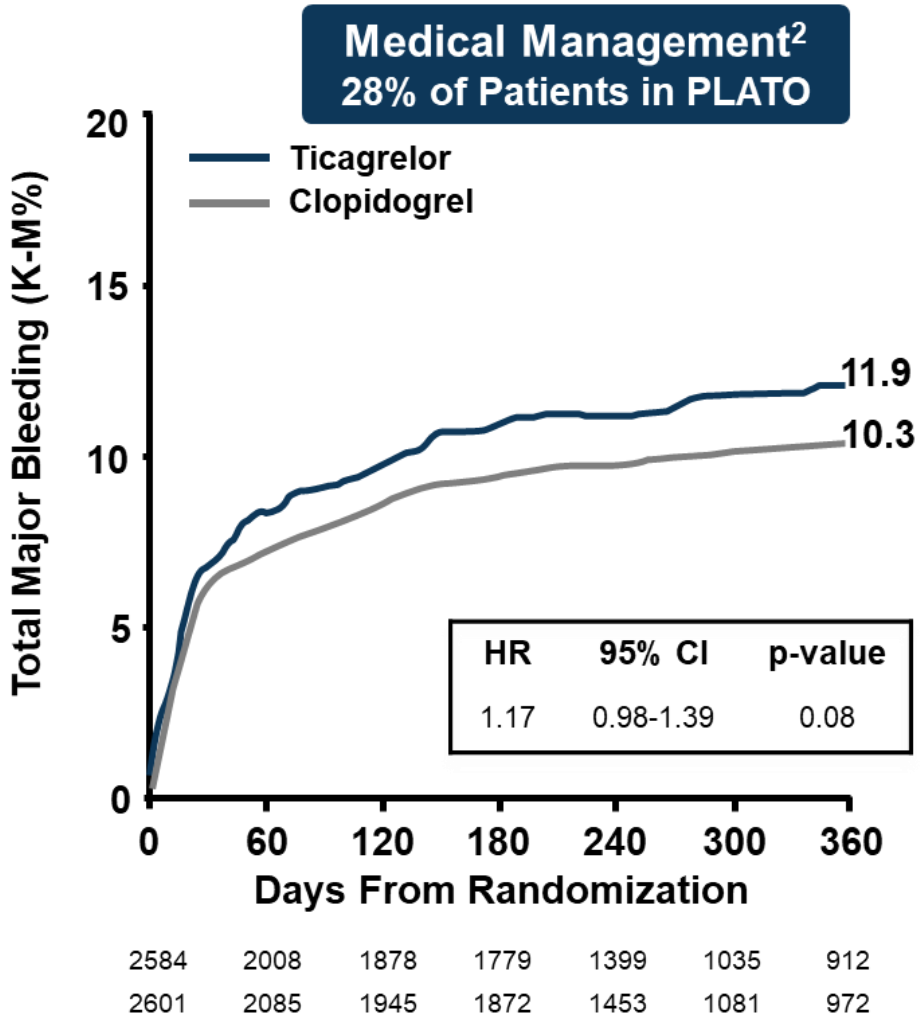
PLATO Planned Treatment Approach Subgroup Analysis Primary Efficacy Endpoint



1. Cannon CP et al. *Lancet*. 2010;375:283-293; 2. James SK et al. *BMJ.* 2011. http://dx.doi.org/10.1136/bmj.d3527.

PLATO Planned Treatment Approach Subgroup Analysis Primary Safety Endpoint



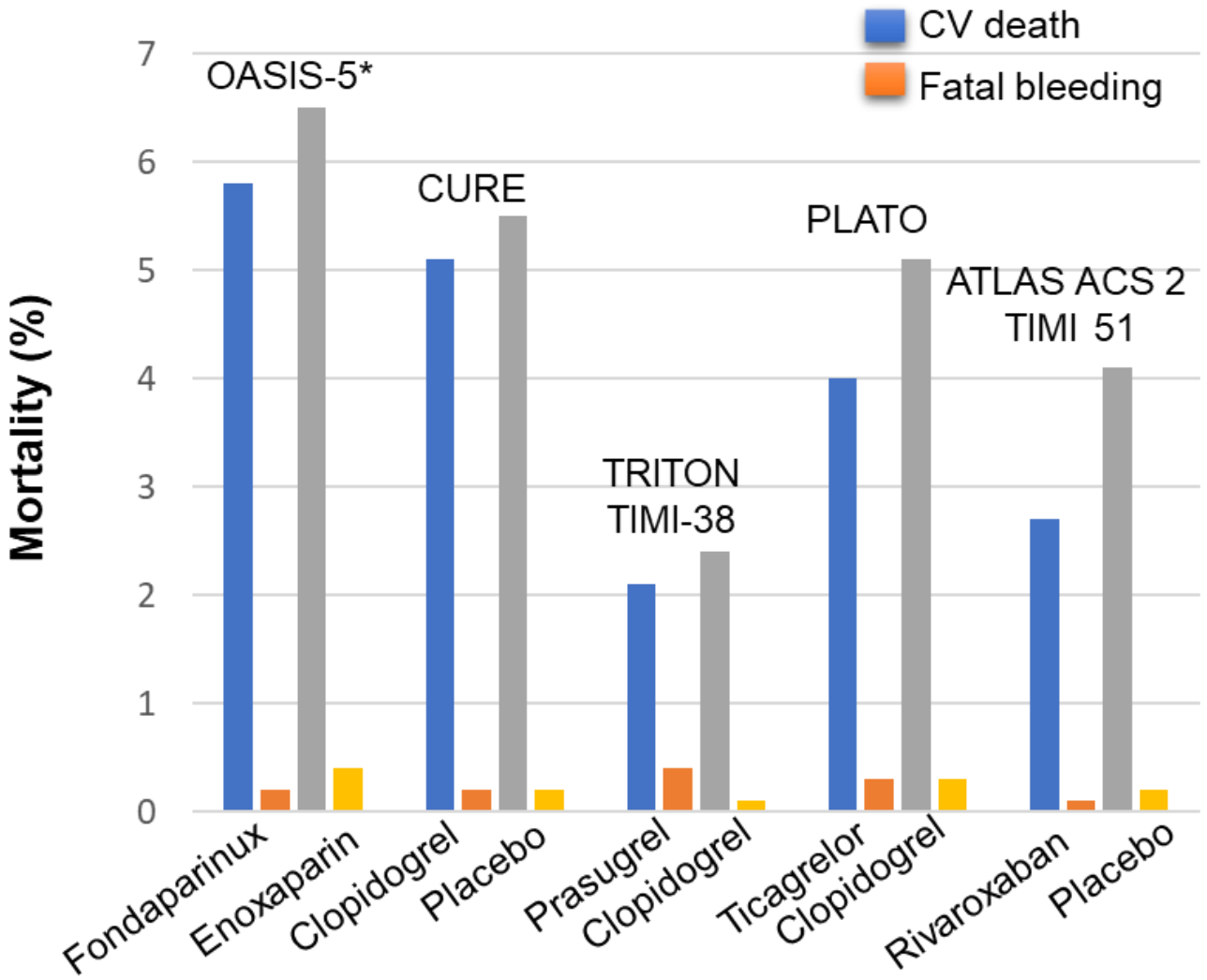


1. Cannon CP et al. *Lancet*. 2010;375:283-293; 2. James SK et al. *BMJ.* 2011. http://dx.doi.org/10.1136/bmj.d3527.

Ischaemic events result in more deaths than major bleeding

RCTs of long-term antithrombotic therapy in patients with ACS

Study	Patient type	Max. duration of follow-up
OASIS-5[1–3]	NSTE-ACS	6 months
CURE[4]	NSTE-ACS	12 months
TRITON TIMI-38[5]	All ACS types	15 months
PLATO[6]	All ACS types	12 months
ATLAS ACS 2 TIMI 51[7]	All ACS types	31 months



*Unclear if 'death' is defined as cardiovascular only or all-cause.

