



Clinical experience with novel antiplatelet therapy ticagrelor: which patients benefit the most?

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Ticagrelor – who benefits most ?

STOP. EFFECTS

The concept ...



The topics

- ▶ **Guidelines**
 - ▶ **Evidence on ticagrelor**
 - ▶ **Evidence analysis**
 - ▶ **Subgroups who benefit most**
 - ▶ **Ticagrelor – a drug for the widest spectrum of ACS ?**
-

Guidelines

ACCF/AHA Practice Guideline



EUROPEAN
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CARDIOLOGY®

European Heart Journal (2011) **32**, 2999–3054

doi:10.1093/eurheartj/ehr236

ESC GUIDELINES



EUROPEAN
SOCIETY OF
CARDIOLOGY®

European Heart Journal (2010) **31**, 2501–2555

doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES



EUROPEAN
SOCIETY OF
CARDIOLOGY®

European Heart Journal (2012) **33**, 2569–2619

doi:10.1093/eurheartj/ehs215

ESC GUIDELINES

Th

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Ca

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

ACCF/AHA NSTEMI 2012

3.2. Recommendations for Antiplatelet/Anticoagulant Therapy in Patients for Whom Diagnosis of UA/NSTEMI Is Likely or Definite (UPDATED)

3.2.1. Antiplatelet Therapy: Recommendations (UPDATED)

2. A loading dose followed by daily maintenance dose of either clopidogrel (*Level of Evidence: B*),^{249,378,379} prasugrel† (in PCI-treated patients) (*Level of Evidence: C*),³⁸⁰ or ticagrelor‡ (*Level of Evidence: C*)³⁸¹ should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major GI intolerance.

A)^{370,372–377} The choice of a second antiplatelet therapy to be added to aspirin on presentation includes 1 of the following (note that there are no data for therapy with 2 concurrent P2Y₁₂ receptor inhibitors, and this is not recommended in the case of aspirin allergy):

Before PCI:

- a. Clopidogrel (*Level of Evidence: B*)^{249,382}; or
- b. Ticagrelor‡ (*Level of Evidence: B*)³⁸¹; or
- c. An IV GP IIb/IIIa inhibitor. (*Level of Evidence: A*)^{135,137,383,385,386} IV eptifibatid and tirofiban are the preferred GP IIb/IIIa inhibitors. (*Level of Evidence: B*)^{135,137}

At the time of PCI:

- a. Clopidogrel if not started before PCI (*Level of Evidence: A*)^{249,382}; or
- b. Prasugrel† (*Level of Evidence: B*)³⁸⁰; or
- c. Ticagrelor‡ (*Level of Evidence: B*)³⁸¹; or
- d. An IV GP IIb/IIIa inhibitor. (*Level of Evidence: A*)^{135,137,387}

4. 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. (*Level of Evidence: B*)^{249,381,388}

ACCF/AHA STEMI 2013

4.4.1. Antiplatelet Therapy to Support Primary PCI for STEMI: Recommendations

CLASS I

1. Aspirin 162 to 325 mg should be given before primary PCI (251–253). (*Level of Evidence: B*)
 2. After PCI, aspirin should be continued indefinitely (254,255,257). (*Level of Evidence: A*)
 3. A loading dose of a P2Y₁₂ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include
 - a. Clopidogrel 600 mg (253,258,259) (*Level of Evidence: B*); or
 - b. Prasugrel 60 mg (260) (*Level of Evidence: B*); or
 - c. Ticagrelor 180 mg (261). (*Level of Evidence: B*)
-

ESC Myocardial Revascularization 2010

Antithrombotic treatment options in myocardial revascularization

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel ^d	IIa	B
	Ticagrelor ^d	I	B

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel ^f (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel ^d	I	B
	Ticagrelor ^d	I	B

ESC NSTEACS 2011

Recommendations for oral antiplatelet agents

Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y ₁₂ -inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications. ^d	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B

ESC STEMI 2012

Periprocedural antithrombotic medication in primary percutaneous coronary intervention

Antiplatelet therapy		
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B
• <u>Ticagrelor.</u>	I	B
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C

The evidence:

- Prasugrel – **TRITON-TIMI 38*** (13.608)
- Ticagrelor – **PLATO**** (18.624)

* Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15

** Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.

Evidence analysis

prasugrel

ticagrelor

▶ patient profile

- older (>75y)
- fragile (<60kg)
- prior stroke/TIA



▶ adverse effects

- dyspnea
- bradycardia



Subgroup analysis

prasugrel

ticagrelor

► efficacy

- CV death



► ACS treatment

- PCI
- CABG
- medical



Who will benefit most ?



