Antiplatelet therapy in ACS

Recommendations for platelet inhibition in non-ST-elevation ACS

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

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Recommendations	Class[a]	Level[b]	Ref.[c]
Oral antiplatelet therapy			
Aspirin is recommended for all patients without contraindications at an initial oral loading dose[d] of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy.	I	A	129–132
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A	137, 148, 153
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B	153
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B	148, 164
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B	137
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A	187–189, 192

Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data fro

Antithrombotic Trial

Summary

Background Low
vascular disease

Methods We un
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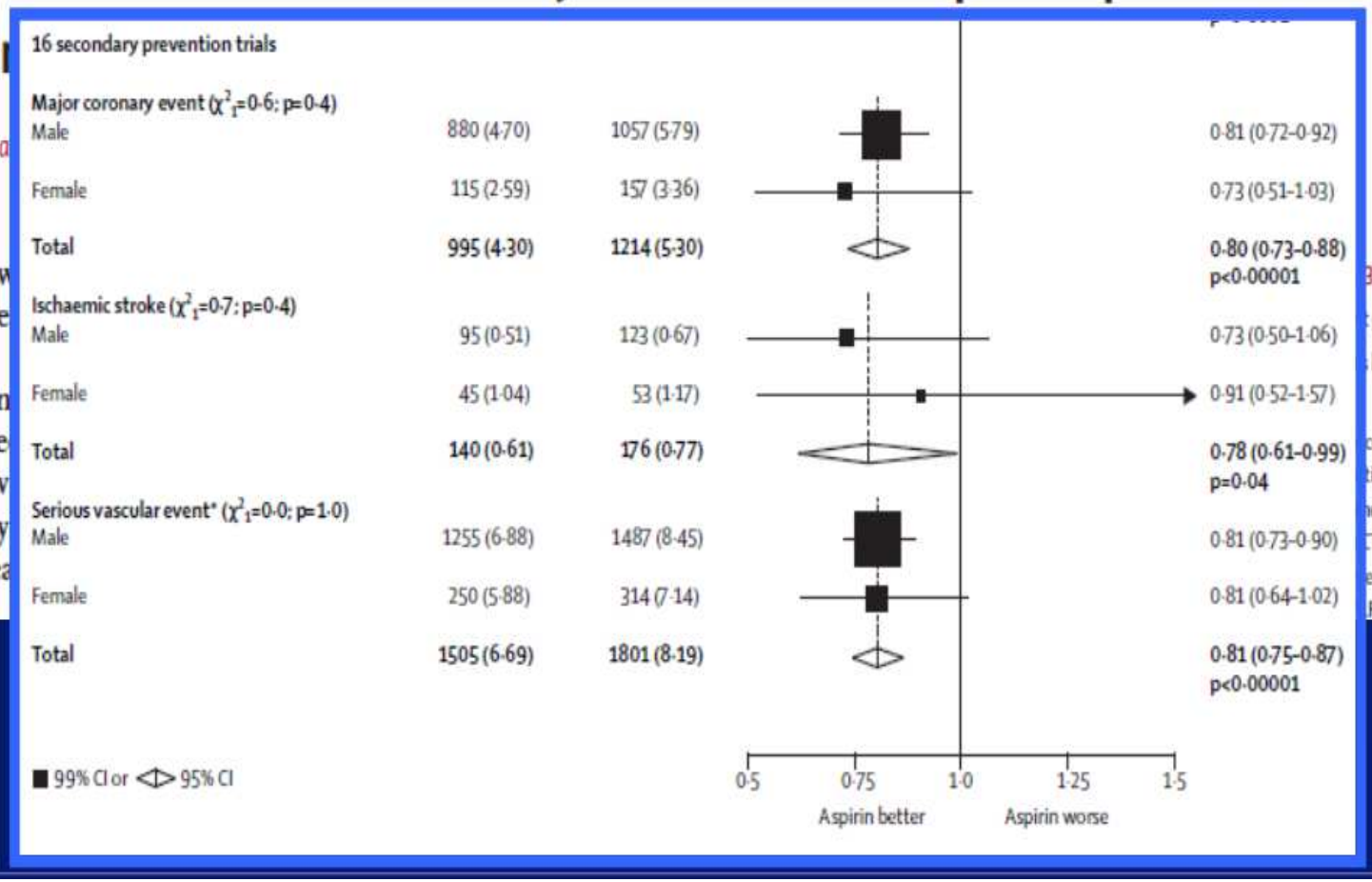

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CTSU), Richard Doll
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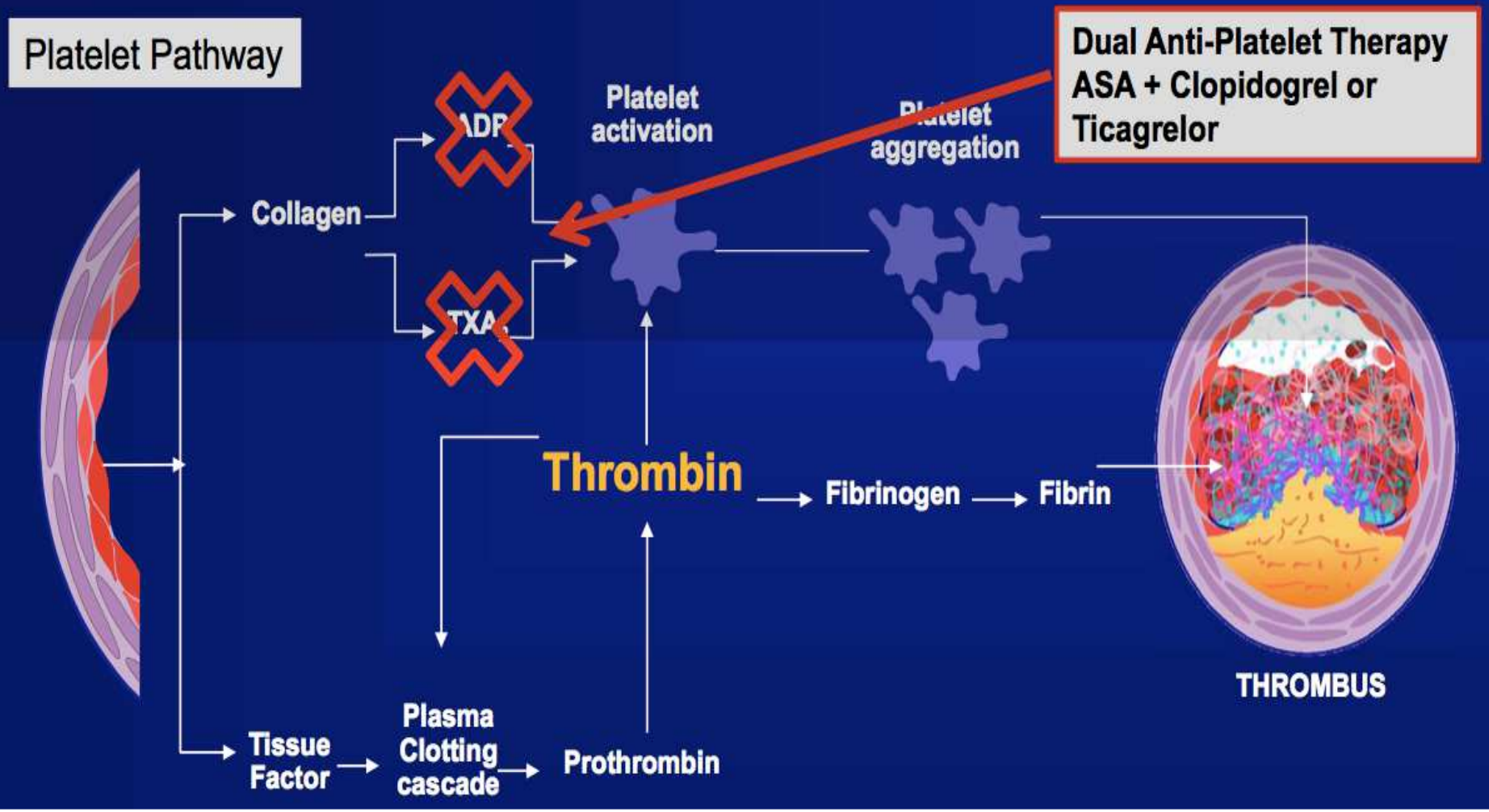
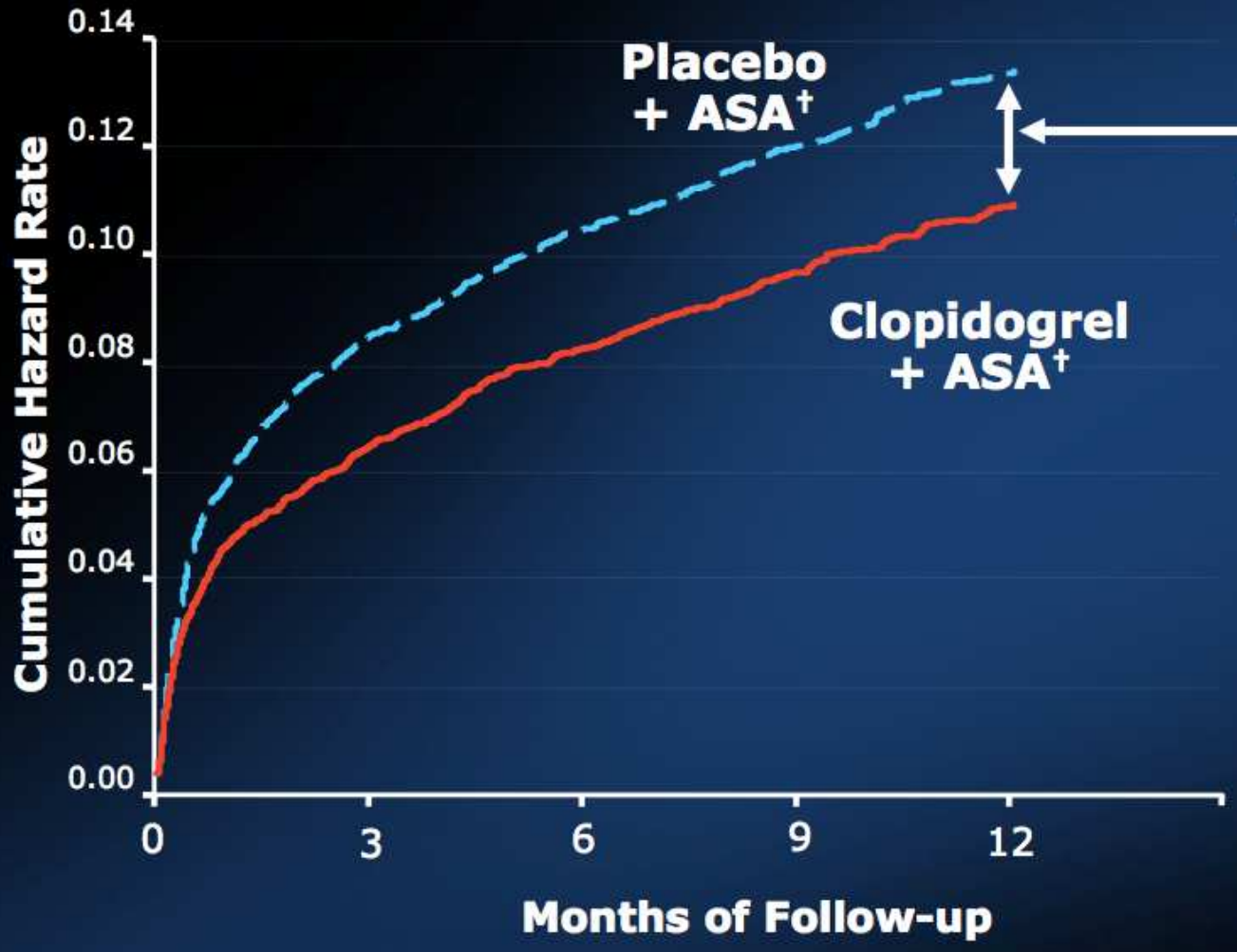
Pathways For Thrombus Formation