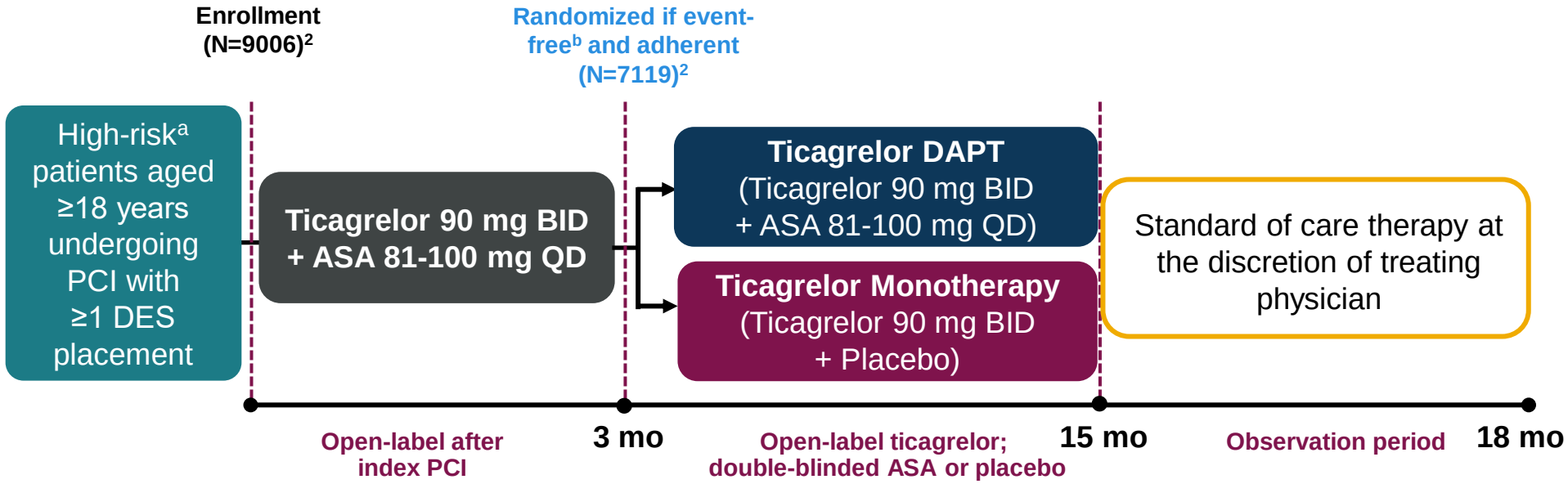
1. MICHELANGELO OASIS-5 Steering Committee. *Am Heart J* 2005; 2. Yusuf *et al. N Engl J Med* 2006; 3. Budaj *et al. Eur Heart J* 2009; 4. Yusuf *et al. N Engl J Med* 2001; 5. Wiviott *et al. N Engl J Med* 2007; 6. Wallentin *et al. N Engl J Med* 2009; 7. Mega *et al. N Engl J Med* 2012.

Bleeding and Long-term Secondary Prevention of ACS

- All antithrombotic therapies carry a risk of bleeding – this is also true in the ACS setting
  - Major bleeding is a concern for clinicians[1]
- Major bleeding is also linked to increased long-term mortality, although how the two factors are linked is unclear[2,3]
- However, bleeding in patients with ACS is generally a manageable problem
  - Bleeding is far outweighed by infarction as a cause of death[4–9]

1. Gibson. *J Interv Cardiol* 2008; 2. Mehran and Stone. *Eur Heart J Suppl* 2009; 3. Mehran *et al. Eur Heart J* 2009;
4. Yusuf *et al. N Engl J Med* 2006; 5. Budaj *et al. Eur Heart J* 2009; 6. Yusuf *et al. N Engl J Med* 2001;
7. Wiviott *et al. N Engl J Med* 2007; 8. Wallentin *et al. N Engl J Med* 2009; 9. Mega *et al. N Engl J Med* 2012.

TWILIGHT Study Design Overview[1]



Primary composite endpoint (ITT): Clinically relevant (BARC type 2, 3, or 5) bleeding during months 3-15

Key secondary endpoint (per protocol): Composite of all-cause death, non-fatal MI, stroke during months 3-15[c]

[a]**High-risk patients must meet ≥1 criteria from both clinical and angiographic criteria (Inclusion criteria):**

- **Clinical:** ≥65 years of age, female, troponin positive ACS, established vascular disease (previous MI, documented PAD or CAD/PAD revascularization), DM treated with medications, CKD (eGFR <60 mL/min/1.73 m^2 or CrCl <60 mLmin)
- **Angiographic:** multivessel CAD, target lesion total stent length >30 mm, thrombotic target lesion, bifurcation lesions with Medina X, 1, 1 classification requiring ≥2 stents, left main ≥50% or proximal LAD ≥70% lesion, calcified target lesion requiring atherectomy

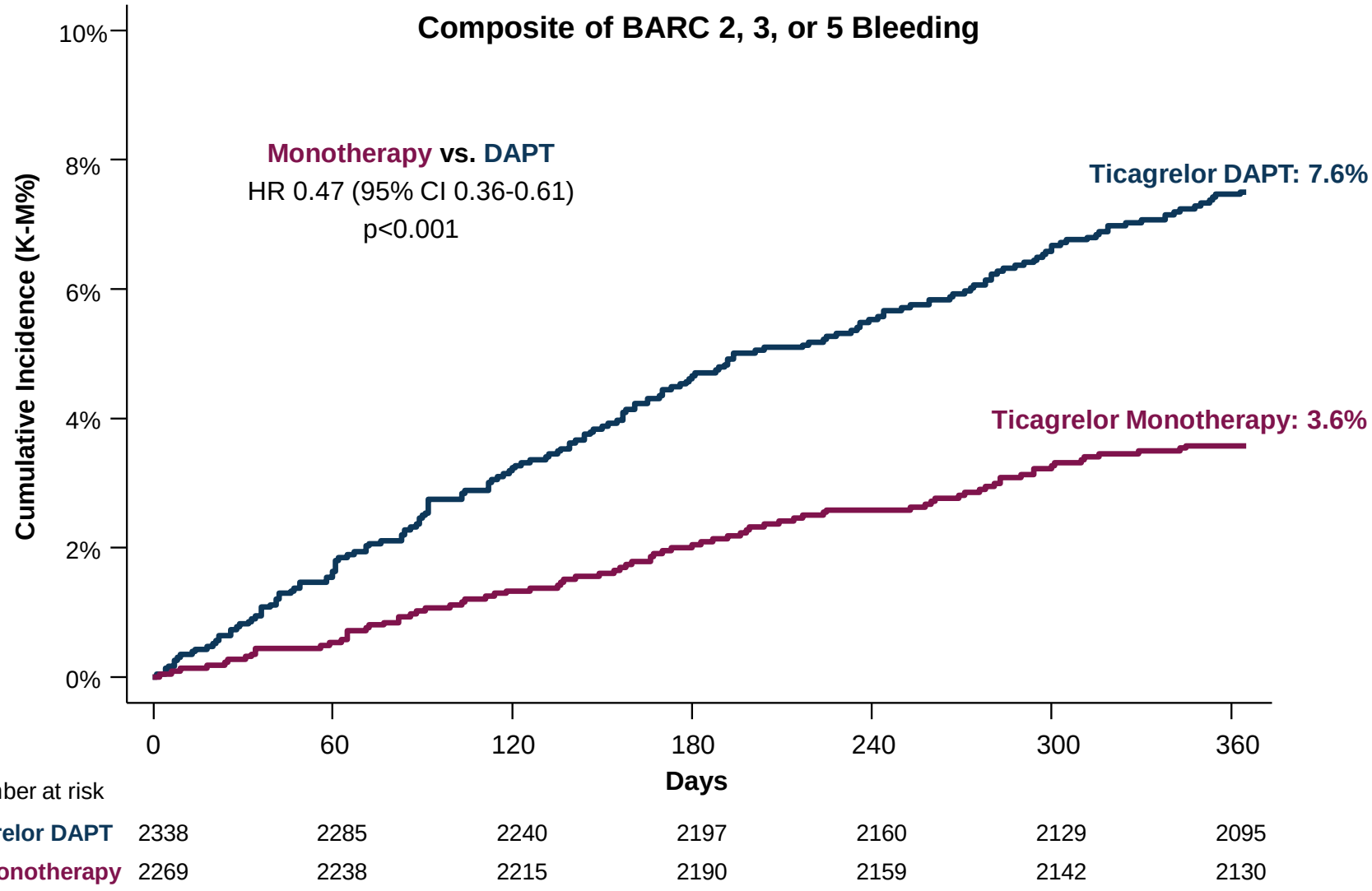
[b]**Event-free if none of the following:**

