DUAL ANTI-PLATELET THERAPY IN ACS

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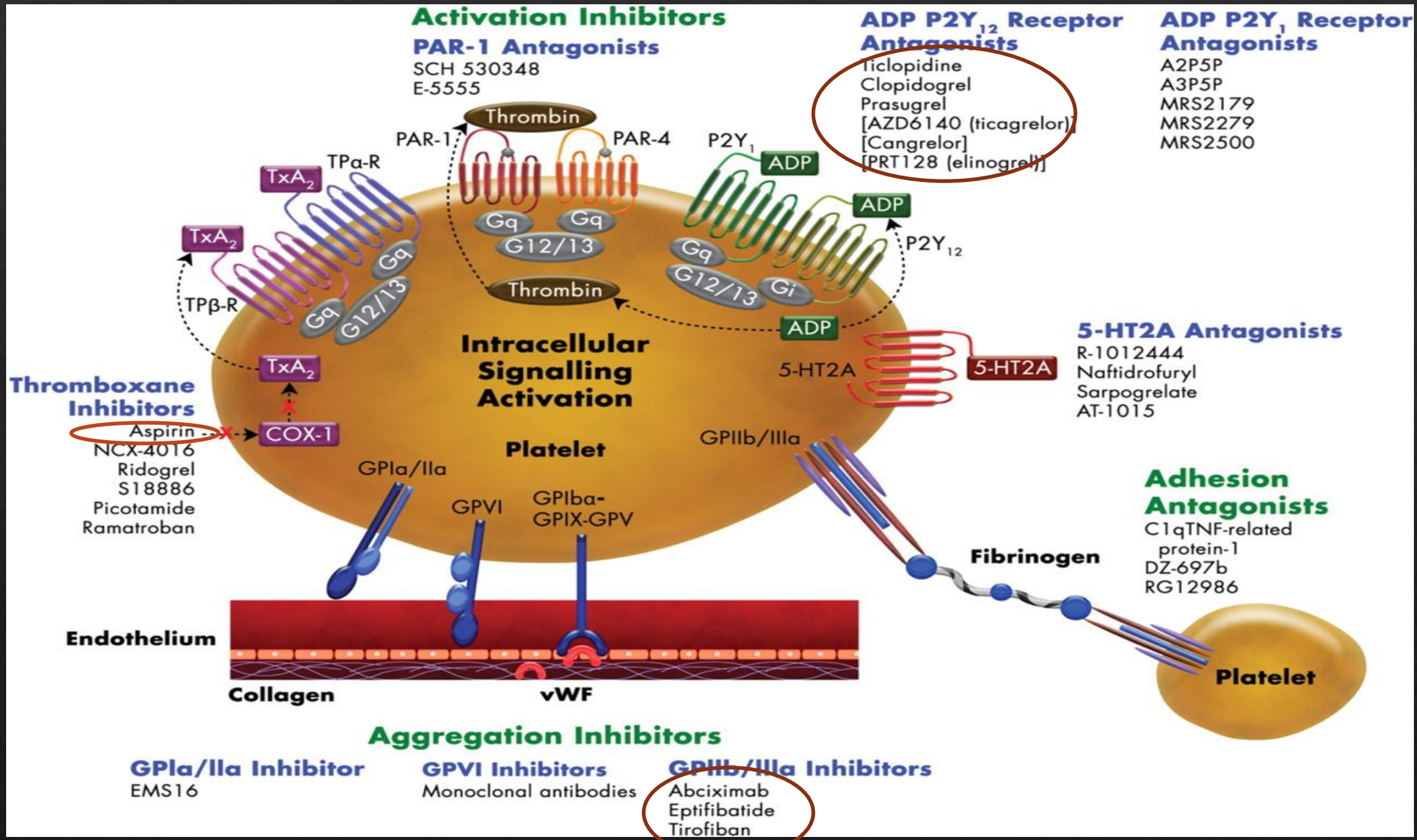
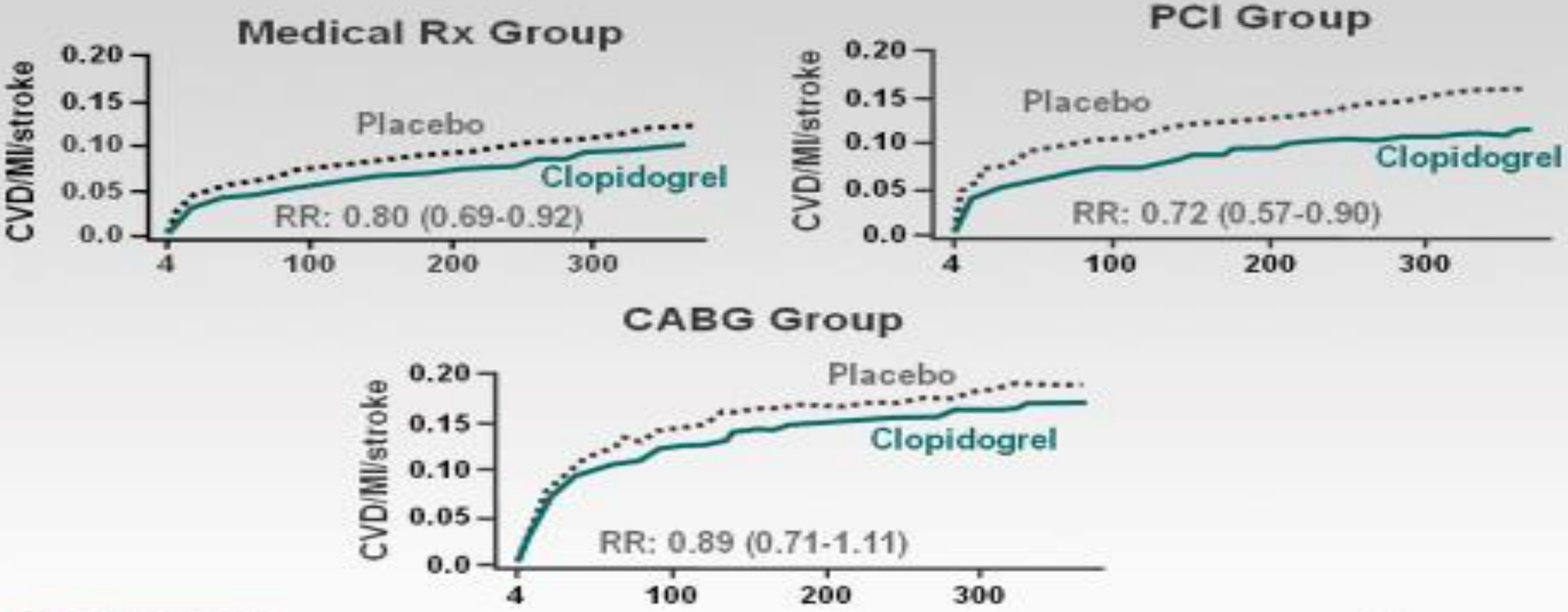

Activation Inhibitors
PAR-1 Antagonists
SCH 530348
E-5555
ADP P2Y12 Receptor Antagonists
Ticlopidine
Clopidogrel
Prasugrel
[AZD6140 (ticagrelor)]
[Cangrelor]
[PRT128 (elinogrel)]
ADP P2Y1 Receptor Antagonists
A2P5P
A3P5P
MRS2179
MRS2279
MRS2500
Thrombin
PAR-1
PAR-4
TPα-R
TxA2
TPβ-R
Gq
G12/13
P2Y1
ADP
P2Y12
Gi
Intracellular Signalling Activation
Platelet
5-HT2A
5-HT2A Antagonists
R-1012444
Naftidrofuryl
Sarpogrelate
AT-1015
Thromboxane Inhibitors
Aspirin
COX-1
NCX-4016
Ridogrel
S18886
Picotamide
Ramatroban
GPIIb/IIIa
GPIa/IIa
GPVI
GPIba-GPIX-GPV
Fibrinogen
Adhesion Antagonists
C1qTNF-related protein-1
DZ-697b
RG12986
Endothelium
Collagen
vWF
Platelet
Aggregation Inhibitors
GPIa/IIa Inhibitor
EMS16
GPVI Inhibitors
Monoclonal antibodies
GPIIb/IIIa Inhibitors
Abciximab
Eptifibatide
Tirofiban