ACS Case

- F, 70y
- hypertension, DM, dyslipidemia, smoker
- 1.2.2013. STEMI inf.

TIMI score 4, mort. 7,6%
GRACE score 141, mort.17%

- agregometry (patient included in a study), randomized to standard clopidogrel dose. Results known later: clopidogrel hypo reactor
-

STEMI 2012: antithrombotic therapy

Antiplatelet therapy

Aspirin oral or i.v. (if unable to swallow) is recommended	I	B
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A
<ul style="list-style-type: none">Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age < 75 years.	I	B
<ul style="list-style-type: none">Ticagrelor.	I	B
<ul style="list-style-type: none">Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C



Tica-grelor

HZZO

Acute STEMI



PCI result



STEMI 2012: antithrombotic therapy

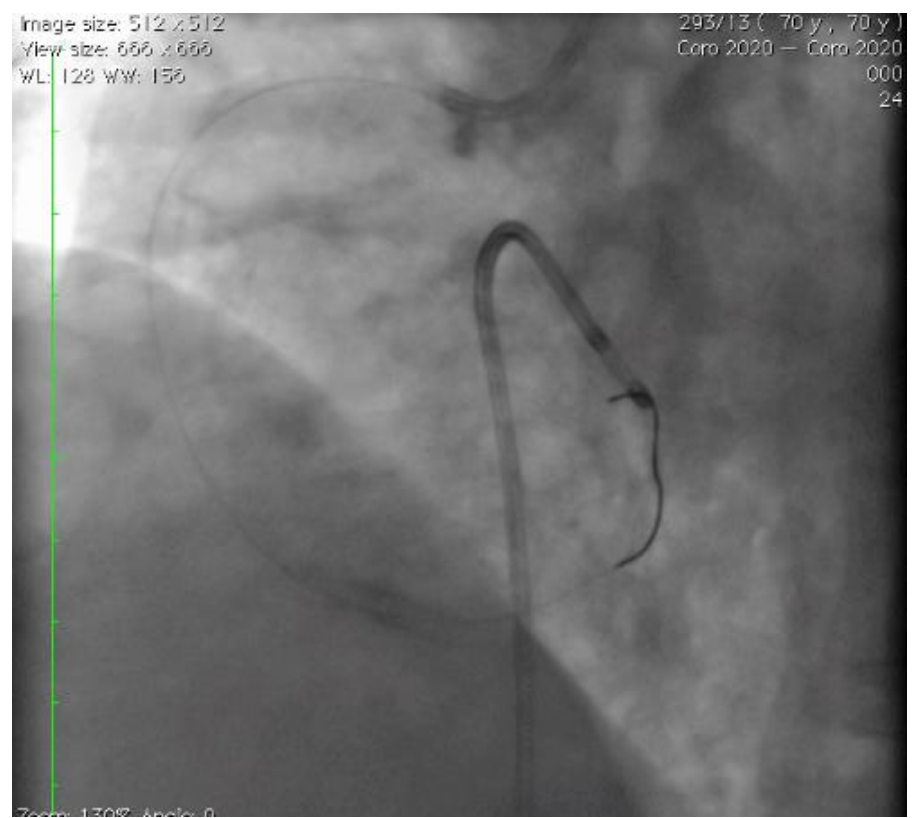
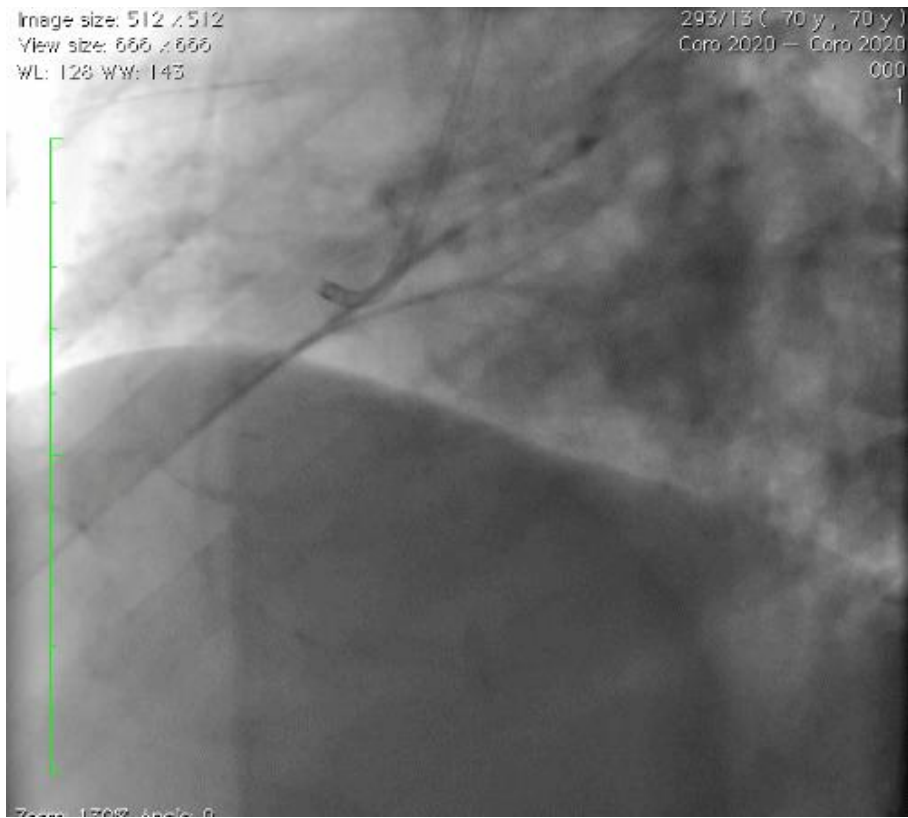
Antiplatelet therapy with low dose aspirin (75-100 mg) is indicated indefinitely after STEMI.	I	A
In patients who are intolerant to aspirin, clopidogrel is indicated as an alternative to aspirin.	I	B
DAPT with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI	I	A
DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of: <ul style="list-style-type: none">• 1 month for patients receiving BMS;• 6 months for patients receiving DES.	I	C
	I	C
	IIb	B