- Major bleeding (≥BARC type 3b); ischemic event after PCI (eg, non-fatal MI, definite or probable stent thrombosis, ischemic stroke, coronary revascularization with DES); no longer taking DAPT with ticagrelor + ASA; non physician-guided cessation of ASA or ticagrelor of ≥5 consecutive days; current indication for oral anticoagulation or high dose ASA; renal failure requiring dialysis; woman of child bearing potential; refusal of randomization by patient or treating physician; withdrawal of consent; lost to follow-up

[c]Other secondary ischemic endpoints included time to first occurrence of: (i) CV death, non-fatal MI, ischemic stroke or clinically-driven revascularization; (ii) CV death, non-fatal MI or ischemic stroke; (iii) definite or probable stent thrombosis; (iv) CV death.

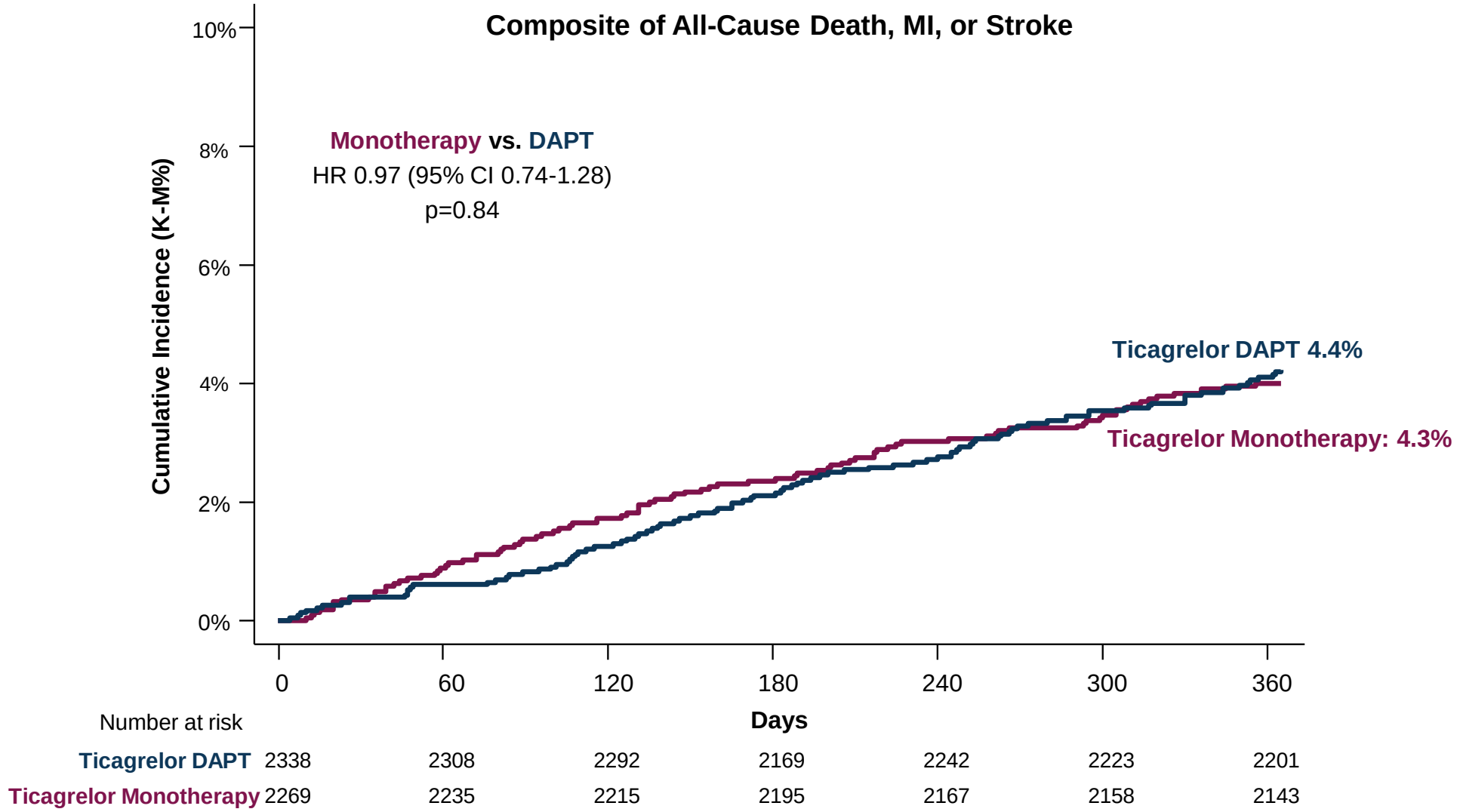
1. Baber U et al. *Am Heart J.* 2016;182:125-134; 2. Mehran R et al. *N Engl J Med*. 2019; 381:2032-2042.

TWILIGHT-ACS Primary Endpoint BARC 2, 3, or 5 Bleeding



Baber U et al. *Am Heart J.* 2016;182:125-134.

TWILIGHT-ACS Secondary Endpoint All-cause Death, MI, or Stroke



Baber U et al. *Am Heart J.* 2016;182:125-134.

ESC 2019 *Chronic Coronary Syndrome* Guideline

Table 9 Treatment options for dual antithrombotic therapy in combination with aspirin 75 – 100 mg daily in patients who have a high[a] or moderate[b] risk of ischaemic events, and do not have a high bleeding risk[c]

Drug option	Dose	Indication	Additional cautions	References
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year		289,290
Prasugrel	10 mg o.d or 5 mg o.d.; if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years	289,290,313
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min	297
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year		291–293,307,314

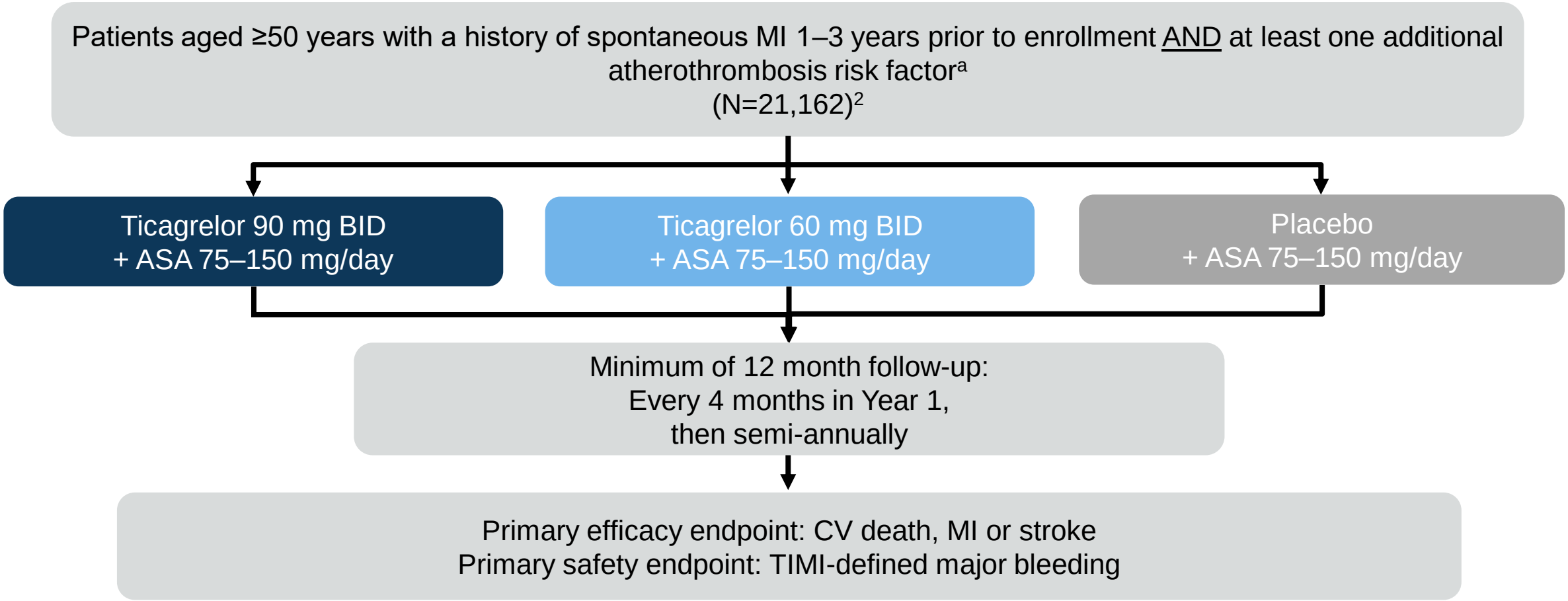
Treatment options are presented in alphabetical order.
b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; o.d. = omni die (once a day); PAD = peripheral artery disease; PCI = percutaneous coronary intervention.
[a]High risk of ischaemic events is defined as diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15 - 59 mL/min/1.73 m^2.
[b]Moderately increased risk of ischaemic events is defined as at least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15 - 59 mL/min/1.73 m^2.
[c]High bleeding risk is defined as history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.