Benefits of DAPT

CURE: Benefit of Clopidogrel Irrespective of Revascularization Status

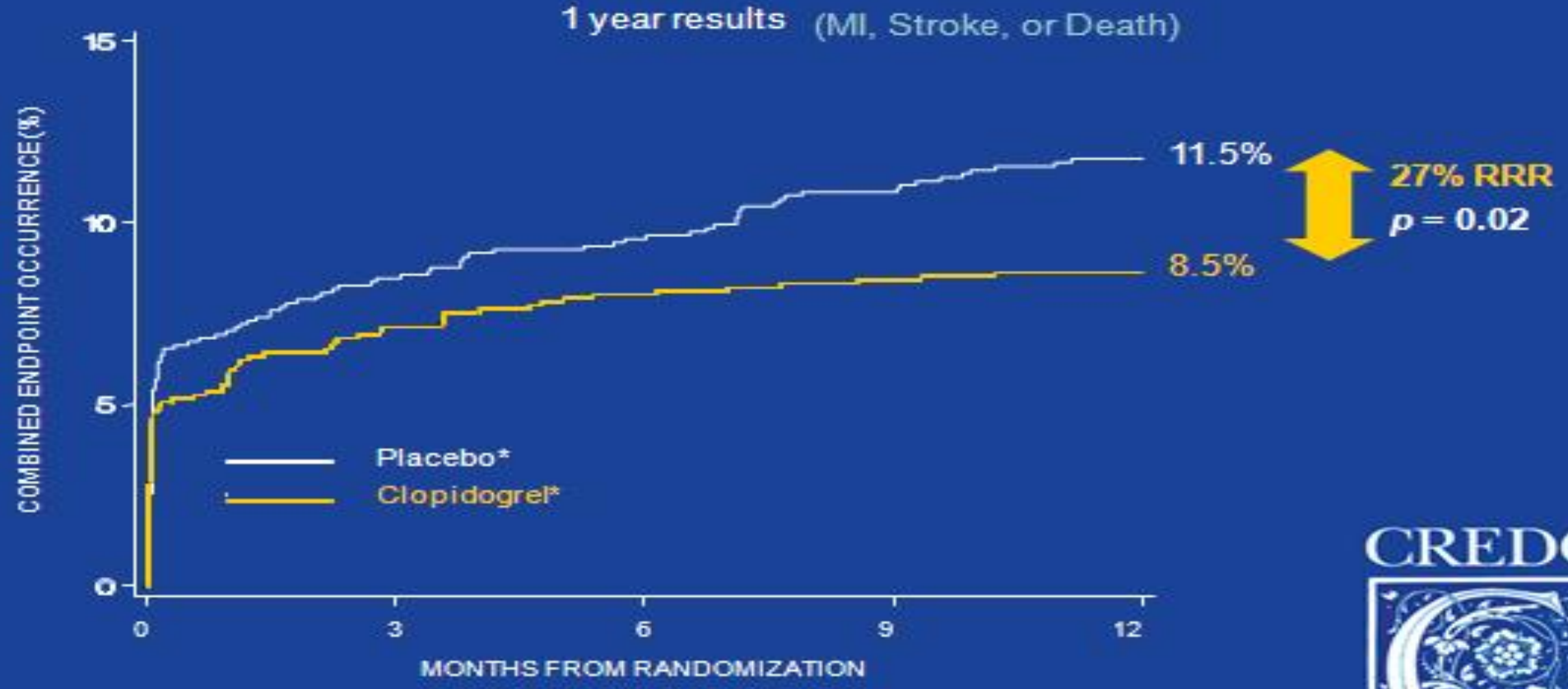


CLINICAL CARDIOLOGY

Fox KA, et al. *Circulation*. 2004;110:1202-1208.
Reproduced with permission.

the heart.org

Long-term Benefits of Clopidogrel in PCI Patients



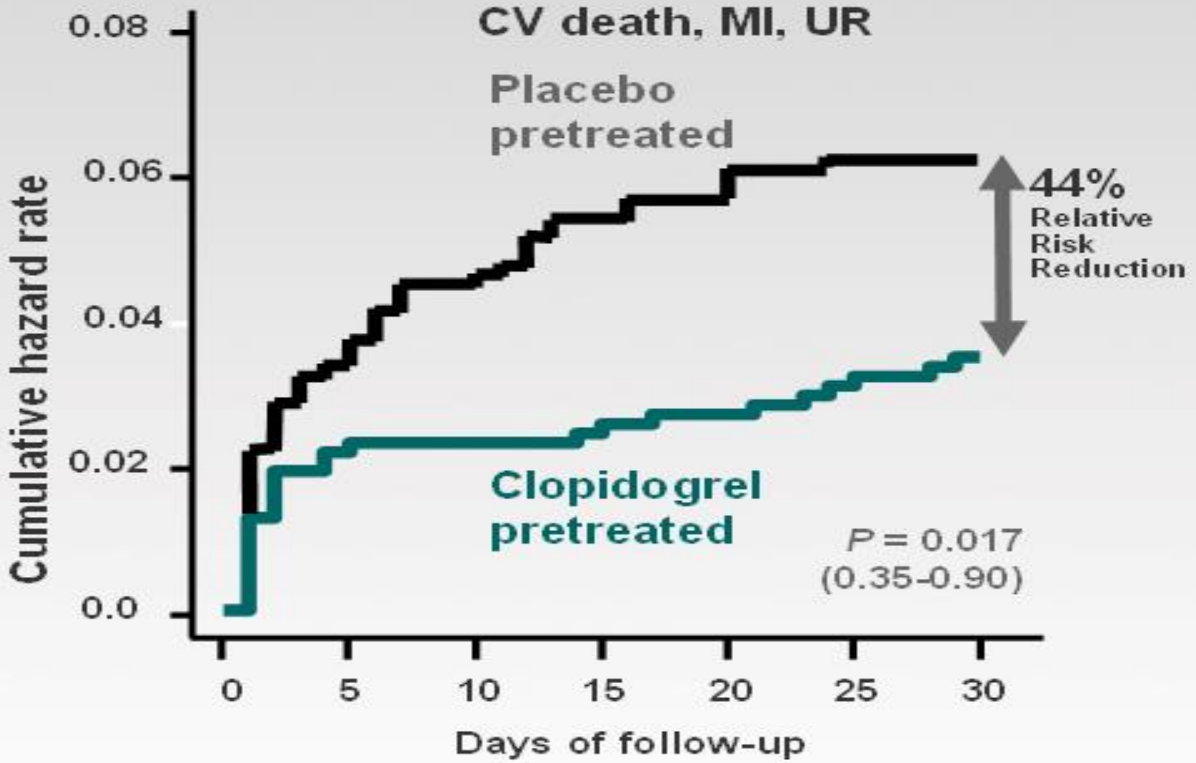
CREDO

* Standard therapy including ASA

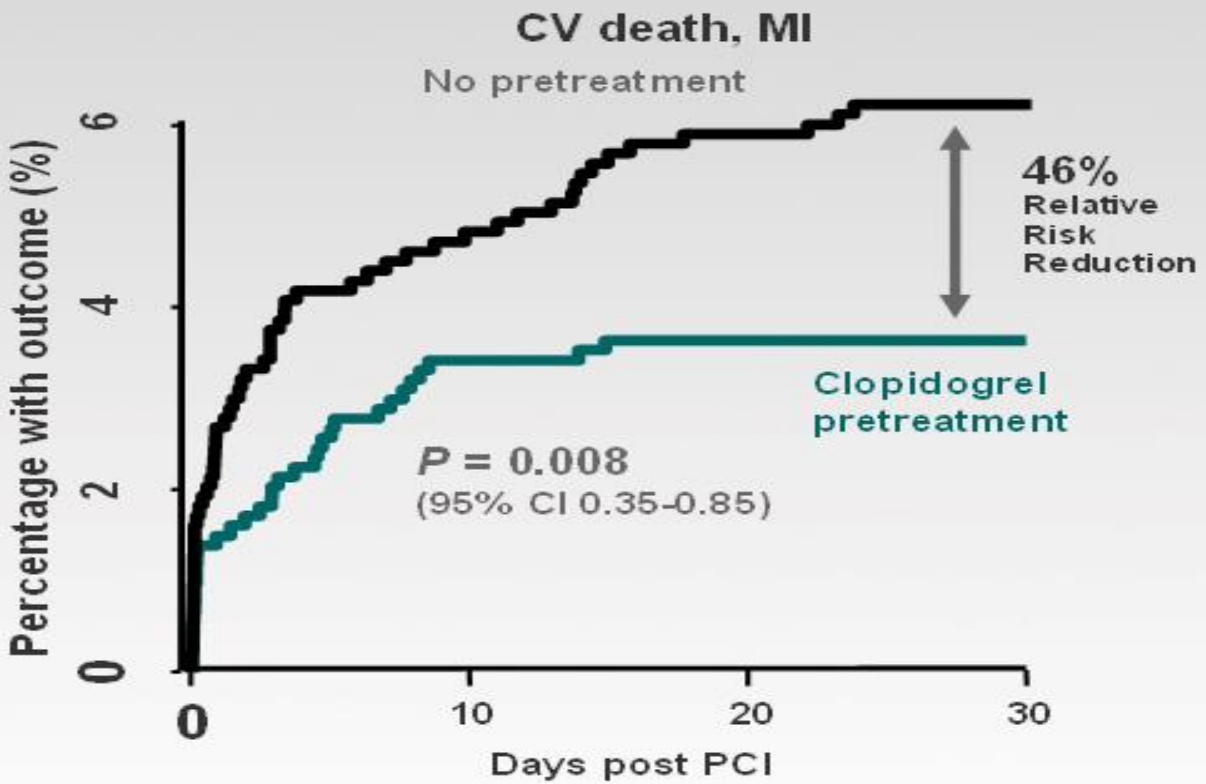
JAMA, November 20, 2002 – Vol 288, No 19: 2411 – 2420

Benefit of Clopidogrel Pretreatment: PCI CURE and PCI CLARITY

PCI-CURE



PCI – CLARITY TIMI 28



CLINICAL CARDIOLOGY

1. Mehta SR, et al. *Lancet*. 2001;358:527-533.
2. Sabatine MS, et al. *JAMA*. 2005;294:1224-1232.

Dose of Clopidogrel?