Two pathways connecting tissue injury, coagulation, and platelet response.



CURE Results:

Primary Endpoint: MI/Stroke/CV Death (N=12,562*)



20%
Relative
Risk Reduction
P=0.00009‡

The primary outcome occurred in 9.3% of patients in the clopidogrel + ASA group and 11.4% in the placebo + ASA group

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in Patients Presenting without Persistent ST-Segment Elevation
of the European Society of Cardiology (ESC)

Table 8 $P2Y_{12}$ inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg orally then 75 mg a day	60 mg orally then 10 mg a day	180 mg orally then 90 mg twice a day	30 μg/kg bolus and 4 μg/kg/min infusion
Dosing in CKD				
• Stage 3 (eGFR 30–59 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 4 (eGFR 15–29 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 5 (eGFR <15 mL/min/1.73m^2)	Use only for selected indications (e.g. stent thrombosis prevention)	Not recommended	Not recommended	No dose adjustment
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with predictable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading dose effect[a]	2–6 hours[b]	30 min[b]	30 min[b]	2 min
Duration of effect	3–10 days	7–10 days	3–5 days	1–2 hours
Withdrawal before surgery	5 days[c]	7 days[c]	5 days[c]	1 hour
Plasma half-life of active $P2Y_{12}$ inhibitor[d]	30–60 min	30–60 min[e]	6–12 hours	5–10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes ('inactive' metabolite only)

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Major limits of clopidogrel

1) Wide inter-patient variability in responsiveness

because of genetic, clinical, environmental and cellular factors

2) Limited degree of platelet inhibition

because of low bioavailability: 15%.... (85% of clopidogrel is inactivated by small-bowel esterases)

3) Slow onset and offset of action

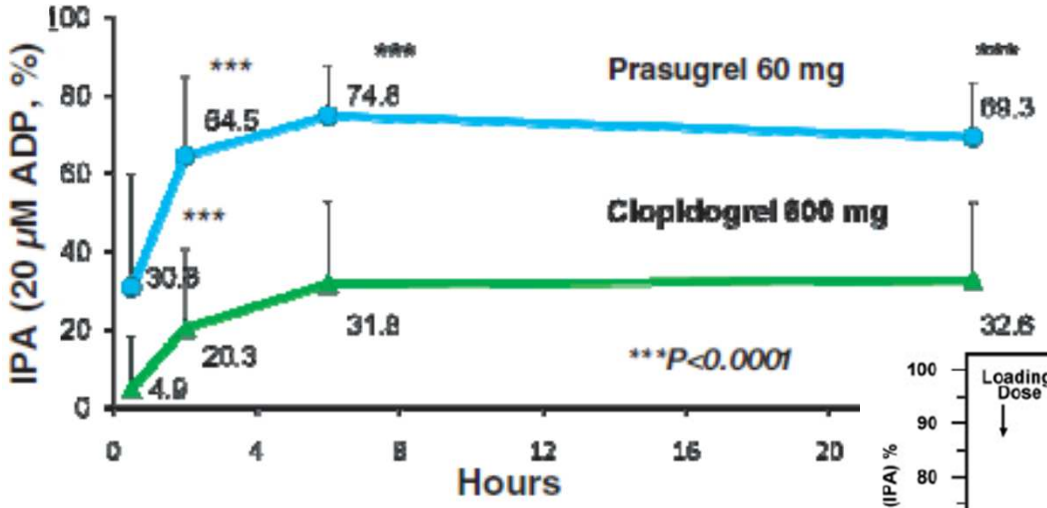
because of pre-epatic and hepatic metabolism (pro-drug) and irreversible binding to the ADP receptor