ESC NSTEMI 2020 Guideline – Thrombotic Risk

Table 11 **Risk criteria for extended treatment with a second antithrombotic agent**

High thrombotic risk (Class IIa)	Moderate thrombotic risk (Class IIb)
Complex CAD and at least 1 criterion	**Non-complex CAD and at least 1 criterion**
Risk enhancers	
Diabetes mellitus requiring medication	Diabetes mellitus requiring medication
History of recurrent MI	History of recurrent MI
Any multivessel CAD	Polyvascular disease (CAD plus PAD)
Polyvascular disease (CAD plus PAD)	CKD with eGFR 15–59 mL/min/1.73 m^2
Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD	
Concomitant systemic inflammatory disease (e.g. human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis)	
CKD with eGFR 15–59 mL/min/1.73 m^2	
Technical aspects	
At least 3 stents implanted	
At least 3 lesions treated	
Total stent length >60 mm	
History of complex revascularization (left main, bifurcation stenting with ≥2 stents implanted, chronic total occlusion, stenting of last patent vessel)	
History of stent thrombosis on antiplatelet treatment	

PEGASUS-TIMI 54 Study Design[1]



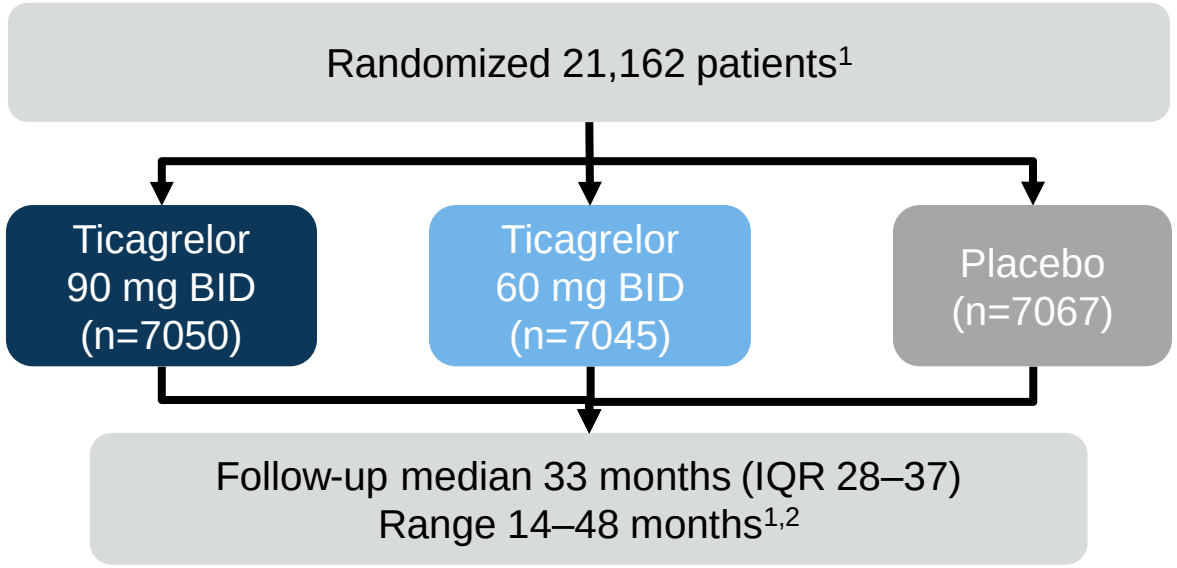
1. Bonaca MP et al. *Am Heart J.* 2014;167:437–444; 2. Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

PEGASUS-TIMI 54 Inclusion Criteria[1,2]

- Age ≥50 years old
- History of a spontaneous MI 1–3 years prior to enrollment and one additional high-risk feature
  - Age ≥65 years old
  - Diabetes mellitus requiring medication
  - Second prior spontaneous MI
  - Angiographic evidence of multivessel CAD
  - Chronic, non-end stage renal dysfunction (CrCl <60 mL/min)
- Prescribed and tolerating ASA at the time of enrollment

1. Bonaca MP et al. *Am Heart J.* 2014;167:437–444; 2. Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

PEGASUS-TIMI 54 Follow Up



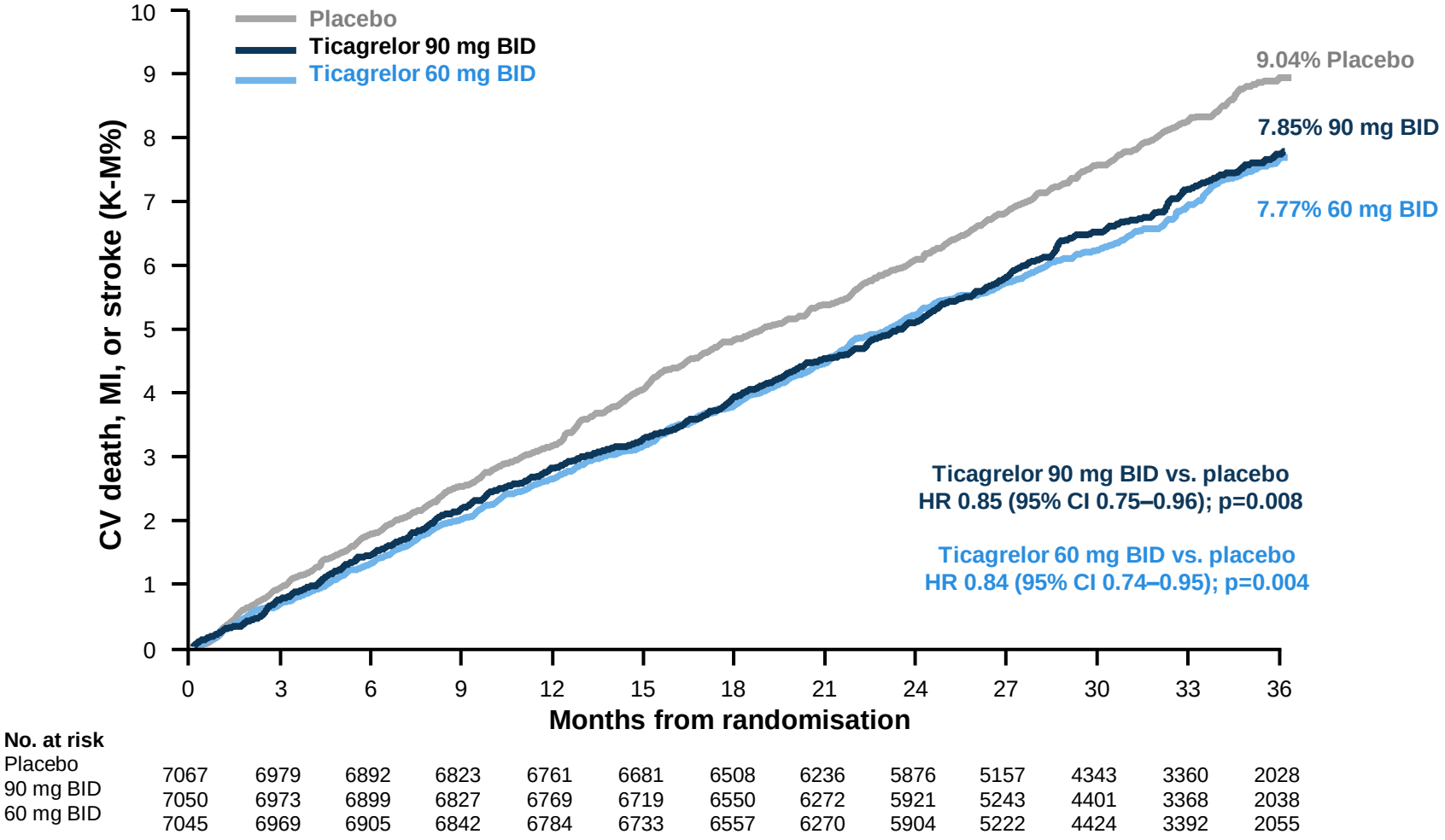
53.6% of the qualifying events were STEMIs