ARMYDA-2 Trial: Primary endpoint

255 patients with stable CAD or UA/NSTEMI

4-8 hours prior to PCI

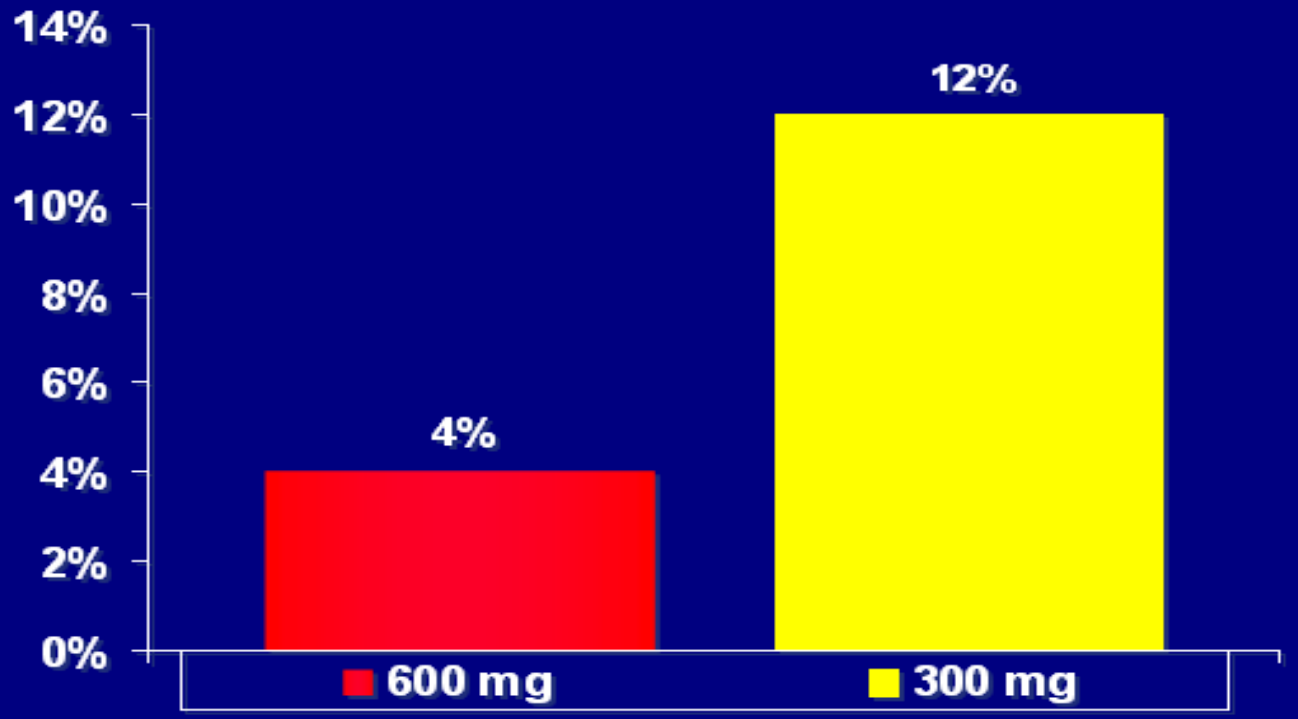
13% received IIb/IIa inhibitors and 20% drug-eluting stents

Primary Endpoint:
Composite of death, MI, or target vessel revascularization (TVR) at 30 days

Circulation 2005

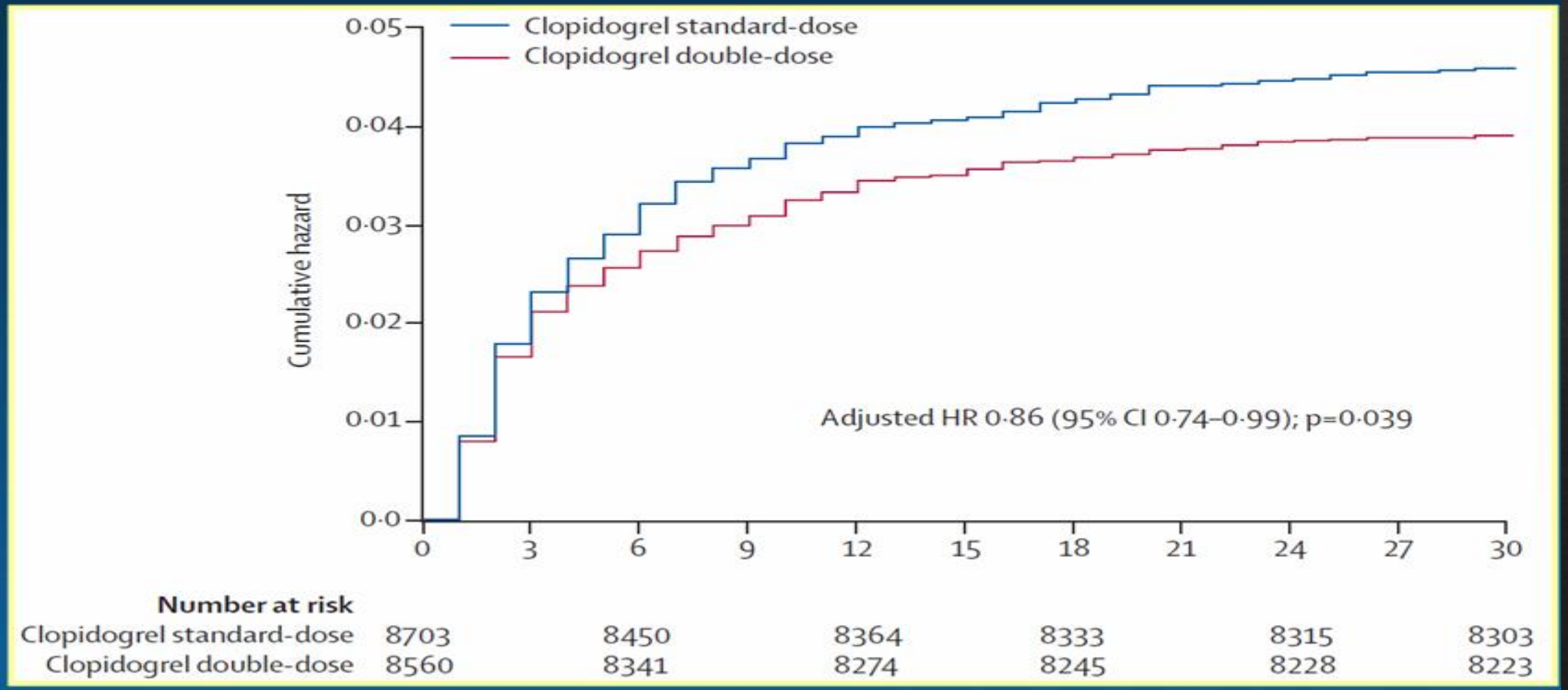
Primary Composite of death, MI, and target vessel revascularization

p = 0.04



New 2012

CURRENT-OASIS 7

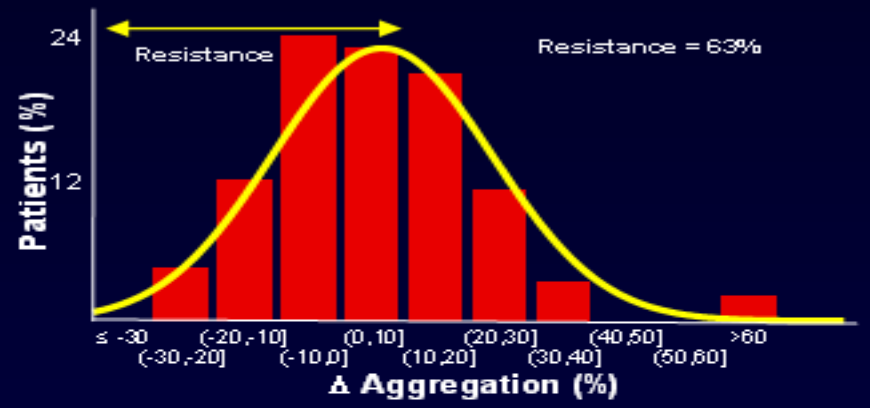


Mehta SR et al. Lancet 2010;376:1233–43

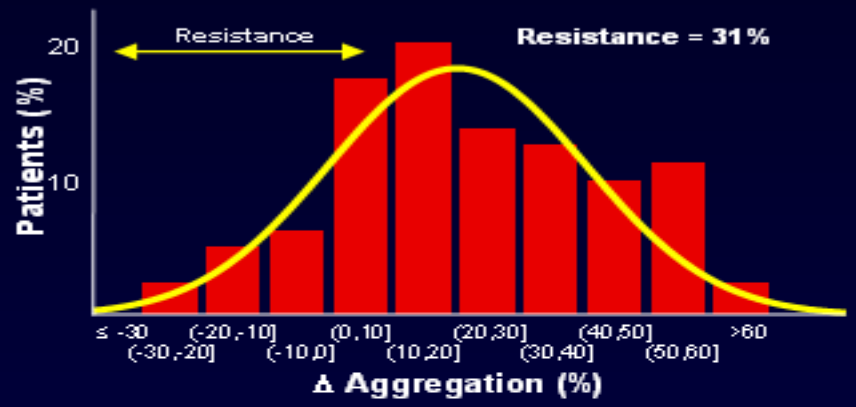
Clopidogrel Resistance

The First Clopidogrel Resistance Study (300 mg): A "Fingerprint" of Clopidogrel Response Variability