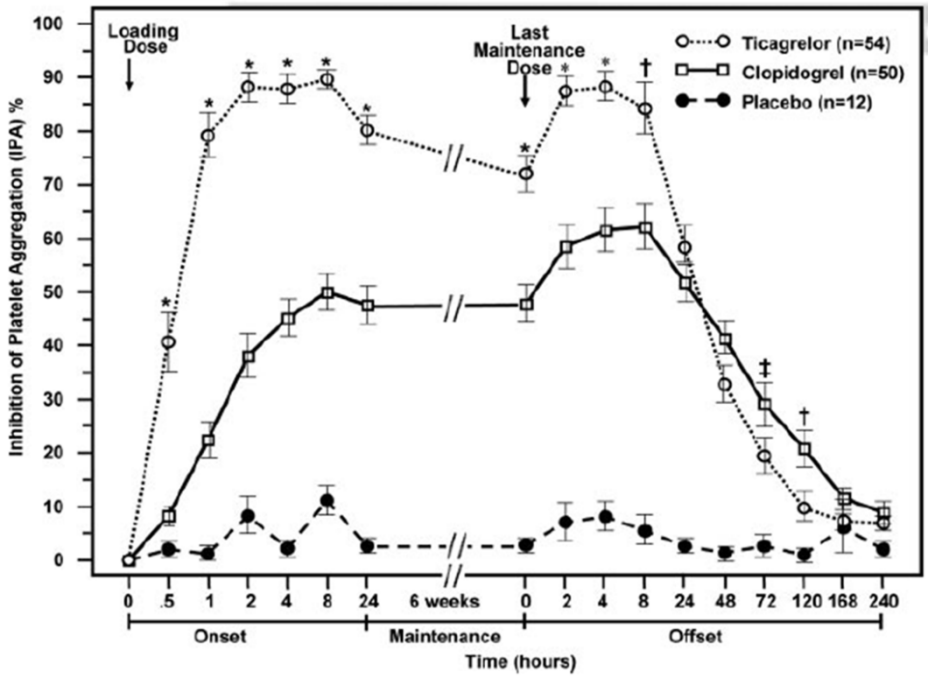
4) Reduced response in STEMI patients undergoing pPCI

because of impaired bioavailability

Prasugrel and Ticagrelor

Faster and more potent than clopidogrel





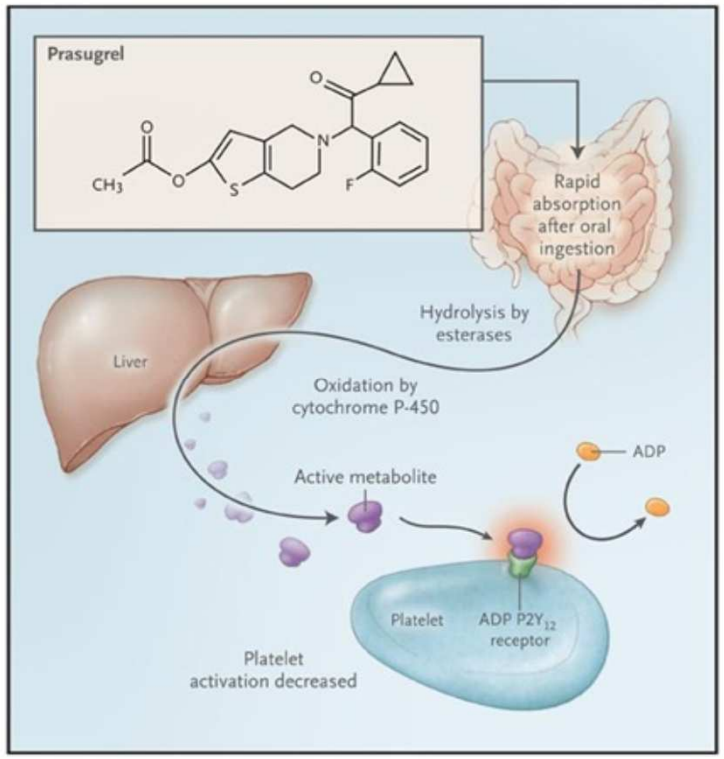
Wiviott s., et al. Circulation 2007;116:2923-32

Gurbel PA., et al. Circulation 2009;120:2577-2585

Prasugrel

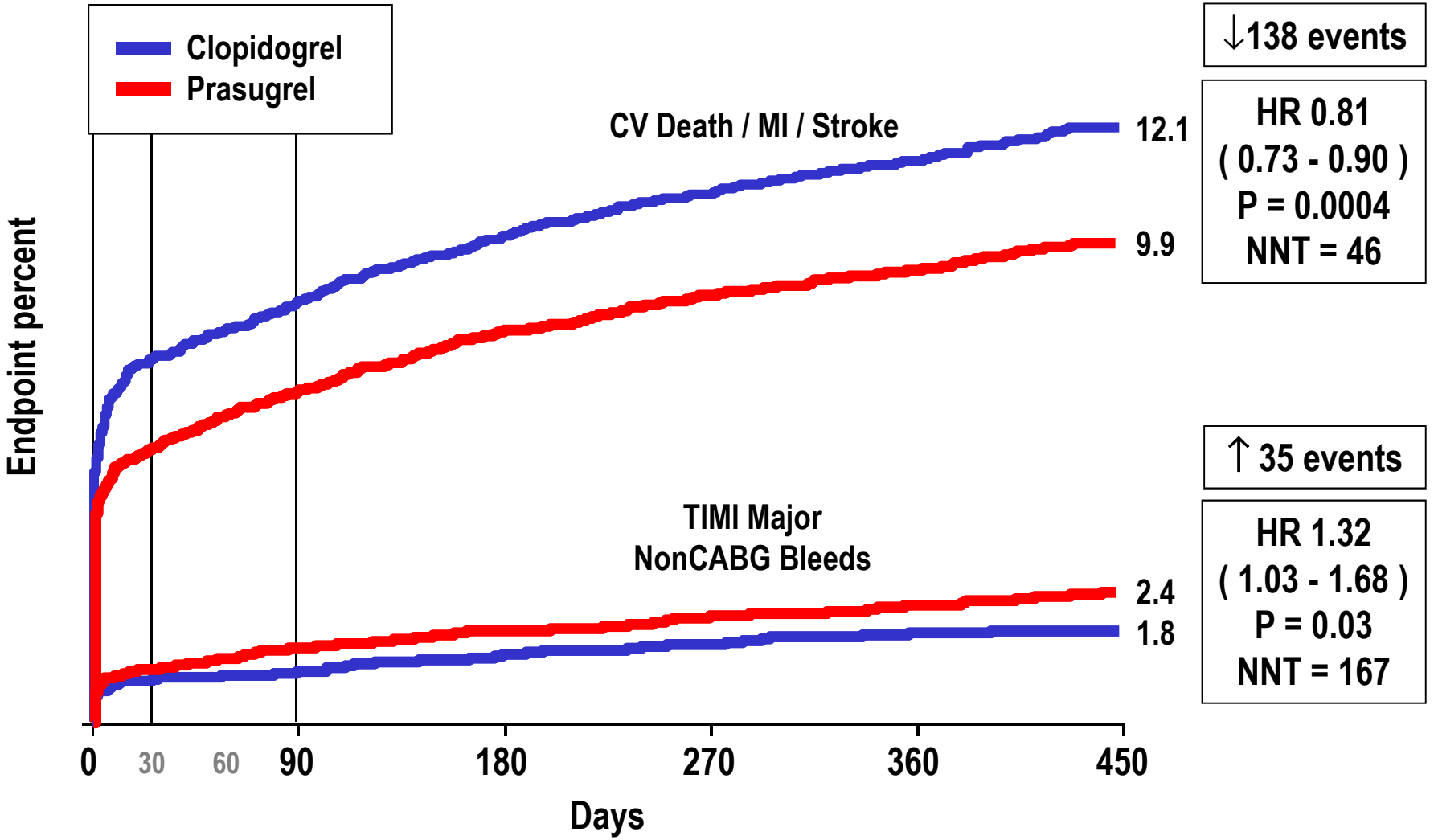
Metabolism and mechanism of action

- ✓ **Pro-drug, no resistance or variability in response**
- ✓ **Rapid onset of antiplatelet effect**
- ✓ **Irreversible effect with slow offset of antiplatelet effect**
- ✓ **Efficacy endpoint (more potent than clopidogrel)**
- ✓ **Safety endpoint**