IST

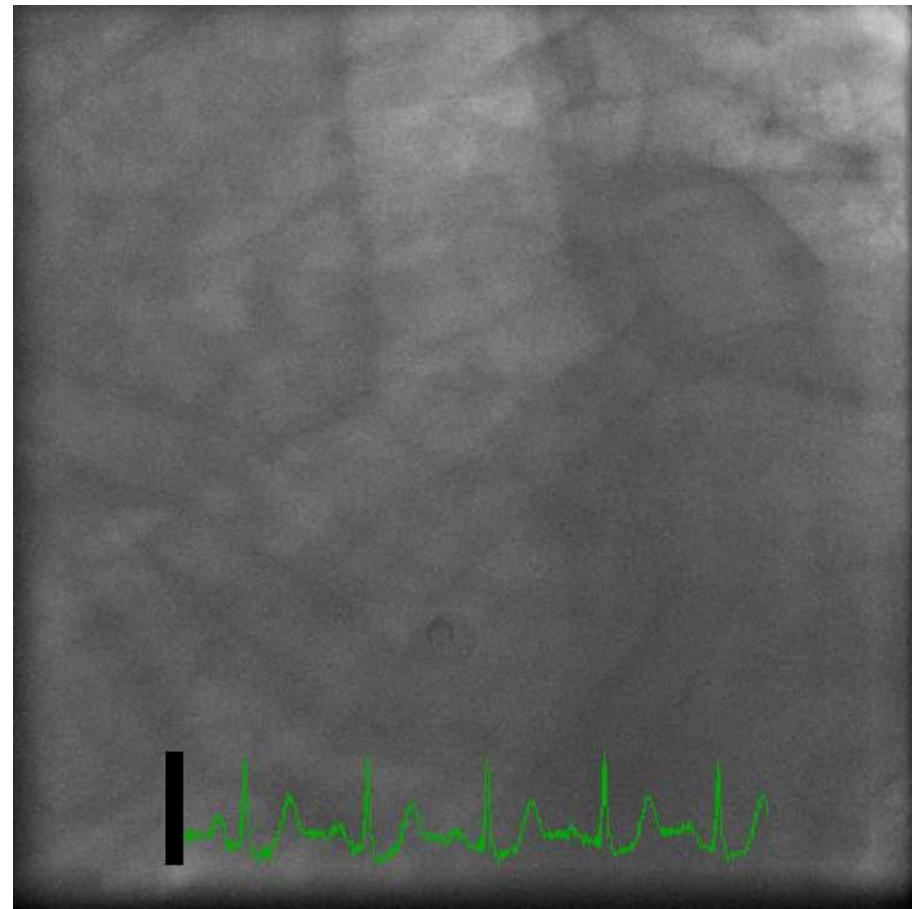
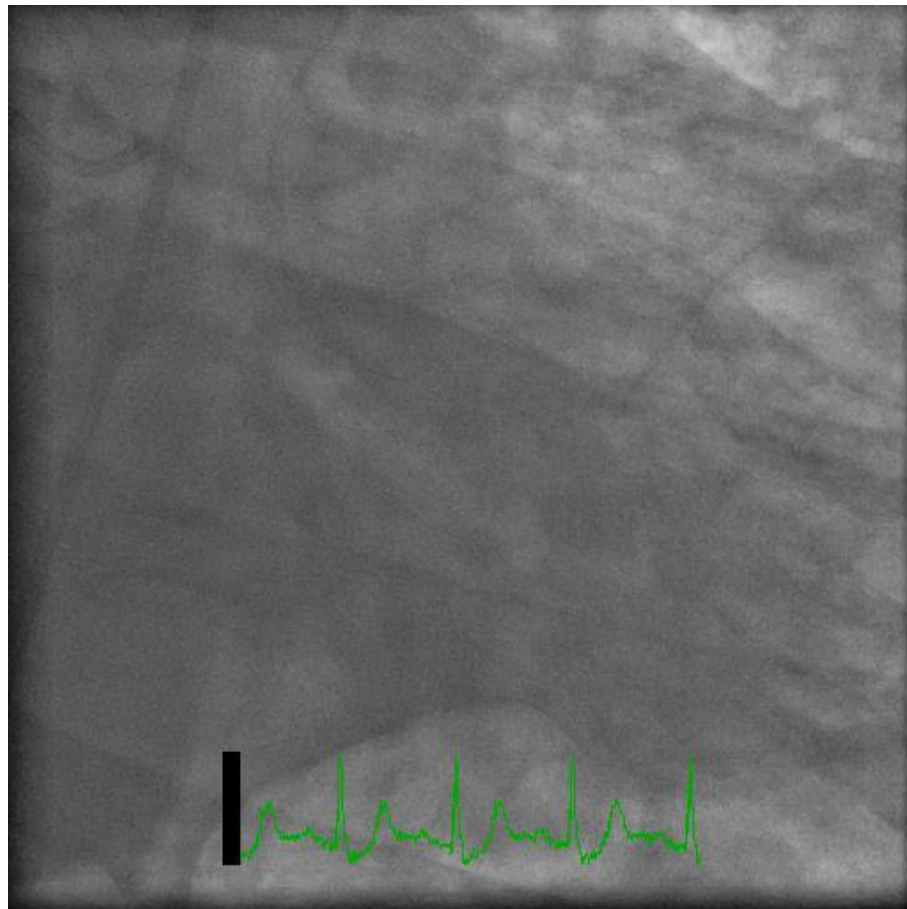
- referred for CABG, surgery delayed (DAPT). Finally patient refused surgery!
- 11.2.2013. re-STEMI, IST, cardiogenic shock, AV block III, VT, mechanic ventilation, TIA?
- rePCI, GP 2b/3a, ECG normalization in inf. leads