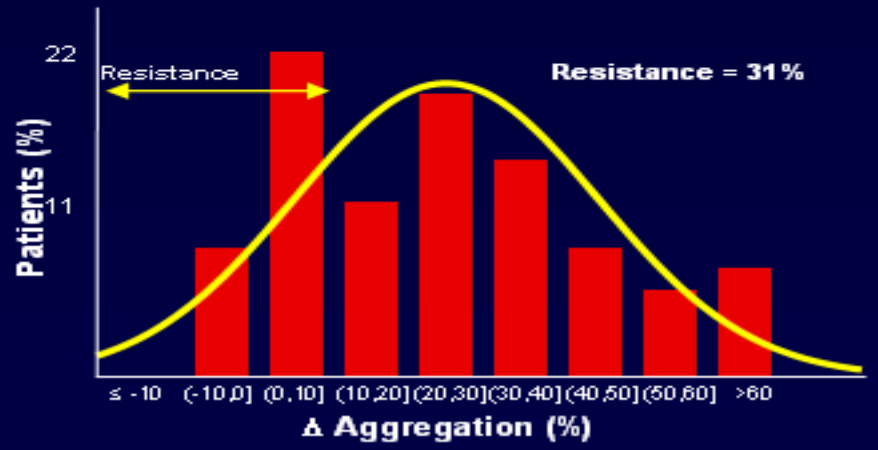
2 Hours



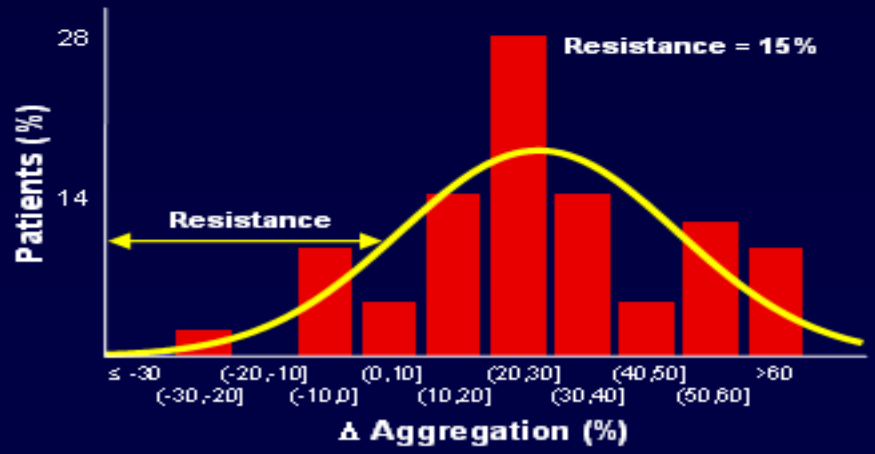
24 Hours



5 Days



30 Days

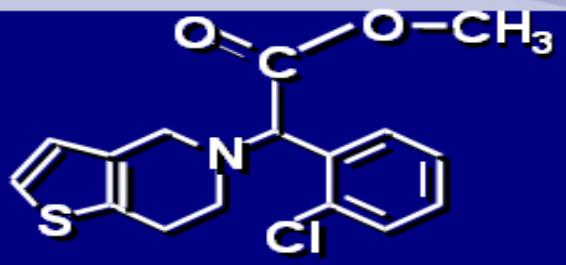


Gurbel P.A. et al. *Circulation*. 2003;107: 2908-2913

Sem Vasc Med 3:113, 2003

Sankyo Ann Report 51:1,1999

Change the Agent?



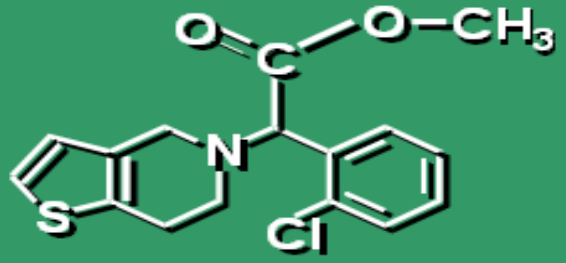
Clopidogrel

Pro-drug

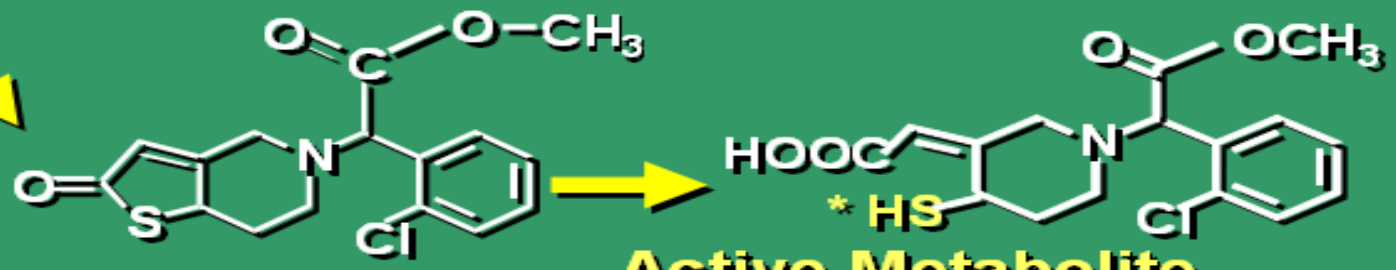
Hydrolysis
(Esterases)

Prasugrel

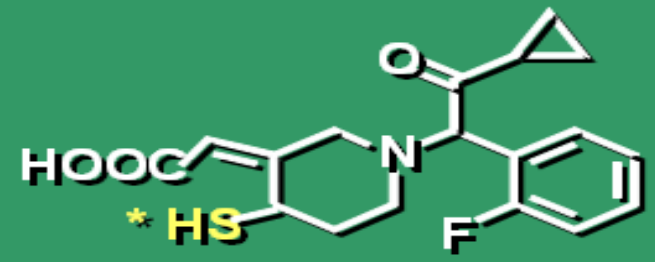
85% Inactive Metabolites
Esterases



Oxidation
(Cytochrome P450)