The TRITON-TIMI 38 trial

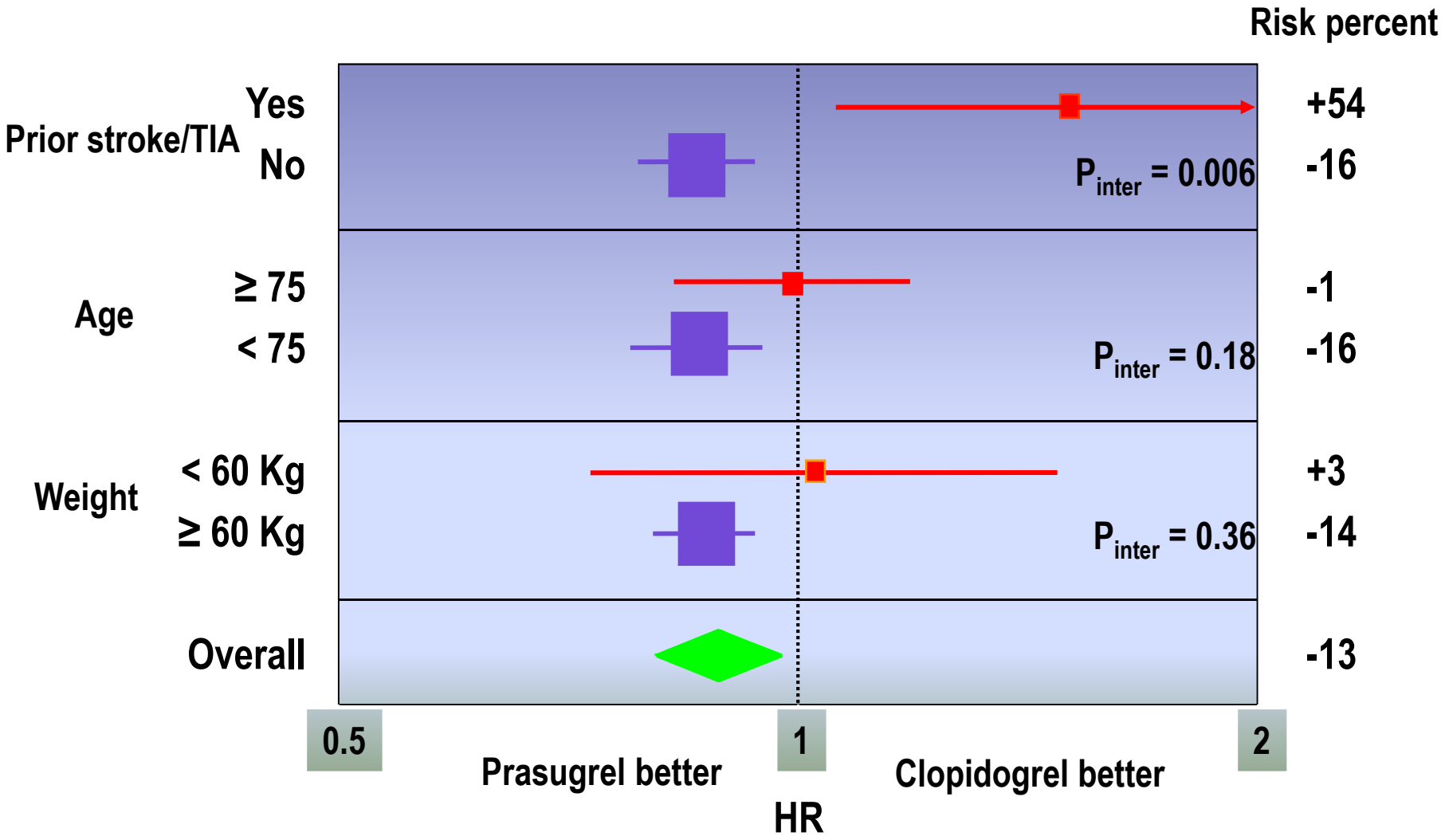
Prasugrel vs clopidogrel in ACS undergoing PCI



Wiviott SD et al. N Engl J Med 2007; 357:2001-2015

TRITON-TIMI 38 posthoc analysis

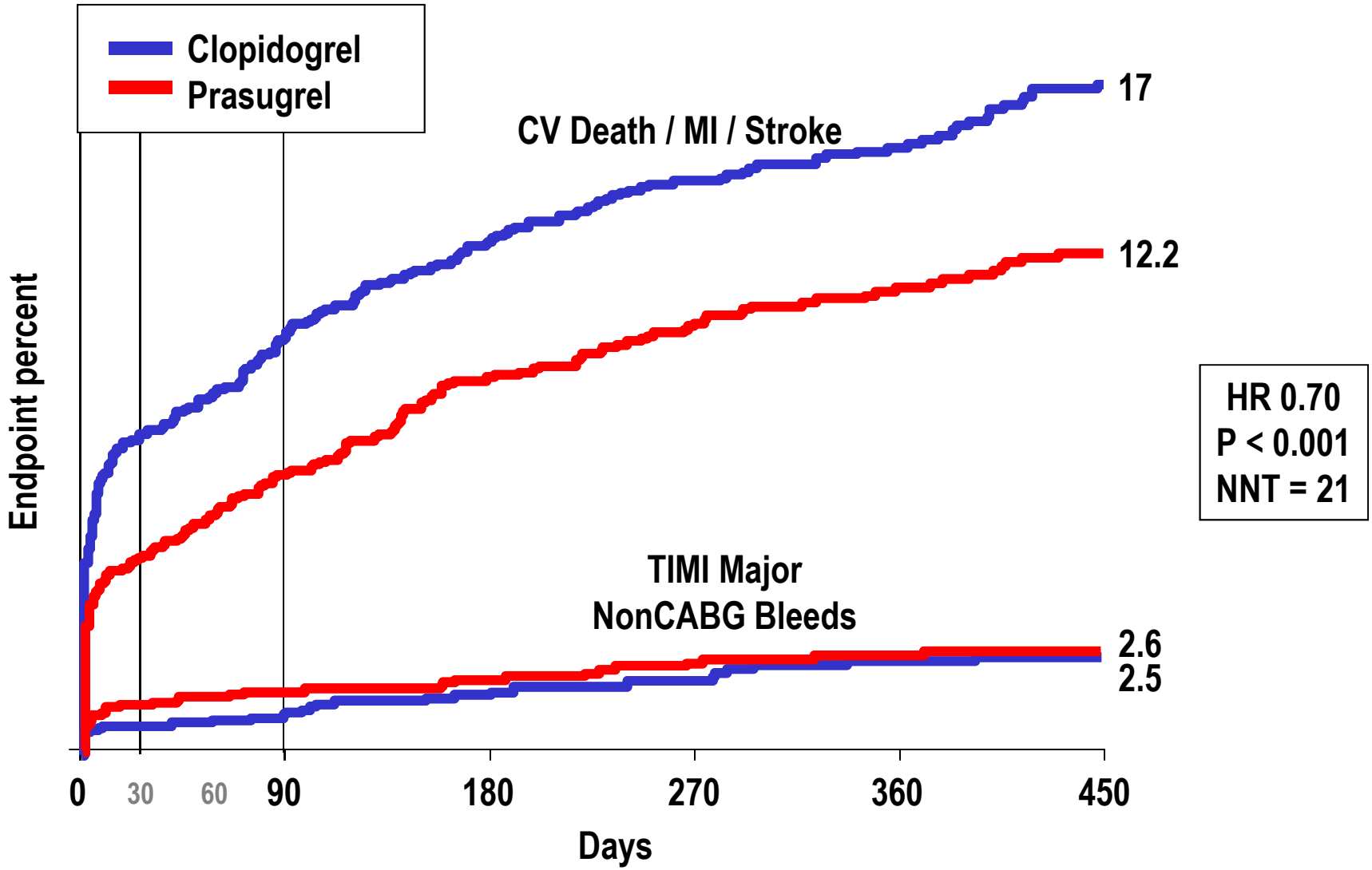
Net clinical benefit: subgroups at increased bleeding risk