Premature permanent drug discontinuation[1]	n=2233 (32%)	n=1999 (29%)	n=1496 (21%)
Withdrew consent[1]	n=52 (0.7%)	n=50 (0.7%)	n=52 (0.7%)
Lost to follow-up[1]	n=3 (<0.1%)	n=6 (<0.1%)	n=1 (<0.1%)

Ascertainment for primary endpoint was complete for 99.2% of potential patient–years of follow-up.

1. Bonaca MP et al. *Am Heart J.* 2014;167:437–444; 2. Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

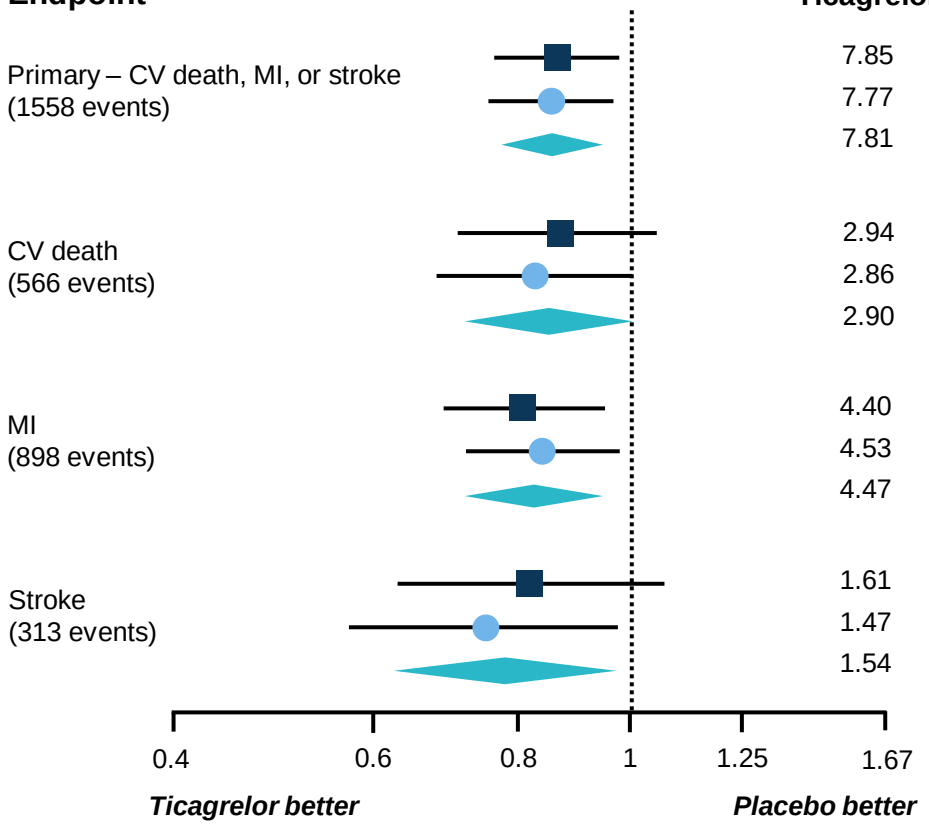
PEGASUS-TIMI 54 Primary Endpoint



Note: p<0.026 indicates statistical significance.

Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

PEGASUS-TIMI 54 Efficacy endpoints



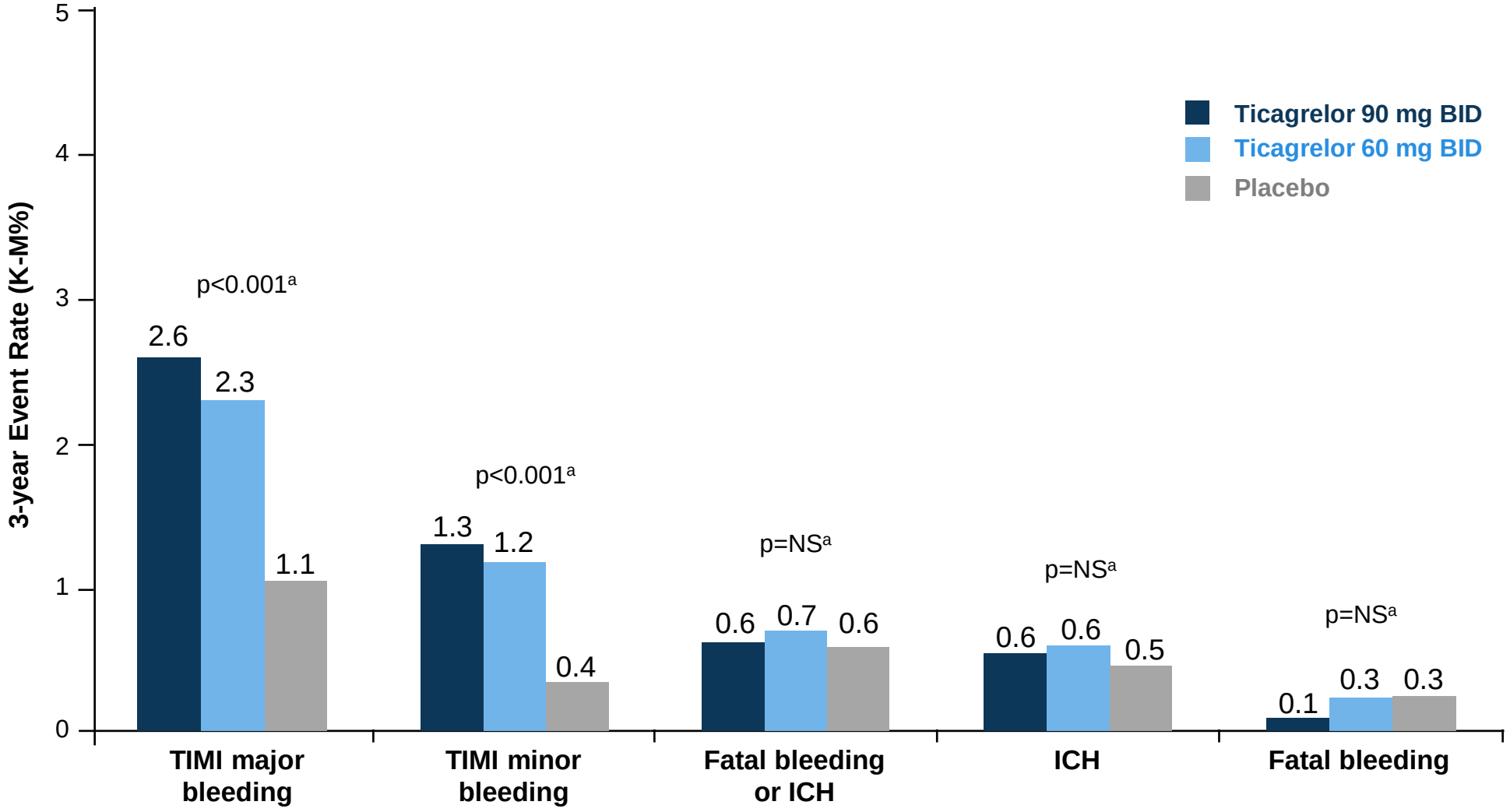
Endpoint	3-year K-M (%) Ticagrelor	Placebo	HR (95% CI)	p-value
Primary – CV death, MI, or stroke (1558 events)	7.85	9.04	0.85 (0.75–0.96)	0.008
	7.77	9.04	0.84 (0.74–0.95)	0.004
	7.81	9.04	0.84 (0.76–0.94)	0.001
CV death (566 events)	2.94	3.39	0.87 (0.71–1.06)	0.15
	2.86	3.39	0.83 (0.68–1.01)	0.07
	2.90	3.39	0.85 (0.71–1.00)	0.06
MI (898 events)	4.40	5.25	0.81 (0.69–0.95)	0.01[a]
	4.53	5.25	0.84 (0.72–0.98)	0.03[a]
	4.47	5.25	0.83 (0.72–0.95)	0.005[a]
Stroke (313 events)	1.61	1.94	0.82 (0.63–1.07)	0.14
	1.47	1.94	0.75 (0.57–0.98)	0.03[a]
	1.54	1.94	0.78 (0.62–0.98)	0.03[a]