Active Metabolite

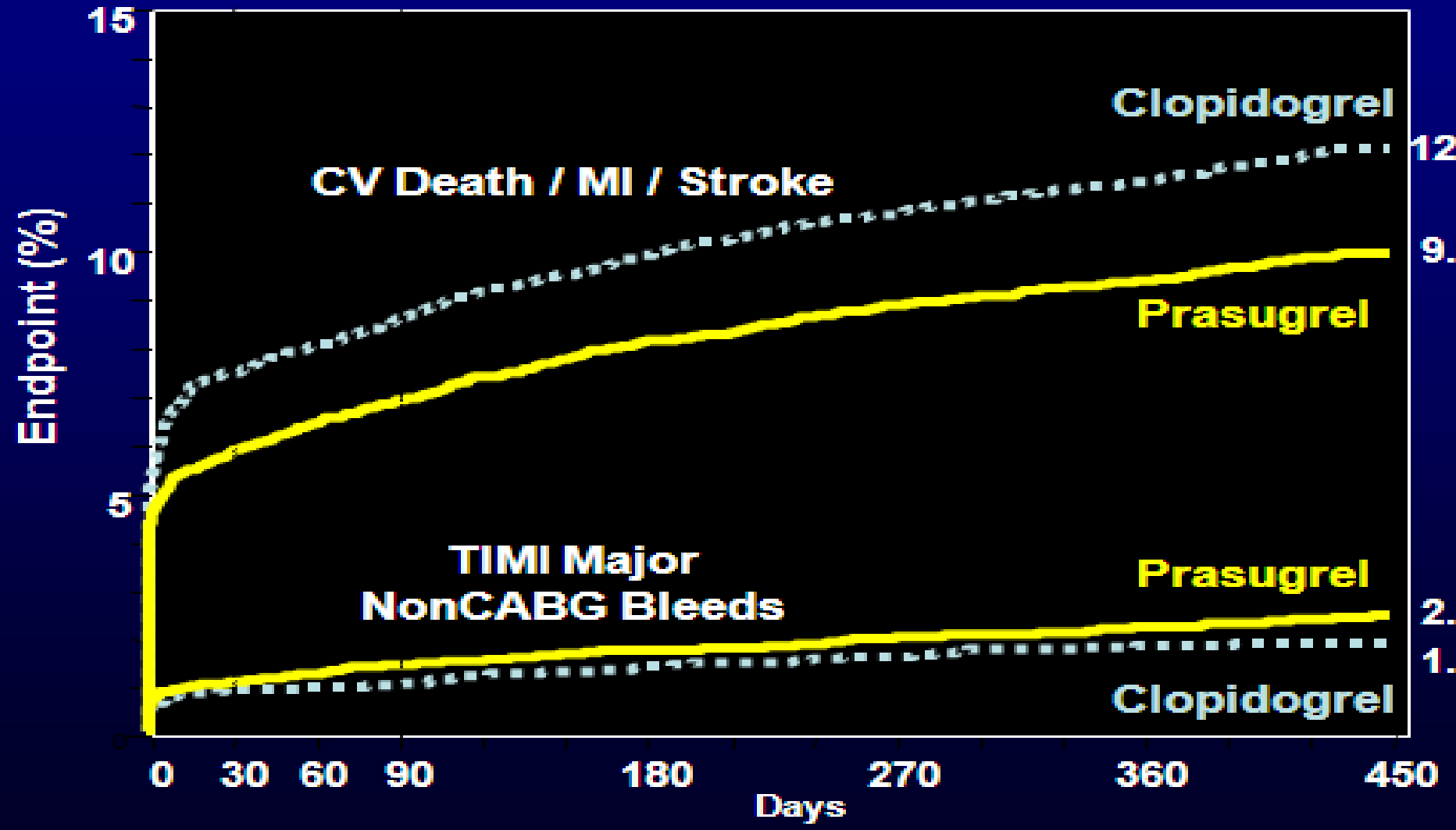


Active Metabolite

The Evidence - Prasugrel

TRÎTON TIMI-38

Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

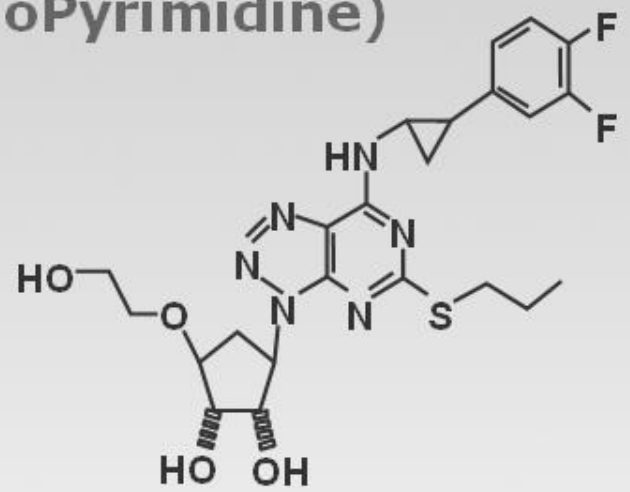
↑ 35 events

HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

AZD6140 (Ticagrelor)

A **non-thienopyridine**, in the chemical class CPTP (CycloPentylTriazoloPyrimidine)



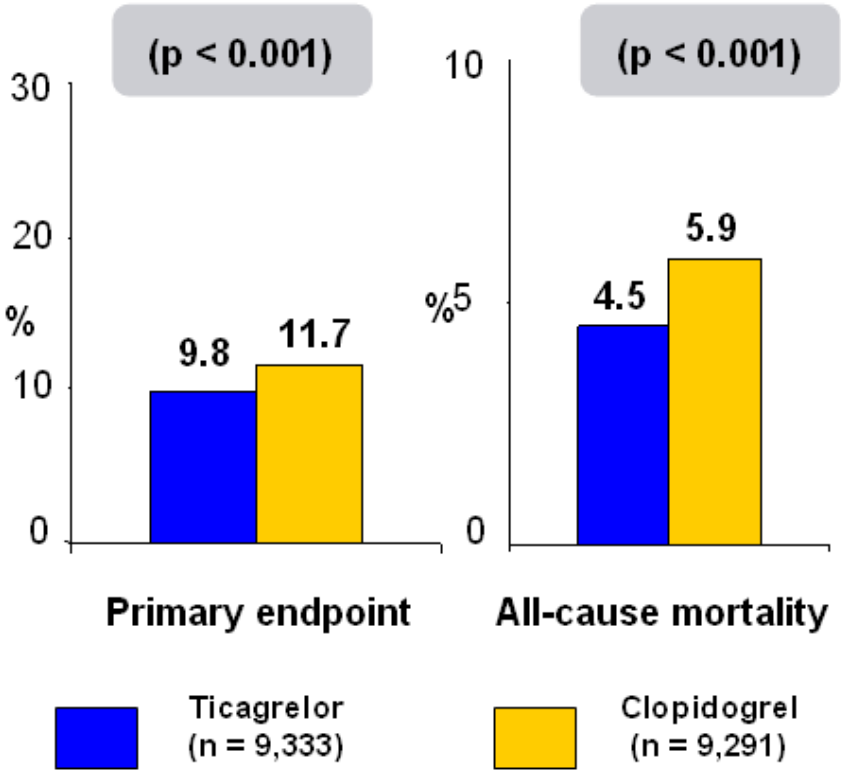
First oral **reversible** ADP $P2Y_{12}$ receptor antagonist

Direct acting via the $P2Y_{12}$ receptor - metabolism not required for activity

More potent platelet inhibitor than clopidogrel

PLATO

Trial design: Patients with ACS were randomized to ticagrelor (180 mg loading dose, 90 mg bid thereafter) or clopidogrel (300 mg loading dose, 75 mg daily thereafter). Patients were followed for 12 months.



Results

- Death from vascular cause, MI, stroke lower in ticagrelor arm, including in patients undergoing PCI
- Mortality, stent thrombosis (p = 0.02) ↓ with ticagrelor; stroke rate similar (p = 0.22)
- No increase in fatal bleeding or overall major bleeding, but higher rate of non-CABG major bleeding (p = 0.03)

Conclusions

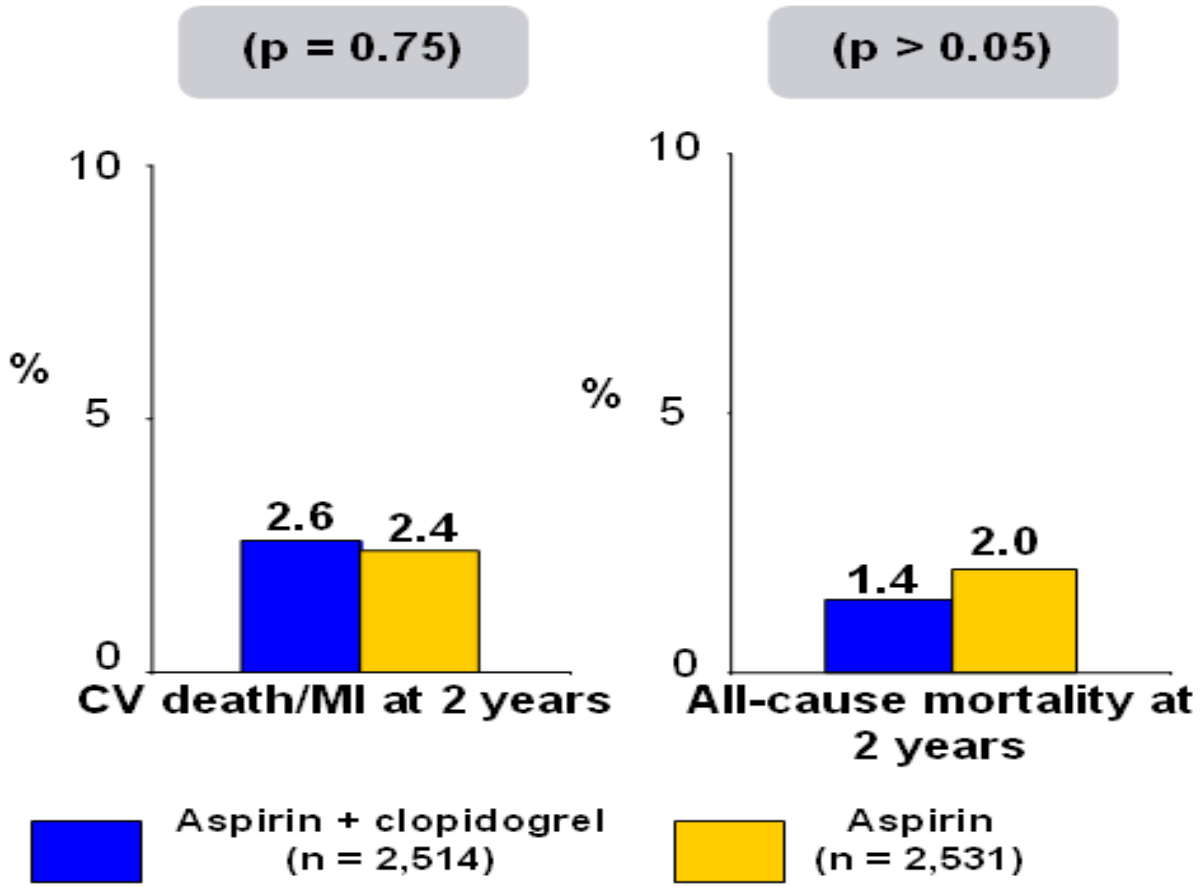
- Ticagrelor superior to clopidogrel for several outcomes including death, MI, and stent thrombosis in patients presenting with ACS
- Very promising results; reduction in CV mortality notable in the modern era of ACS

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

DAPT – duration of therapy

DES-LATE

Trial design: Patients on dual antiplatelet therapy (DAT) and with no adverse events 12 months after DES implantation were randomized to continuation of DAT for 4 years or aspirin alone. Patients were followed for a mean of 42 months.