TIMI score 10, mort. 38,7%
GRACE score 215, mort. 80%

IST

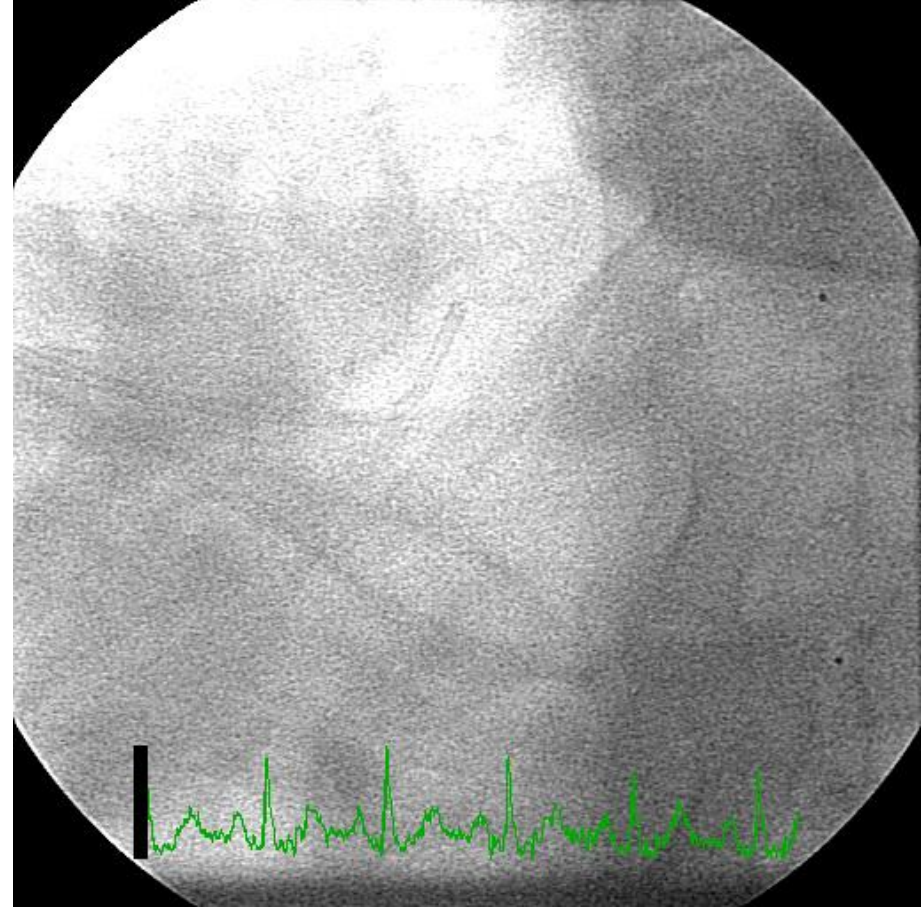
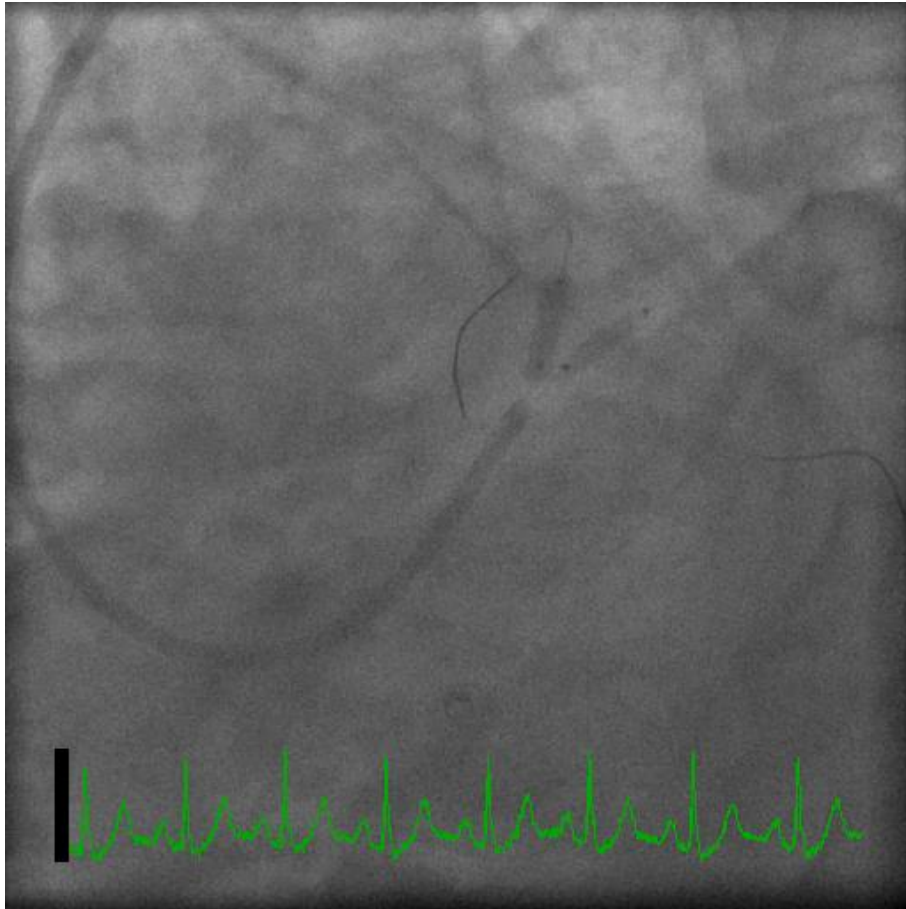