Ticagrelor 90 mg BID
Ticagrelor 60 mg BID
Ticagrelor pooled

[a]Pre-specified exploratory endpoint with nominal statistical significance.

Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

PEGASUS-TIMI 54 Bleeding

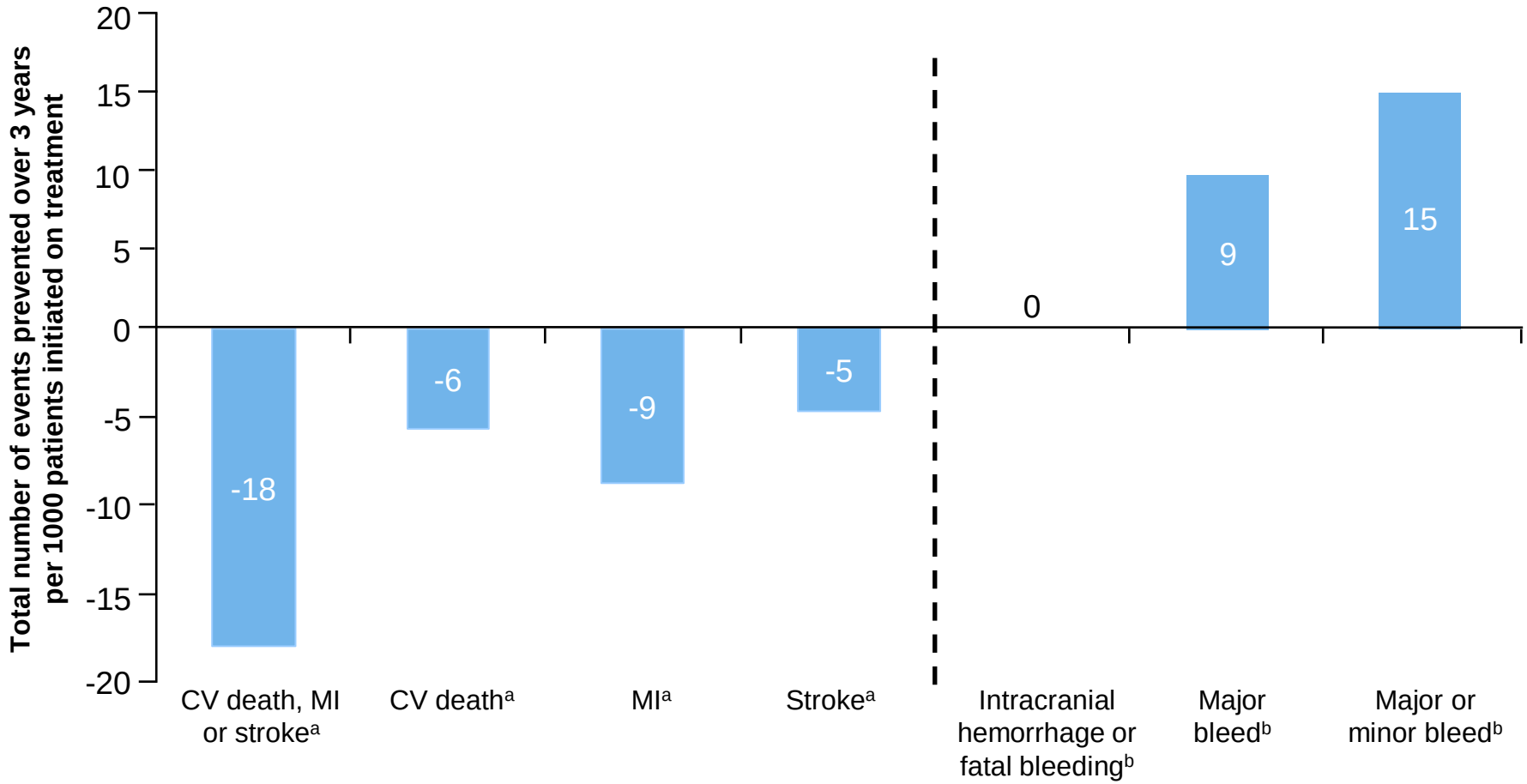


[a]p-values are for comparisons of each dose vs. placebo.

Bonaca MP et al. *N Engl J Med.* 2015;372:1791–1800.

PEGASUS-TIMI 54 Total Events Prevented and Caused per 1000 patients over 3 years based on ITT population for efficacy and OT population for safety