Results

- CV death/MI were similar between DAT and aspirin arms at 2 years: 2.6% vs. 2.4%, p = 0.75; at 4 years: 4.4% vs. 5.1%, p > 0.05
- At 2 years: all-cause mortality (1.4% vs. 2.0%, p = 0.12), MI (1.2% vs. 0.8%, p = 0.23), definite stent thrombosis (0.5% vs. 0.3%, p = 0.34)
- TIMI major bleeding similar (1.1% vs. 1.4%, p = 0.20)

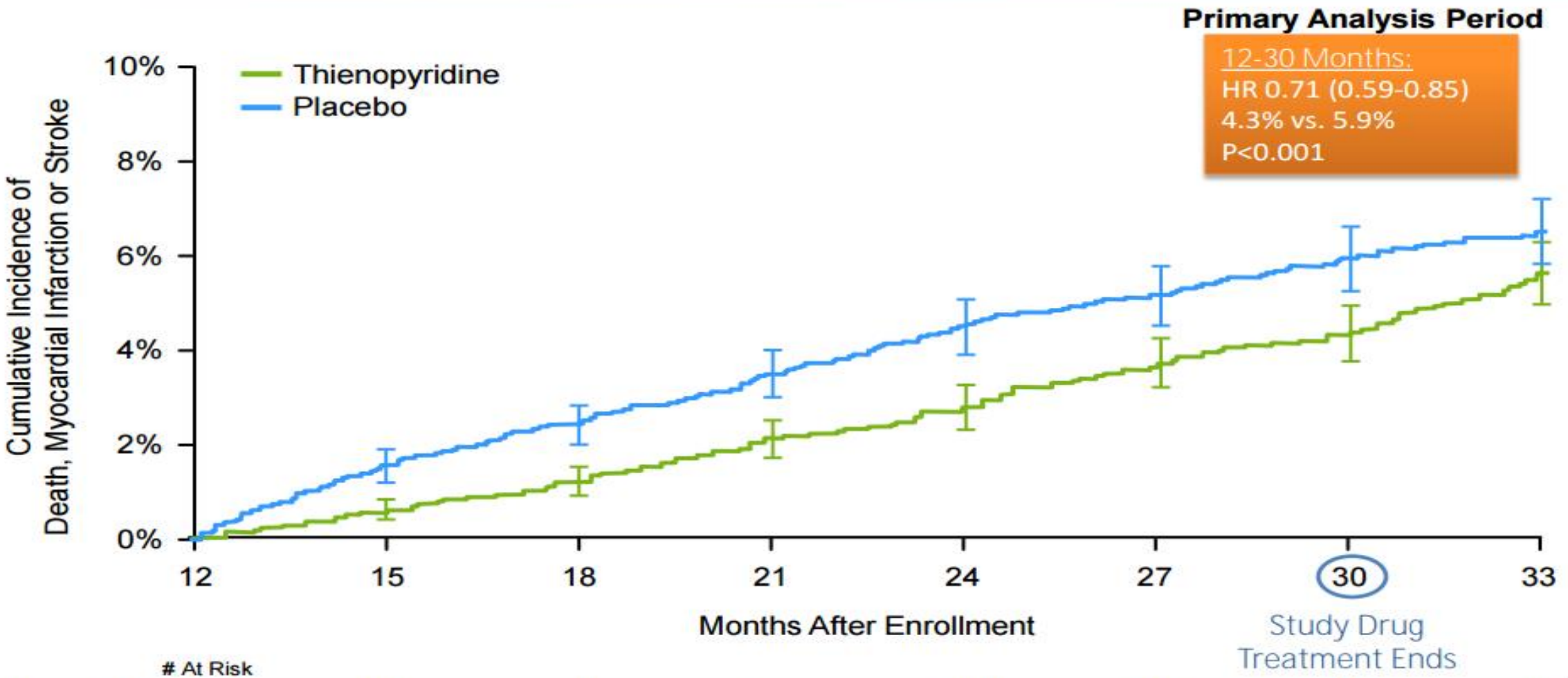
Conclusions

- Optimal duration of DAT following DES implantation is unclear; current trial suggests aspirin is similar to DAT beyond 12 months
- Significantly lower event rate than anticipated; thus, trial may be underpowered to detect differences in clinical outcomes
- Results from ongoing trials are awaited

Park SJ, et al. N Engl J Med 2010;362:1374-82
Presented by Dr. Seung-Jung Park at ACC 2013

Co-Primary Effectiveness End Point MACCE

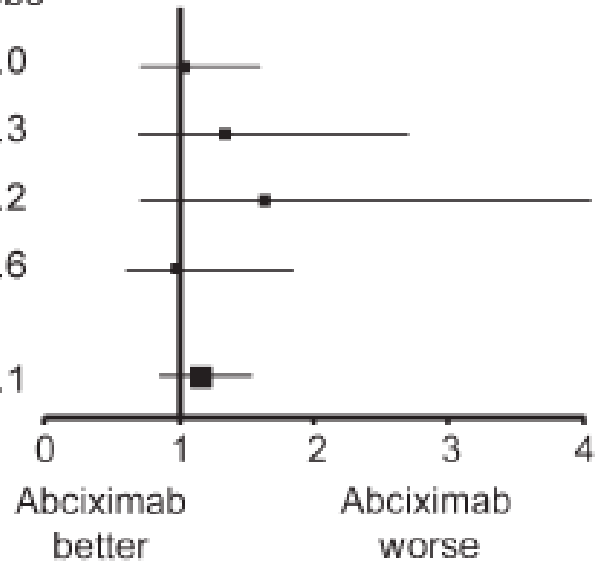
DAPT STUDY



# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

The Evidence – GP IIb/IIIa inhibitors

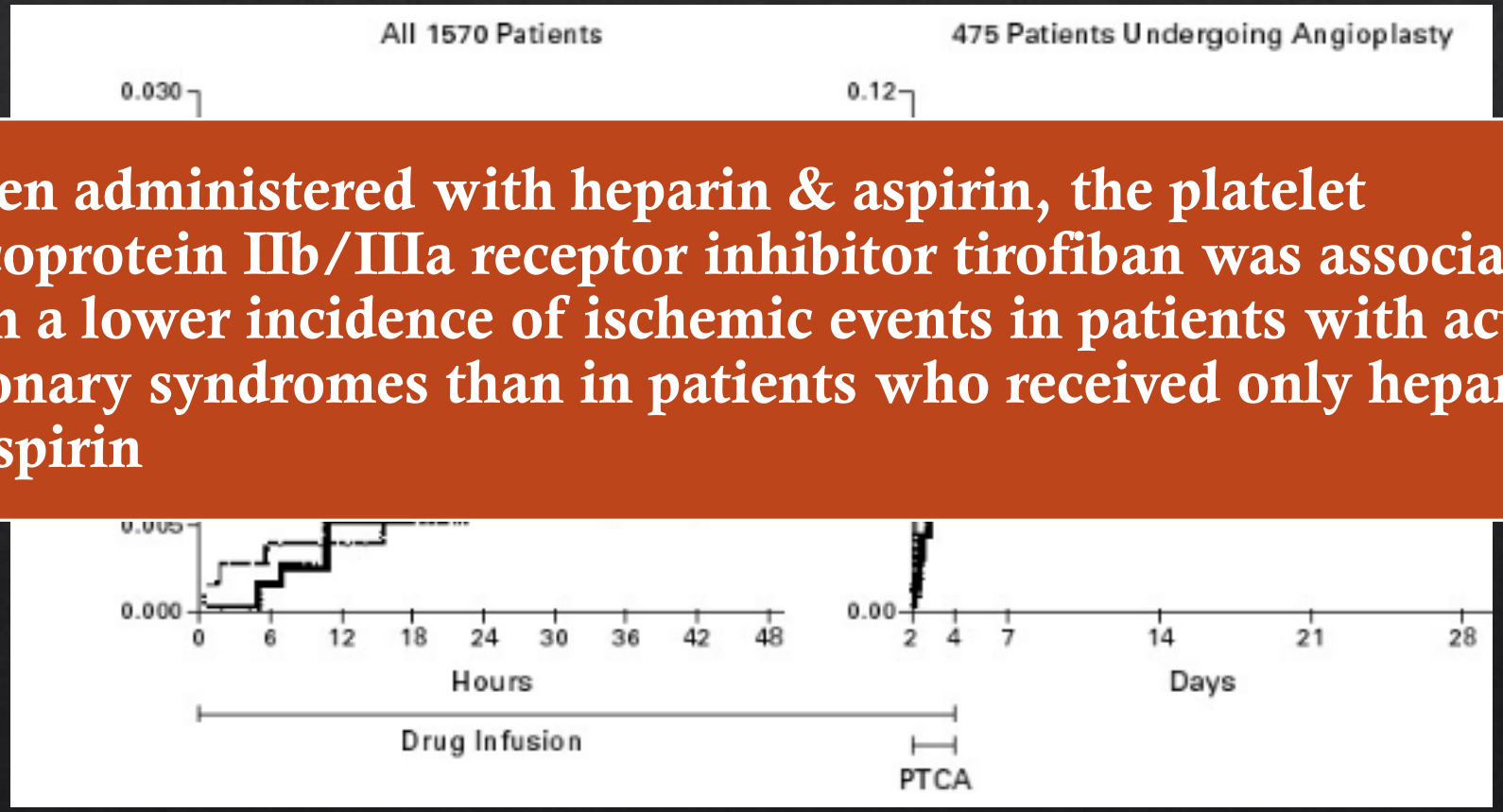
Trial	*n*	30-day Death/MI/UTVR (%) Abciximab	Placebo	Estimated odds ratio	95% CI
ISAR-REACT	2159	4.2	4.0	1.05	0.69–1.61
ISAR-SWEET	701	5.7	4.3	1.35	0.68–2.68
ISAR-SMART-2	502	5.2	3.2	1.66	0.68–4.08
ISAR-REACT-2 (T–)	973	4.6	4.6	0.99	0.55–1.81
Combined	4335	4.6	4.1	1.14	0.85–1.53