Wiviott S, et al. N Engl J Med 2007;2001-15

TRITON – TIMI 38

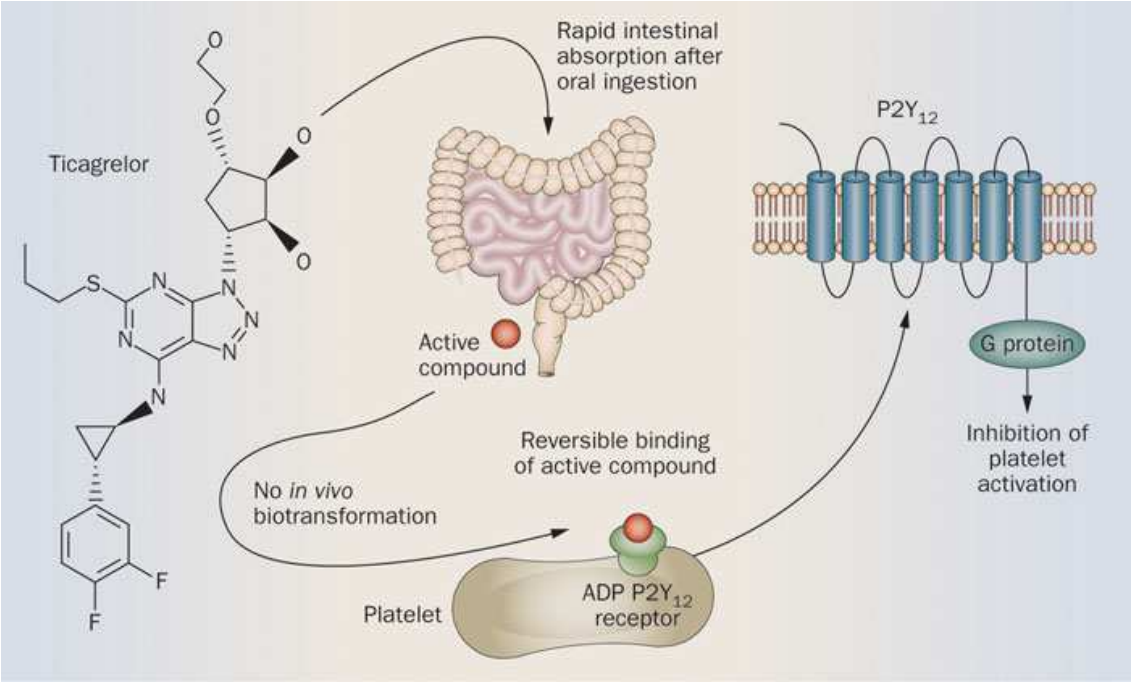
Prasugrel vs clopidogrel in diabetic patients (N =3,146)



Wiviott SD et al. N Engl J Med 2007; 357:2001-2015

Ticagrelor
Metabolism and mechanism of action

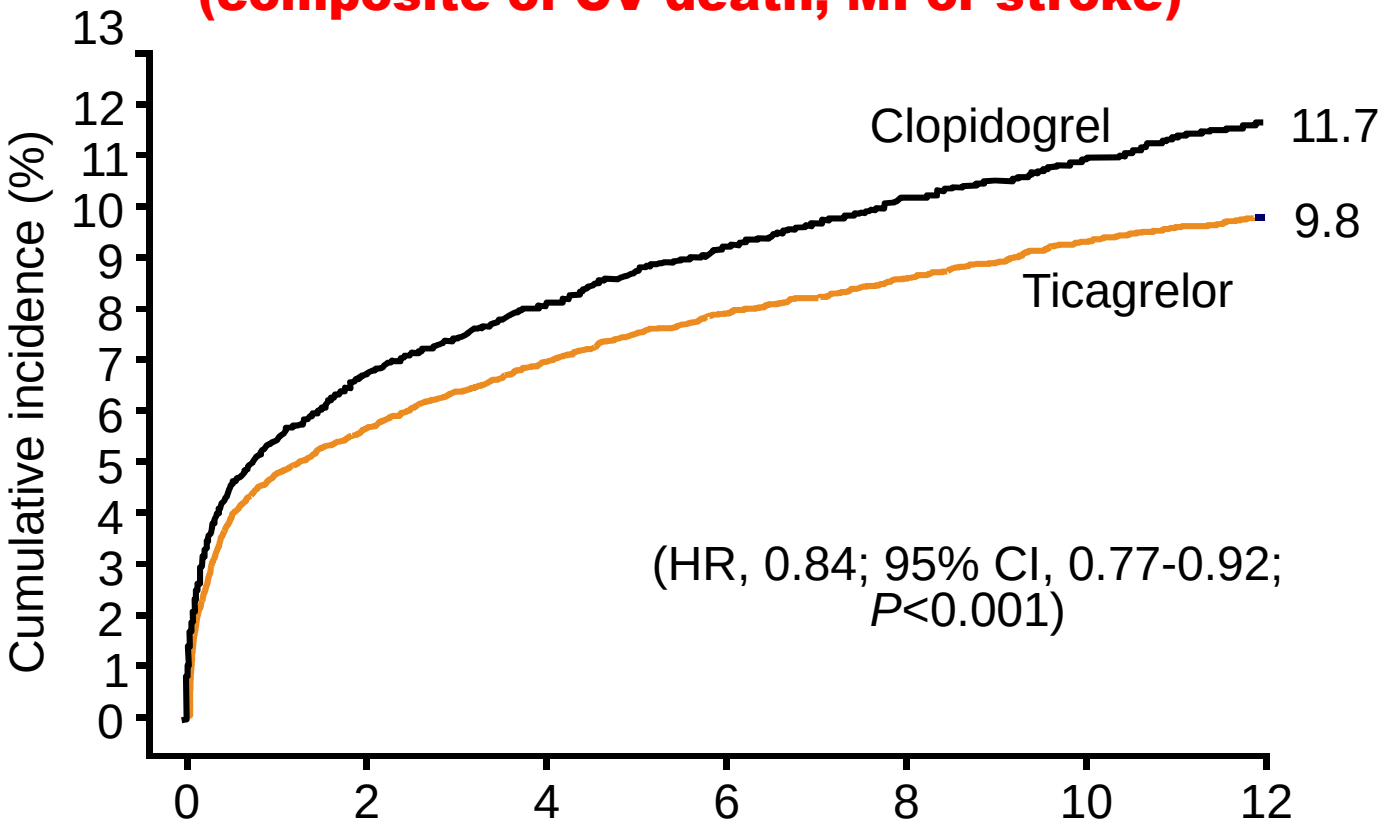
- ✓ **Active drug, no resistance or variability in response**
- ✓ **Reversible effect with rapid onset and offset of antiplatelet effect**
- ✓ **Efficacy endpoint more potent than clopidogrel**
- ✓ **Safety endpoint**



Nature Review Cardiology 2009;6:737-8

PLATO study
Ticagrelor vs clopidogrel in ACS

Primary efficacy endpoint
(composite of CV death, MI or stroke)



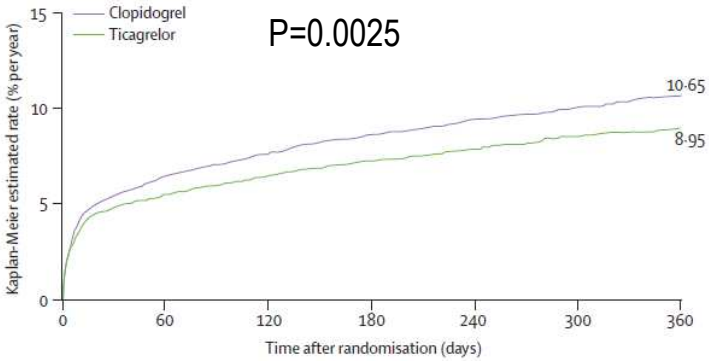
No. at risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

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

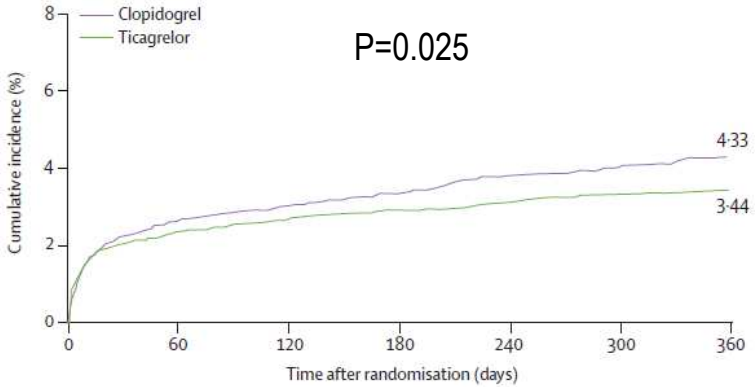
The PLATO trial

Ticagrelor vs clopidogrel in ACS with a planned invasive strategy

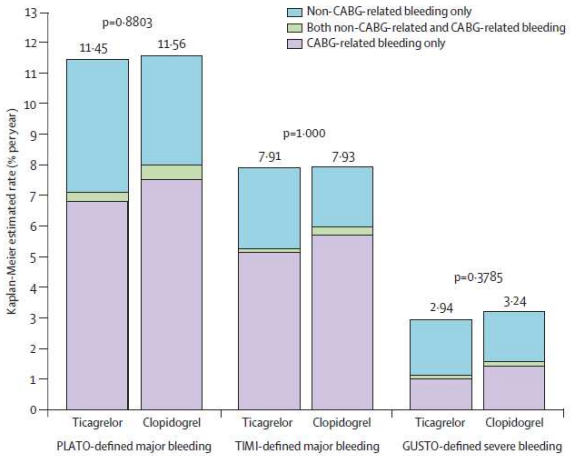
Primary endpoint: CV death, MI or stroke