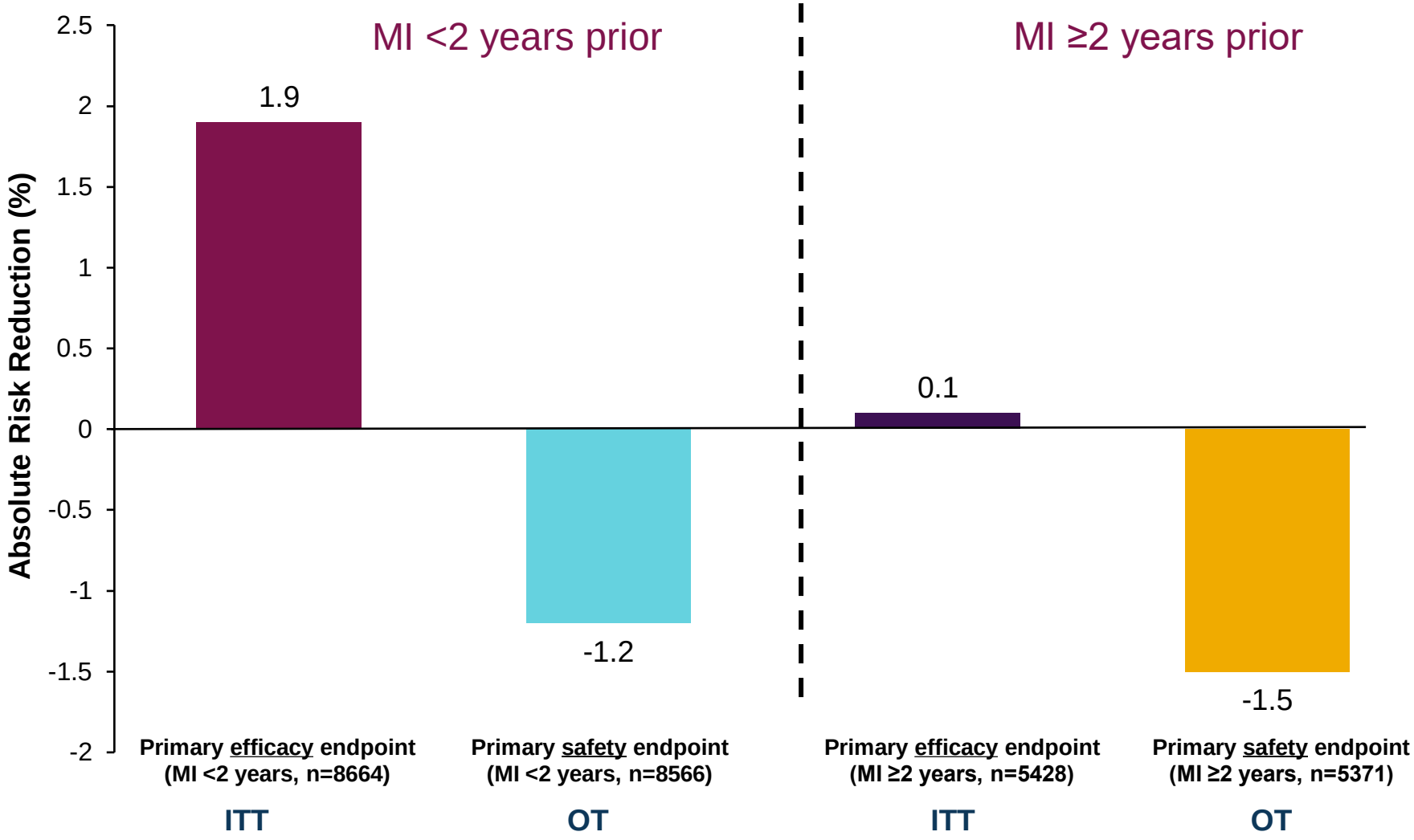
Events prevented and caused for 1000 patients initiated on ticagrelor 60 mg BID and followed for 3 years



[a]Events from ITT population; [b]Events from OT population.

Bonaca MP et al. *J Am Coll Cardiol.* 2017;70:1368-1375.

PEGASUS-TIMI 54 Effect of Ticagrelor 60 mg BID on Primary Efficacy and Safety Endpoints at 3 Years by Time from MI



In House Data, AstraZeneca Pharmaceuticals LP. DoF 3541.

PEGASUS-TIMI 54 *Post hoc* Analysis Patient Selection Algorithm

Patient selection algorithm

Step 1
Assess bleeding risk and exclude patients at high risk

Low haemoglobin or prior hospitalisation for bleeding

Step 2
Assess number of ischaemic risk factors

Recent $P2Y_{12}$ inhibitor (<1yr) or recent MI (<2 yrs)

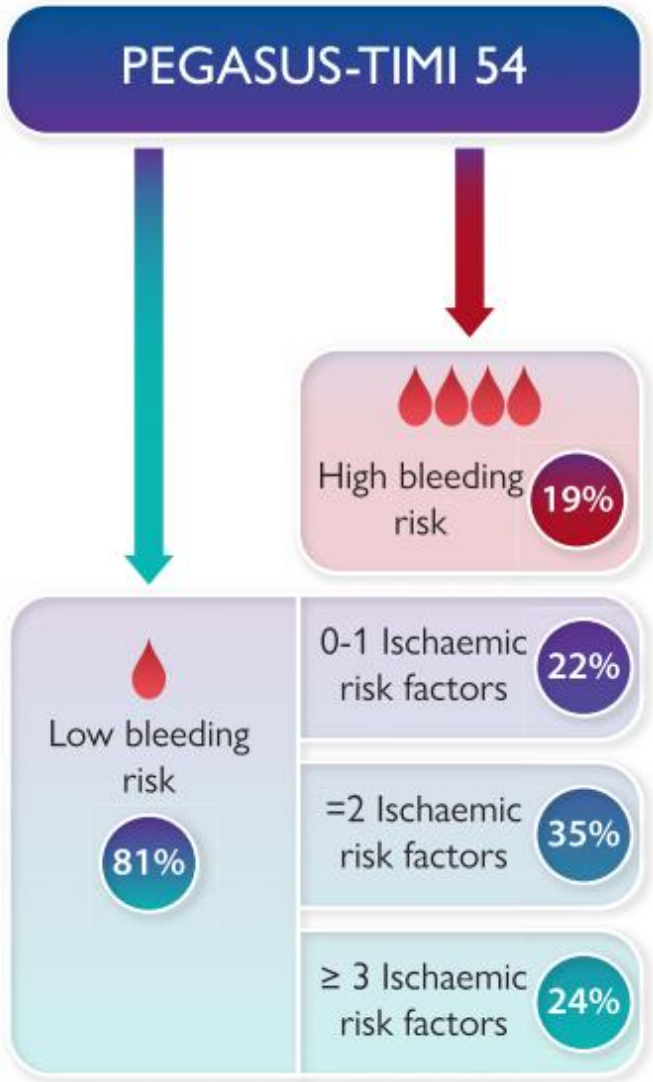
Multivessel CAD

Diabetes mellitus

Peripheral artery disease

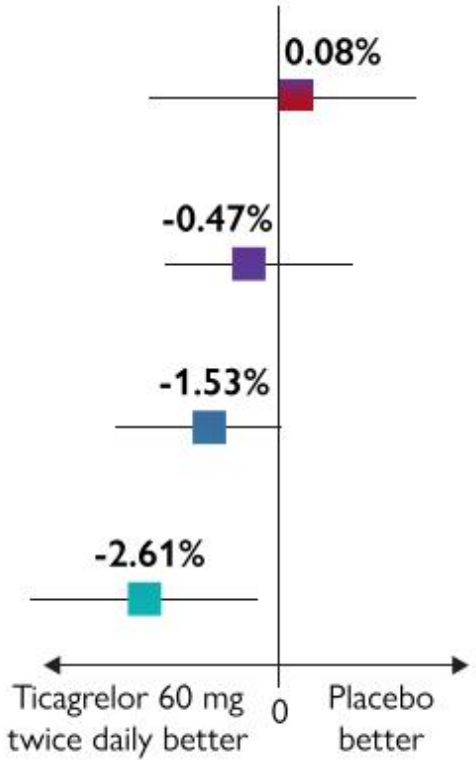
Chronic kidney disease

Multiple prior MIs



Absolute risk difference in CV death, MI or stroke with Ticagrelor vs Placebo by risk group

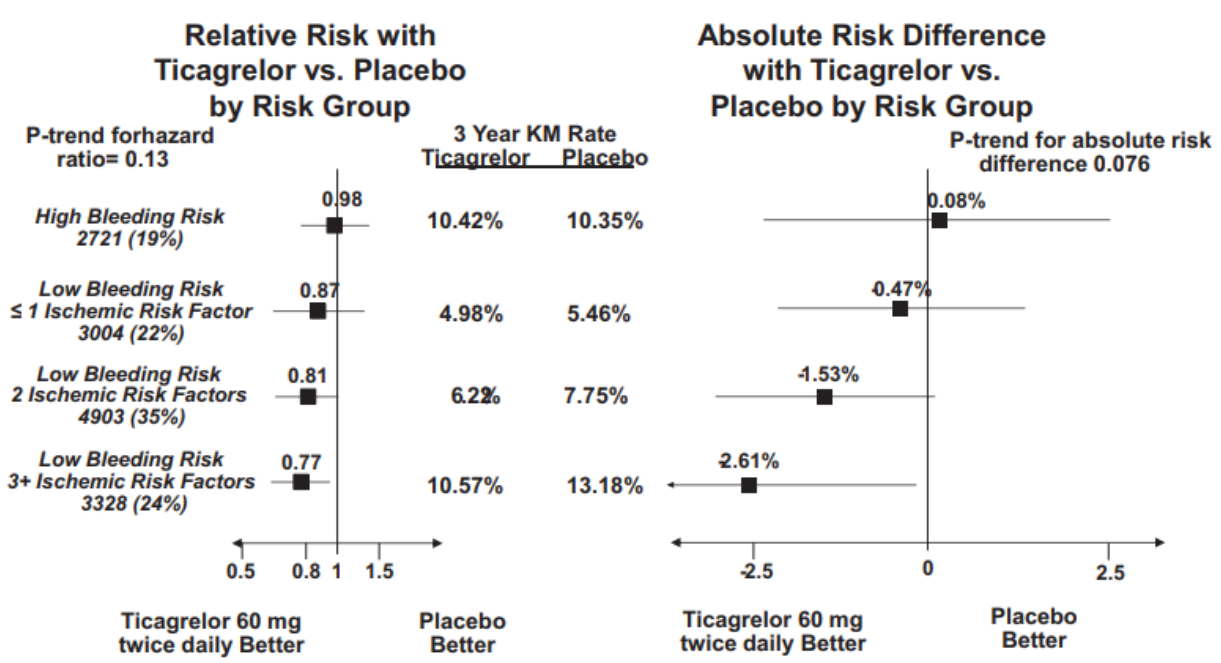
(P-trend 0.076)