MI, myocardial infarction
UTVR, urgent target vessel revascularization
(T–), troponin negative

Inhibition of the Platelet Glycoprotein IIb/IIIa Receptor with Tirofiban in Unstable Angina & Non–Q-Wave MI

PRISM PLUS Study



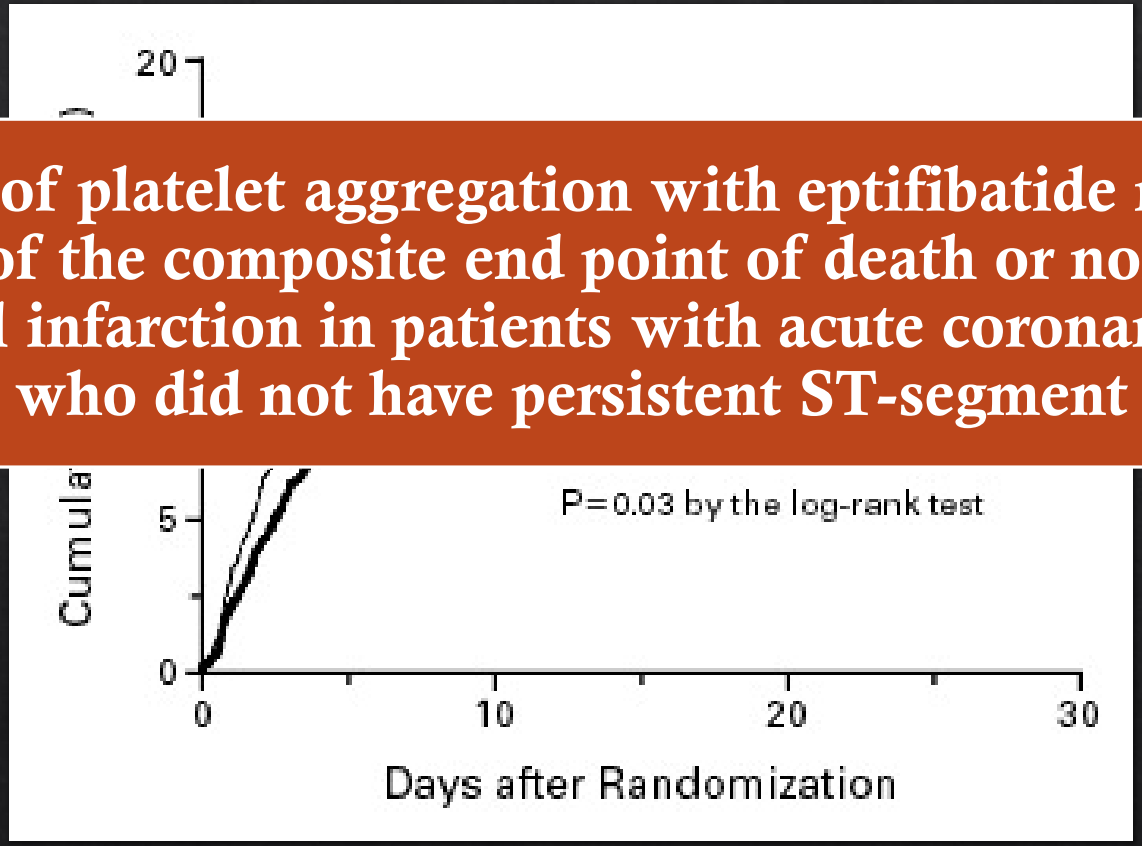
When administered with heparin & aspirin, the platelet glycoprotein IIb/IIIa receptor inhibitor tirofiban was associated with a lower incidence of ischemic events in patients with acute coronary syndromes than in patients who received only heparin & aspirin

N Engl J Med 1998; 338:1488-1497

Inhibition of Platelet Glycoprotein IIb/IIIa with Eptifibatide in Patients with NSTE – ACS:

PURSUIT Trail

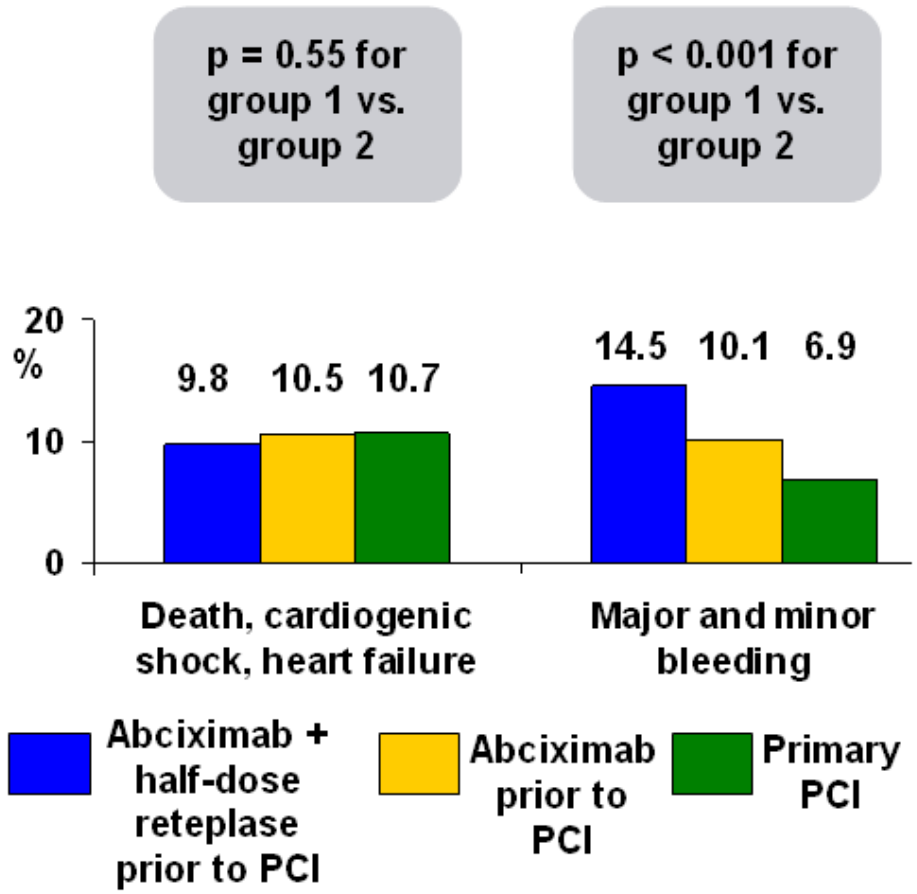
Inhibition of platelet aggregation with eptifibatide reduced the incidence of the composite end point of death or nonfatal myocardial infarction in patients with acute coronary syndromes who did not have persistent ST-segment elevation



N Engl J Med 1998; 339:436-443

FINESSE

Trial design: STEMI patients were randomized to abciximab and half-dose reteplase (n = 828), abciximab alone (n = 818), or placebo (n = 806) prior to PCI. All patients received abciximab in the catheterization laboratory, which was continued for 12 hours.



Results

- ST-segment resolution: 44% for abciximab/half-dose reteplase, 33% for abciximab alone, 31% for primary PCI (p = 0.003, group 1 vs. group 2)
- Death, cardiogenic shock, heart failure, or ventricular fibrillation at 90 days: 9.8%, 10.5%, 10.7% (p = 0.55), respectively
- Bleeding: 14.5%, 10.1%, 6.9% (p < 0.001), respectively

Conclusions

- PCI facilitated by abciximab and half-dose reteplase or abciximab alone is not superior to primary PCI with abciximab
- Facilitated PCI is associated with improved ST-segment resolution; however, this approach results in similar major adverse events and increased bleeding

Ellis SG, et al. N Engl J Med 2008;358:2205-17

Early versus Delayed, Provisional Eptifibatide in ACS

Early ACS trial

The use of eptifibatide ≥12 h before angiography was not superior to the provisional use of eptifibatide after angiography, and was associated with an increased risk of non–life-threatening bleeding and need for transfusion

New 2012

Giugliano RP, et al. N Engl J Med 2009;360:2176

GUIDELINES

Antiplatelet Therapy to Support Primary PCI for STEMI

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

- DAPT with a combination of aspirin and prasugrel or aspirin & ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI
- Prasugrel 10mg/day and ticagrelor 90mg BD for 1 year with DES & BMS

Recommendation is based on the 2 studies namely TRITION TIMI and PLATO

European Heart Journal (2012) 33, 2569–2619

Maintenance dose of Antiplatelets

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day*

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

GP IIb/IIIa to Support Primary PCI for STEMI

It is reasonable to start treatment with an intravenous GP IIb/IIIa receptor antagonist at the time of primary PCI (with or without stenting or clopidogrel pretreatment) in selected patients with STEMI who are receiving UFH.