Secondary endpoint: CV death



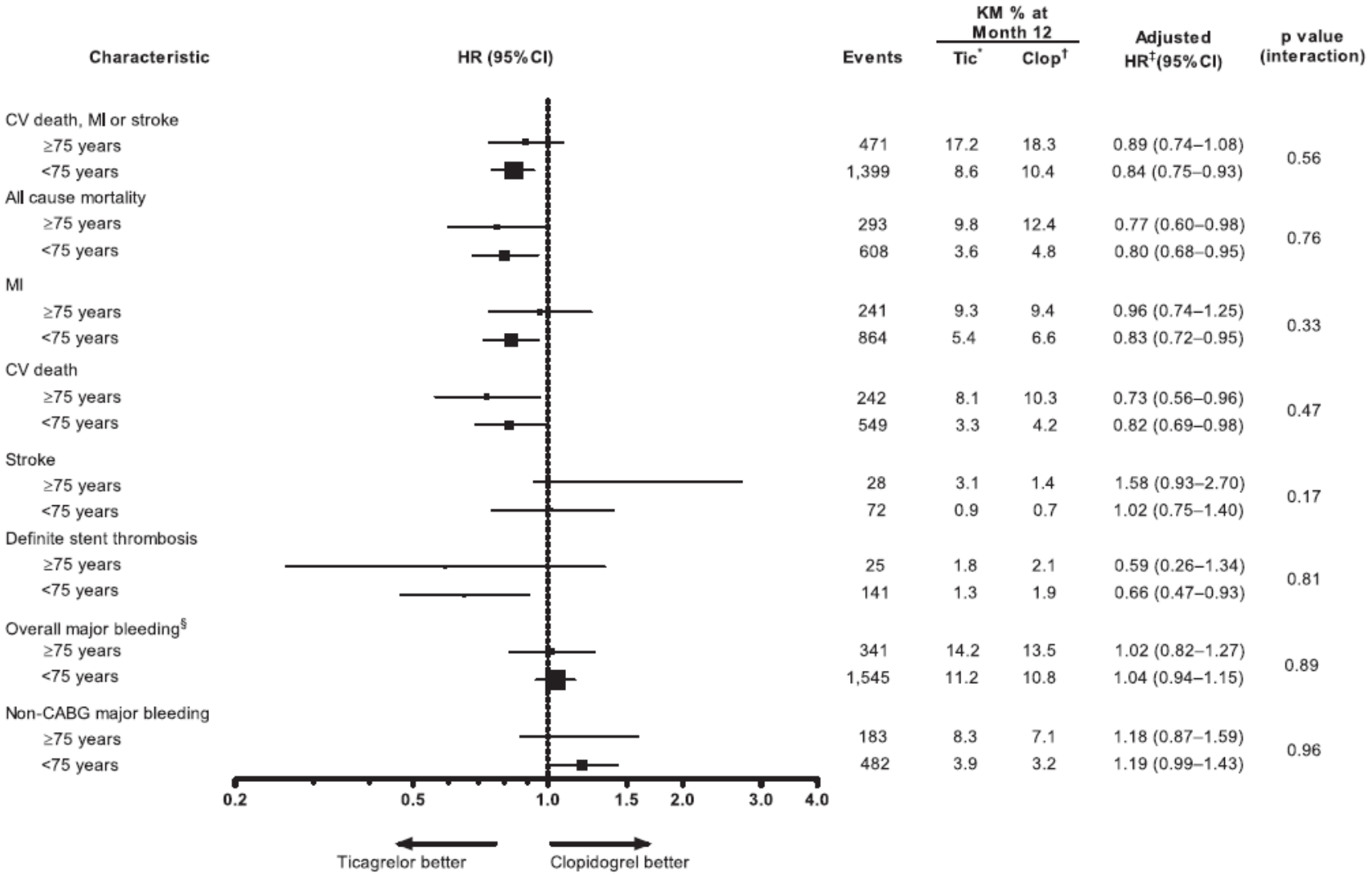
Rates of major bleeding



Cannon CP., et al. Lancet 2010;375:283-93

The PLATO trial

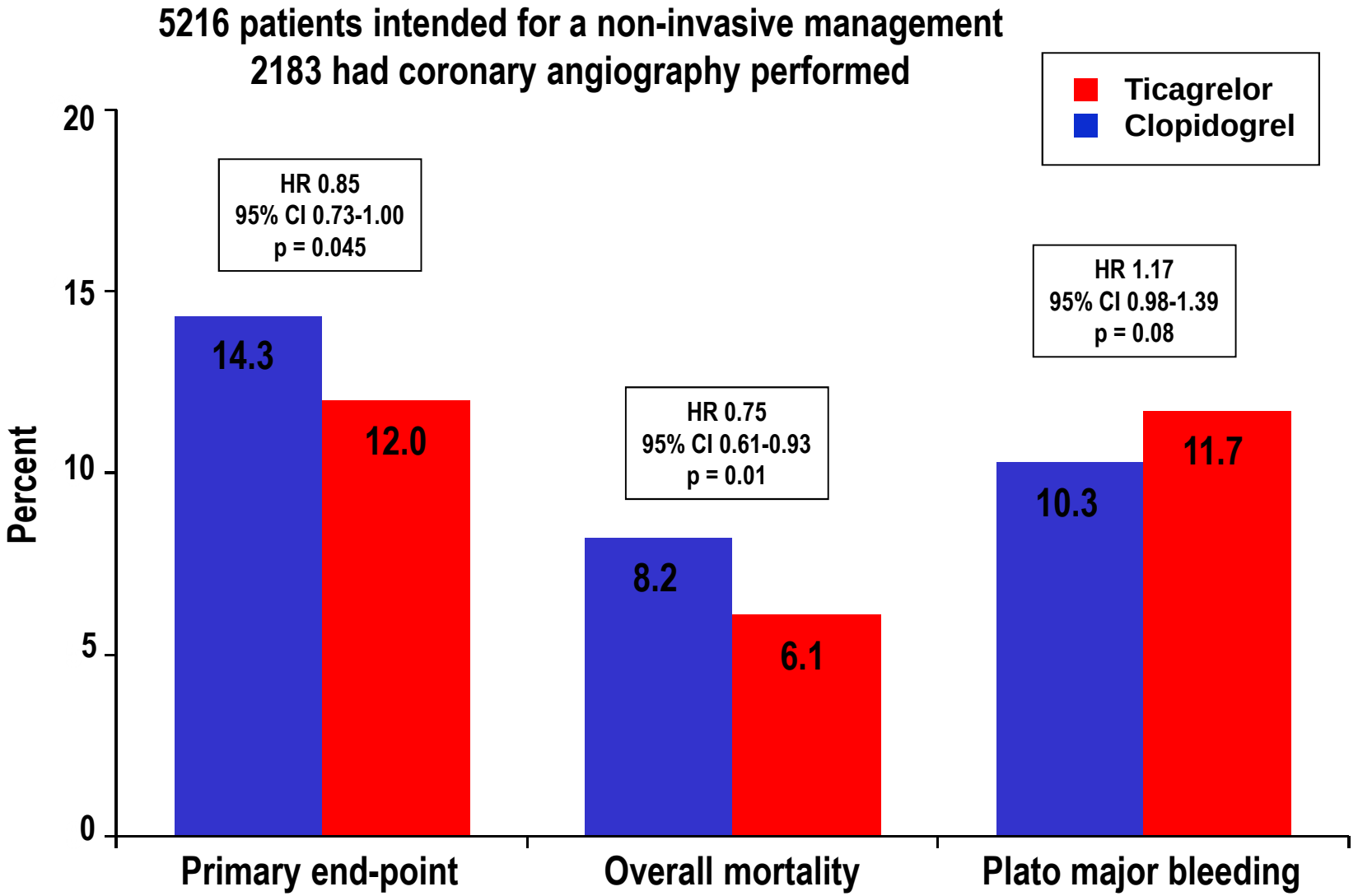
Ticagrelor vs clopidogrel in elderly patients with ACS



Husted S, et al. *Circ Cardiovasc Qual Outcomes* 2012;5:680–688.