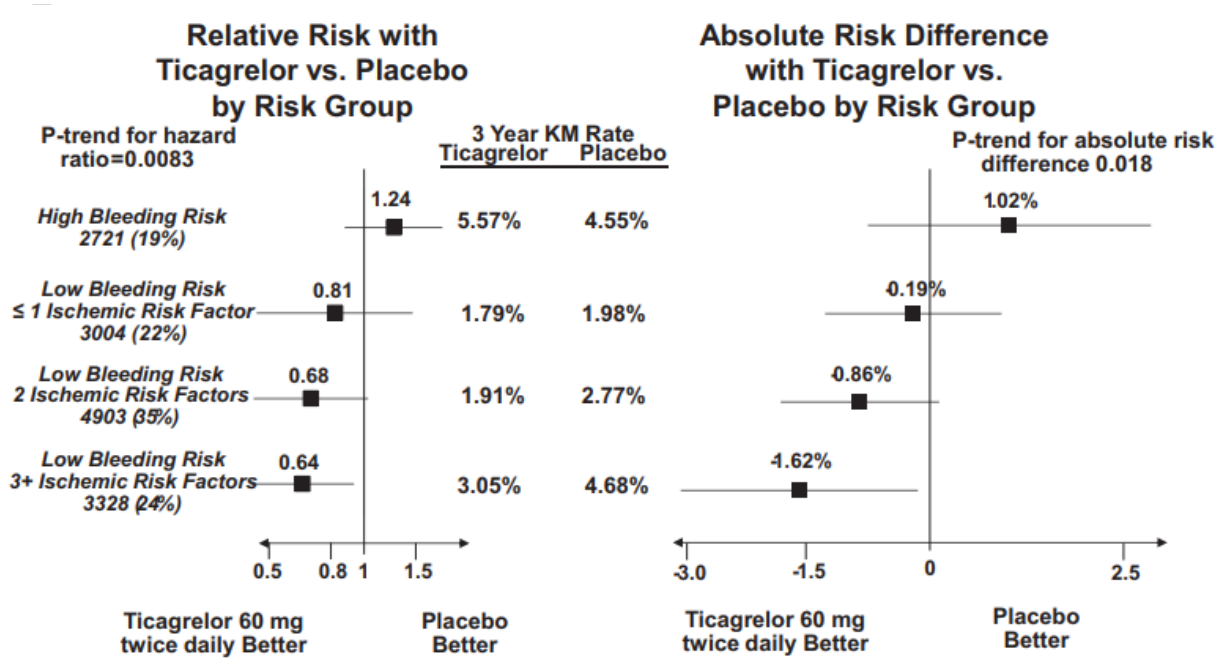
Bonaca MP et al. European Heart Journal 2022;00:1-8.

Patient Selection Algorithm

Outcomes at 3 years with ticagrelor 60 mg BID vs. placebo by difference in hazard and absolute risk difference



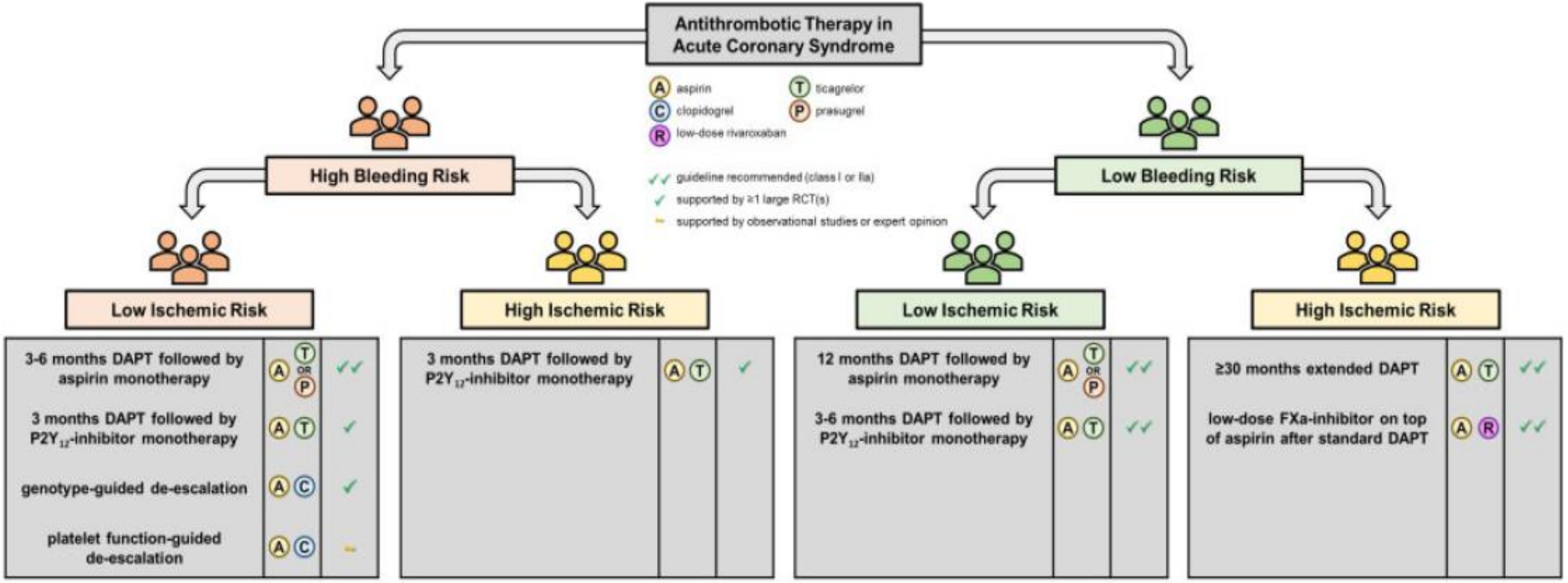
Composite of CV death, MI or stroke



CV death

Bonaca MP et al. European Heart Journal 2022;00:1-8.

Patient-tailored antithrombotic strategies for ACS and CCS



Van der Sangen NMR et al. EHJ. 2021;42:1038-1046.

Conclusions

- DAPT with ASA + ticagrelor confers efficacy and mortality benefits after ACS
- Patients who have had an MI remain at heightened risk for ischemic events over the long term[1-4]
- PEGASUS-TIMI 54, the first prospective RCT appropriately powered to assess the benefit of long-term DAPT in patients with prior MI, demonstrated that prolonged antiplatelet therapy with ticagrelor plus low-dose ASA may represent a new strategy to reduce atherothrombotic events in appropriately selected patients with prior MI

1. Bhatt DL et al. *JAMA.* 2010;304:1350-1357; 2. Fox KA et al. *Eur Heart J.* 2010;31:2755-2764; 3. Jernberg T et al. *Eur Heart J.* 2015;36:1163-1170; 4. Bonaca MP et al. *N Engl J Med.* 2015;372:1791-1800.