- **Abciximab:** 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min); or
- **High-bolus-dose tirofiban**: 25 mcg/kg IV bolus, then 0.15 mcg/kg/min; or
- **Double-bolus eptifibatide**: 180 mcg/kg IV bolus, then 2 mcg/kg/min; a 2nd 180-mcg/kg bolus is administered 10 min after the 1st bolus.

Antiplatelet Therapy to Support Primary PCI for STEMI

It may be reasonable to administer intravenous GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, ED) to patients with STEMI for whom primary PCI is intended.

It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI.

Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy

Aspirin		
• 162- to 325-mg loading dose given with fibrinolytic agent (before PCI). (Section 5.1.4.1 and Table 7)	I	A
• 81- to 325-mg daily maintenance dose after PCI (indefinite)	I	A
• 81 mg daily is the preferred daily maintenance dose	IIa	B
P2Y$_{12}$ receptor inhibitors		
Loading doses		
For patients who received a loading dose of clopidogrel with fibrinolytic therapy:		
• Continue clopidogrel 75 mg daily without an additional loading dose	I	C
For patients who have not received a loading dose of clopidogrel:		
• If PCI is performed ≤24 h after fibrinolytic therapy: clopidogrel 300-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 h after fibrinolytic therapy: clopidogrel 600-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 h after treatment with a fibrin-specific agent or >48 h after a non–fibrin-specific agent: prasugrel 60 mg at the time of PCI	IIa	B
For patients with prior stroke/TIA: prasugrel	III: Harm	B
Maintenance doses and duration of therapy		
DES placed: Continue therapy for at least 1 y with:		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B
BMS placed: Continue therapy for at least 30 d and up to 1 y with:*		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

- DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:
  - 1 month for patients receiving BMS
  - 6 months for patients receiving DES
- DAPT should be used up to 1 year in patients with STEMI who did not receive a stent

European Heart Journal (2012) 33, 2569–2619

2012 ACC/AHA Guidelines for UA/NSTEMI

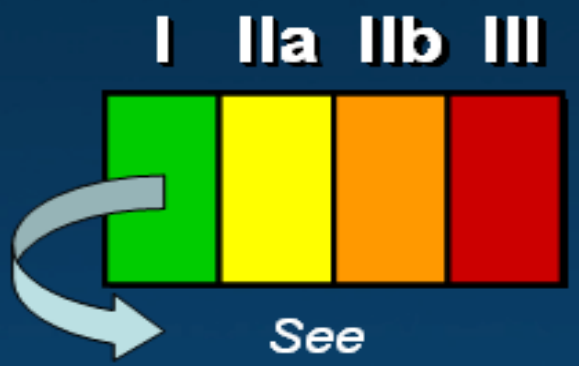
Before PCI:

- Clopidogrel *(Level of Evidence: B)*; or
- Ticagrelor *(Level of Evidence: B)*; or
- An IV GP IIb/IIIa inhibitor. *(Level of Evidence: A)* IV eptifibatide and tirofiban are the preferred GP IIb/IIIa inhibitors. *(Level of Evidence: B)*

At the time of PCI:

- Clopidogrel if not started before PCI *(Level of Evidence: A)*; or
- Prasugrel *(Level of Evidence: B)*; or
- Ticagrelor *(Level of Evidence: B)*; or
- An IV GP IIb/IIIa inhibitor. *(Level of Evidence: A)*

2012 ACC/AHA Guidelines for UA/NSTEMI



A loading dose of $P2Y_{12}$ receptor inhibitor therapy is recommended for UA/NSTEMI patients for whom PCI is planned. One of the following regimens should be used:

a. Clopidogrel 600 mg should be given as early as possible before or at the time of PCI *(Level of Evidence: B) or*

b. Prasugrel 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and

a decision is made to proceed with PCI *(Level of Evidence: B) or*

c. Ticagrelor 180 mg should be given as early as possible before or at the time of PCI. *(Level of Evidence: B)*

Prasugrel should not be used in…

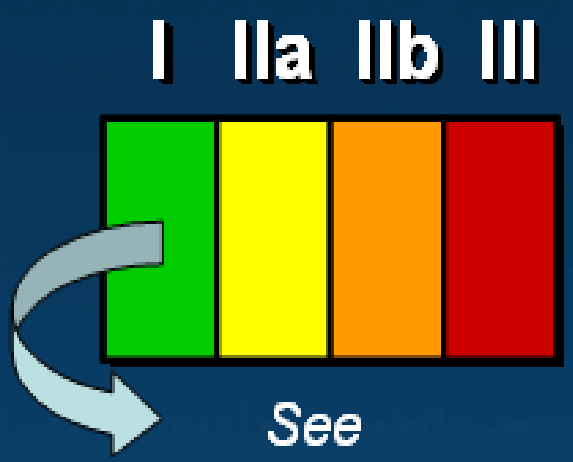
- Previous history of Stroke / TIA
- Weight < 60 kg
- Age > 75 years

2012 ACC/AHA Guidelines for UA/NSTEMI

Abciximab **should not be administered** to patients in whom PCI is not planned.

In UA/NSTEMI patients who are at low risk for ischemic events (e.g., TIMI risk score 2) or at high risk of bleeding and who are already receiving aspirin and a P2Y12 receptor inhibitor, upstream GP IIb/IIIa inhibitors **are not recommended**.

2012 ACC/AHA Guidelines for UA/NSTEMI



The duration and maintenance dose of $P2Y_{12}$ receptor inhibitor therapy should be as follows:

a. In UA/NSTEMI patients undergoing PCI, either clopidogrel 75 mg daily, prasugrel 10 mg daily, or Ticagrelor 90 mg twice daily should be given for at least 12 months. *(Level of Evidence: B)*

b. If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered. *(Level of Evidence: C)*

MEDICAL MANAGEMENT IN ACS

Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy in STEMI

Aspirin		
• 162- to 325-mg loading dose	I	A
• 81- to 325-mg daily maintenance dose (indefinite)	I	A
• 81 mg daily is the preferred maintenance dose	IIa	B
$P2Y_{12}$ receptor inhibitors		
• Clopidogrel:	I	A
• Age ≤75 y: 300-mg loading dose		
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d)
		C (up to 1 y)
• Age >75 y: no loading dose, give 75 mg	I	A
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d)
		C (up to 1 y)

ACC/ AHA 2012 UA/NSTEMI

- For UA/NSTEMI patients in whom an initial conservative (ie, noninvasive) strategy is selected, clopidogrel or ticagrelor (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for up to 12 months

Conclusions

- Overall, in the TRILOGY ACS Trial prasugrel did not reduce cardiovascular events among patients managed medically for ACS.
- When treated with prasugrel compared to clopidogrel, patients triaged to medical therapy following angiography tended to have:
  - Lower rates of the combined endpoint of CVD/MI/CVA
  - Lower rates of MI, CVA alone, and recurrent ischemic events
  - A trend to higher rates of TIMI major bleeding.
- Though hypothesis generating, these results are consistent with previous trials and suggest that when angiography is performed and coronary disease is confirmed, the benefits and risks of intensive antiplatelet therapy exist whether medical therapy or PCI is elected.

Antiplatelets in patients on anticoagulants

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

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Summary

Background If percutaneous coronary intervention (PCI) is required in patients taking oral anticoagulants, antiplatelet therapy with aspirin and clopidogrel is indicated, but such triple therapy increases the risk of serious bleeding. We investigated the safety and efficacy of clopidogrel alone compared with clopidogrel plus aspirin.

Methods We did an open-label, multicentre, randomised, controlled trial in 15 centres in Belgium and the Netherlands. From November, 2008, to November, 2011, adults receiving oral anticoagulants and undergoing PCI were assigned clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). The primary outcome was any bleeding episode within 1 year of PCI, assessed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00769938.

Findings 573 patients were enrolled and 1-year data were available for 279 (98·2%) patients assigned double therapy and 284 (98·3%) assigned triple therapy. Mean ages were 70·3 (SD 7·0) years and 69·5 (8·0) years, respectively. Bleeding episodes were seen in 54 (19·4%) patients receiving double therapy and in 126 (44·4%) receiving triple therapy (hazard ratio [HR] 0·36, 95% CI 0·26–0·50, p<0·0001). In the double-therapy group, six (2·2%) patients had multiple bleeding events, compared with 34 (12·0%) in the triple-therapy group. 11 (3·9%) patients receiving double therapy required at least one blood transfusion, compared with 27 (9·5%) patients in the triple-therapy group (odds ratio from Kaplan-Meier curve 0·39, 95% CI 0·17–0·84, p=0·011).

Interpretation Use of clopiogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events.

Conclusion

- Dual antiplatelet therapy with aspirin and P2Y12 antagonists is the cornerstone of therapy after ACS.
- Prasugrel reduces ischemic events, compared to clopidogrel, in pt undergoing PCI but at the cost of higher bleeding risk.
- Ticagrelor also reduces ischemic events and cardiovascular mortality while not increasing the overall bleeding risk but non CABG related bleeding was increased.
- Genetic polymorphism which can alter clopidogrel efficacy but does not influence clinical effectiveness of prasugrel or ticagrelor

THANK YOU