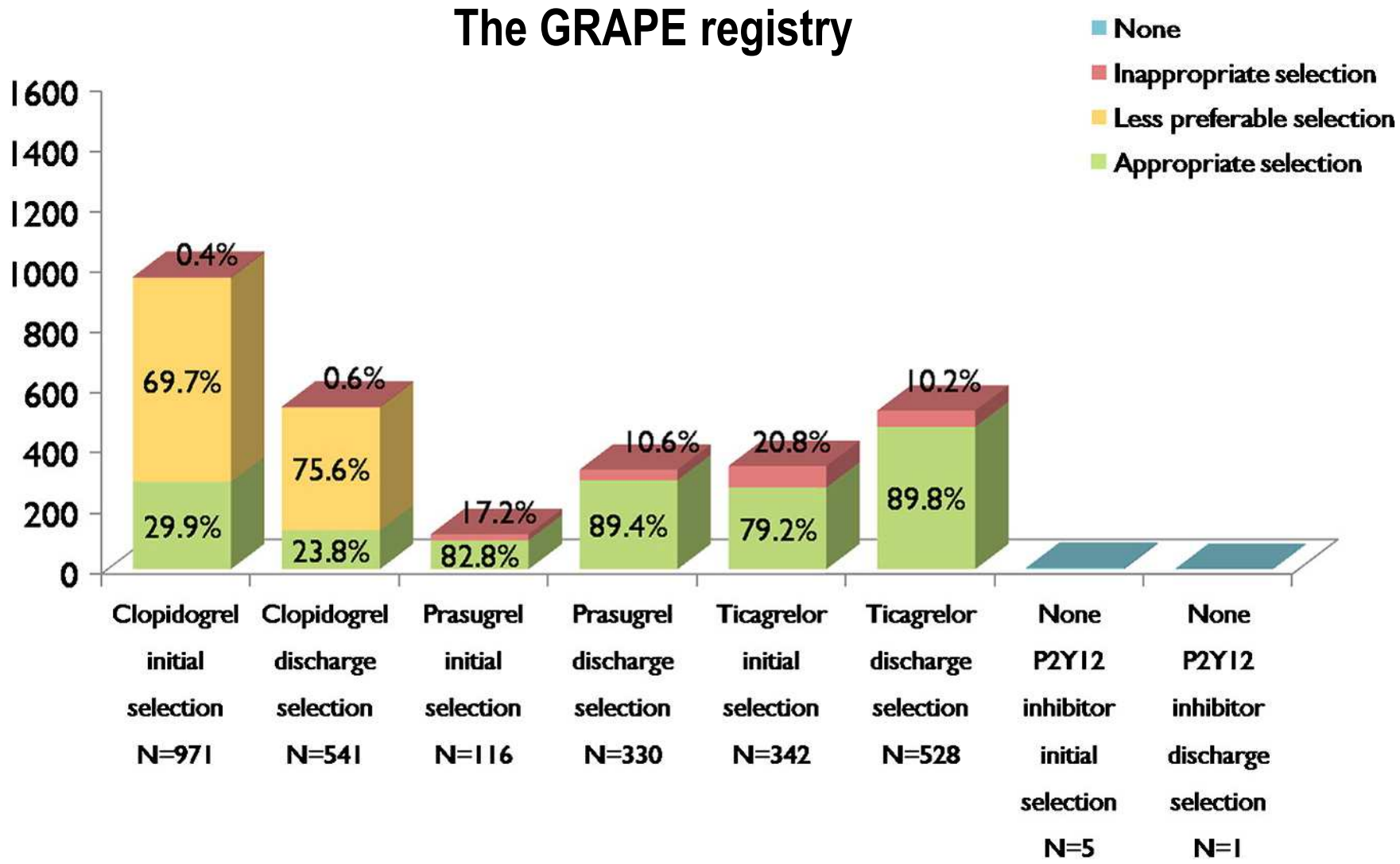
The Plato Trial

Ticagrelor vs Clopidogrel in ACS intended for a non-invasive management



James SK, et al. BMJ 2011;342:d3527

Contemporary use of oral antiplatelet agents



Alexopoulos A, et al. International Journal of Cardiology 2013

Antiplatelet therapy in ACS
STEMI

Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI

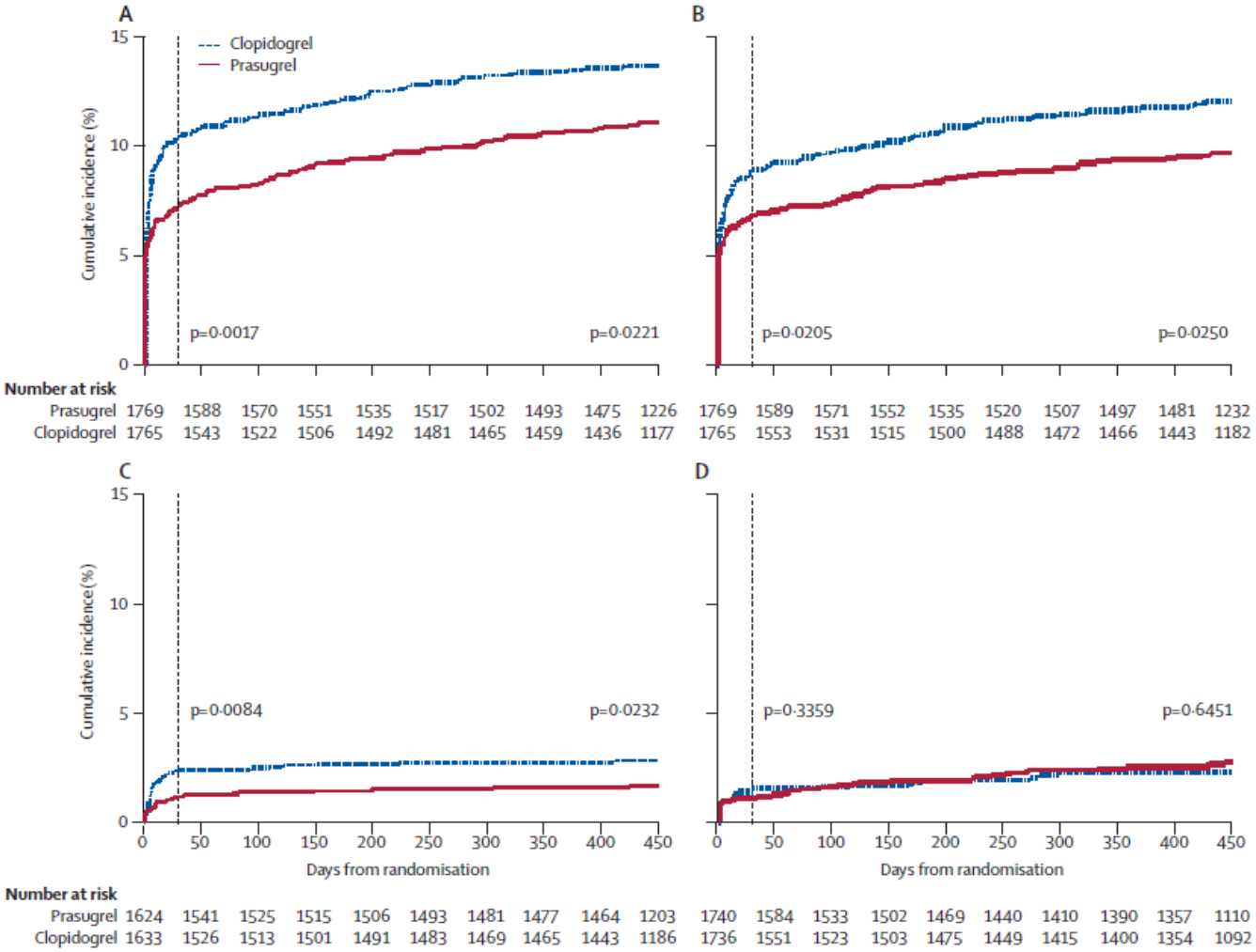
Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	776,794
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	–
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B	828
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B	823
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B	812
It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact.	I	B	777,846–848
GP IIb/IIIa inhibitors should be considered for bail-out or evidence of no-reflow or a thrombotic complication.	IIa	C	–
Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.	IIb	B	271,834, 835,849
Anticoagulants			
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A	–
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C	
Unfractionated heparin: 70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned; 50–70 U/kg i.v. bolus with GP IIb/IIIa inhibitor.	I	C	
Bivalirudin 0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for up to 4 hours after the procedure.	IIa	A	243,840,841
Enoxaparin i.v. 0.5 mg/kg with or without GP IIb/IIIa inhibitor.	IIa	B	788, 842–844,850

2014 ESC/EACTS Guidelines on myocardial revascularization EHJ (2014)35,2541-2619

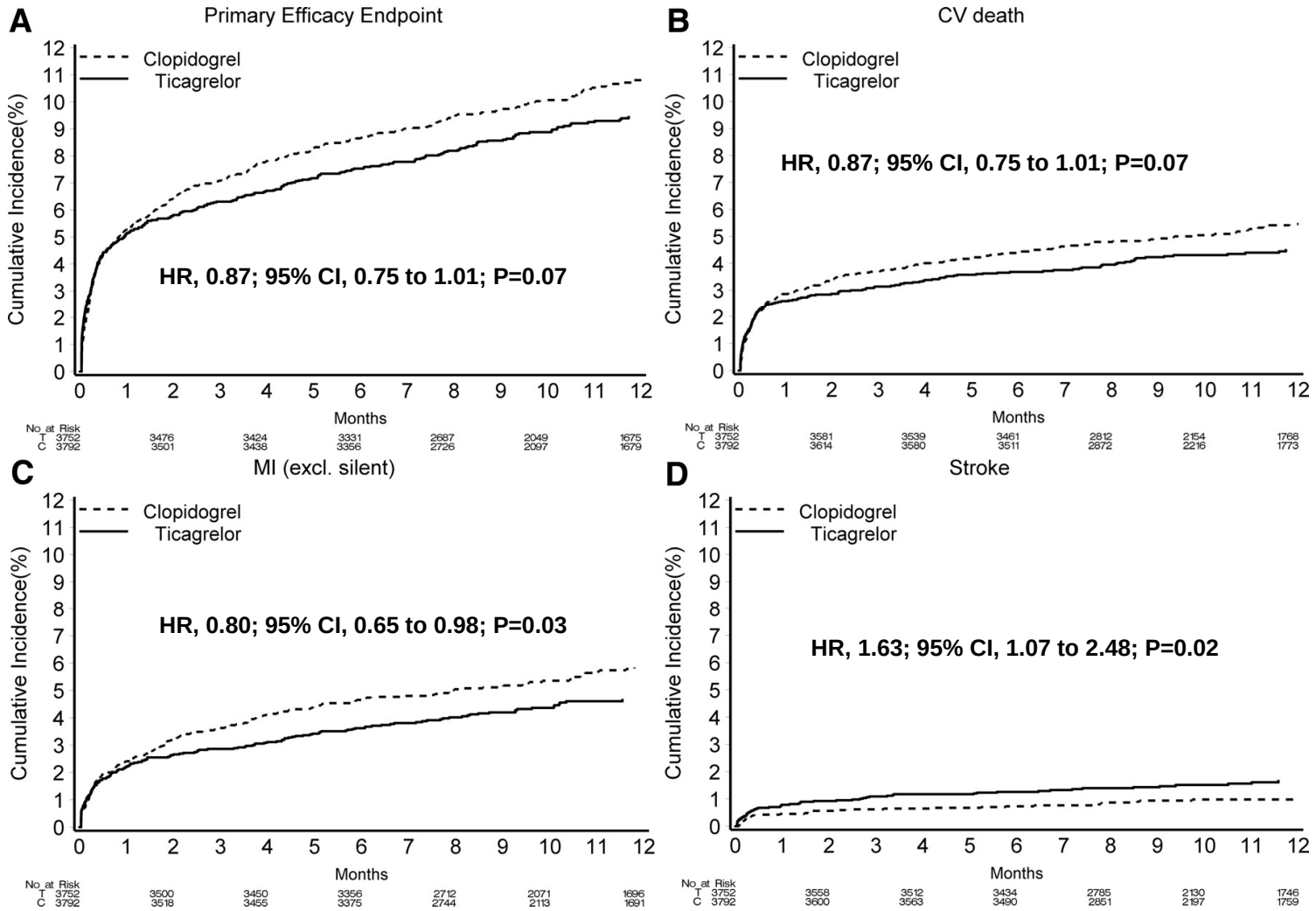
Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial

Lancet 2009; 373: 723–31

Gilles Montalescot, Stephen D Wiviott, Eugene Braunwald, Sabina A Murphy, C Michael Gibson, Carolyn H McCabe, Elliott M Antman, for the TRITON-TIMI 38 investigators

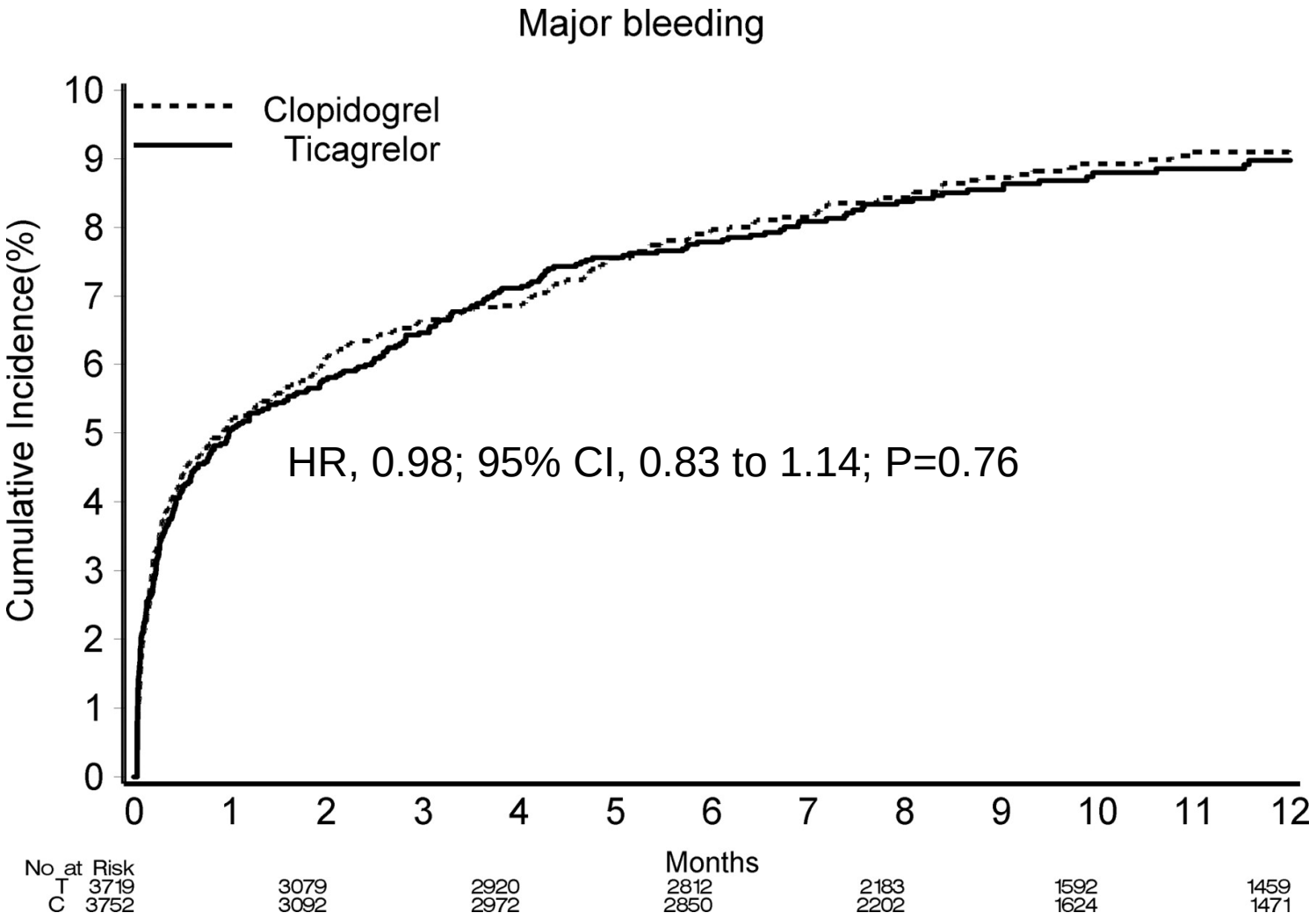


Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention



Philippe Gabriel Steg et al. Circulation. 2010;122:2131-2141

Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention



Philippe Gabriel Steg et al. Circulation. 2010;122:2131-2141