Case 2 – How would you treat ?



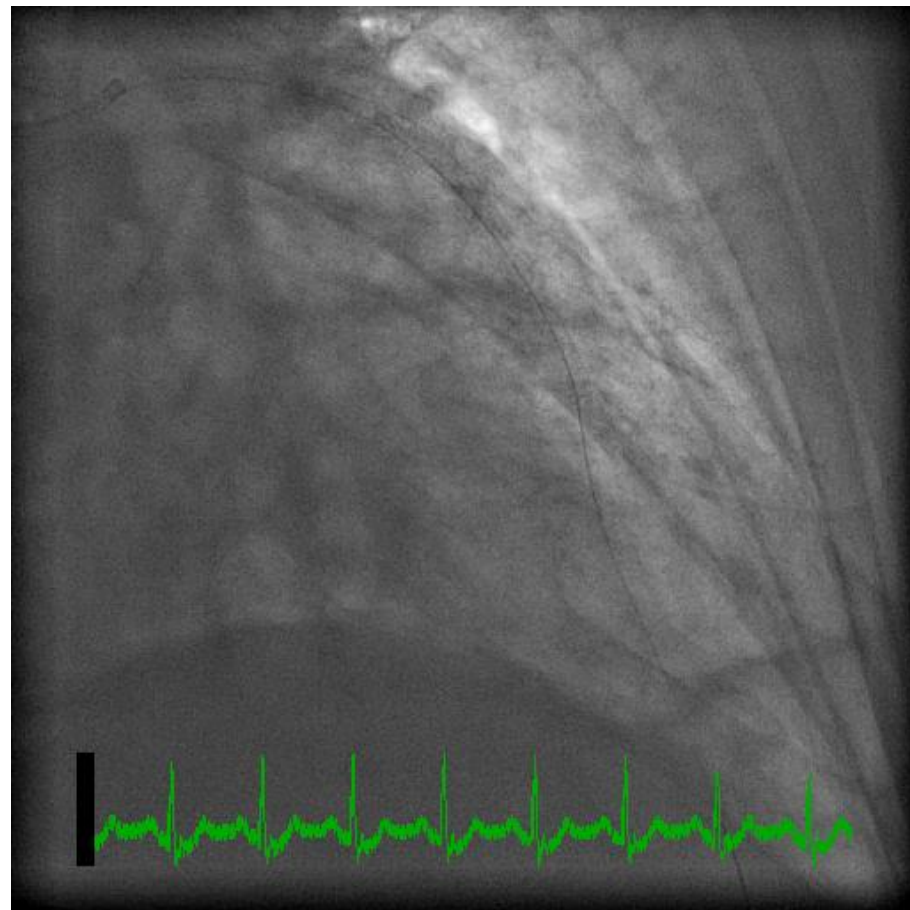
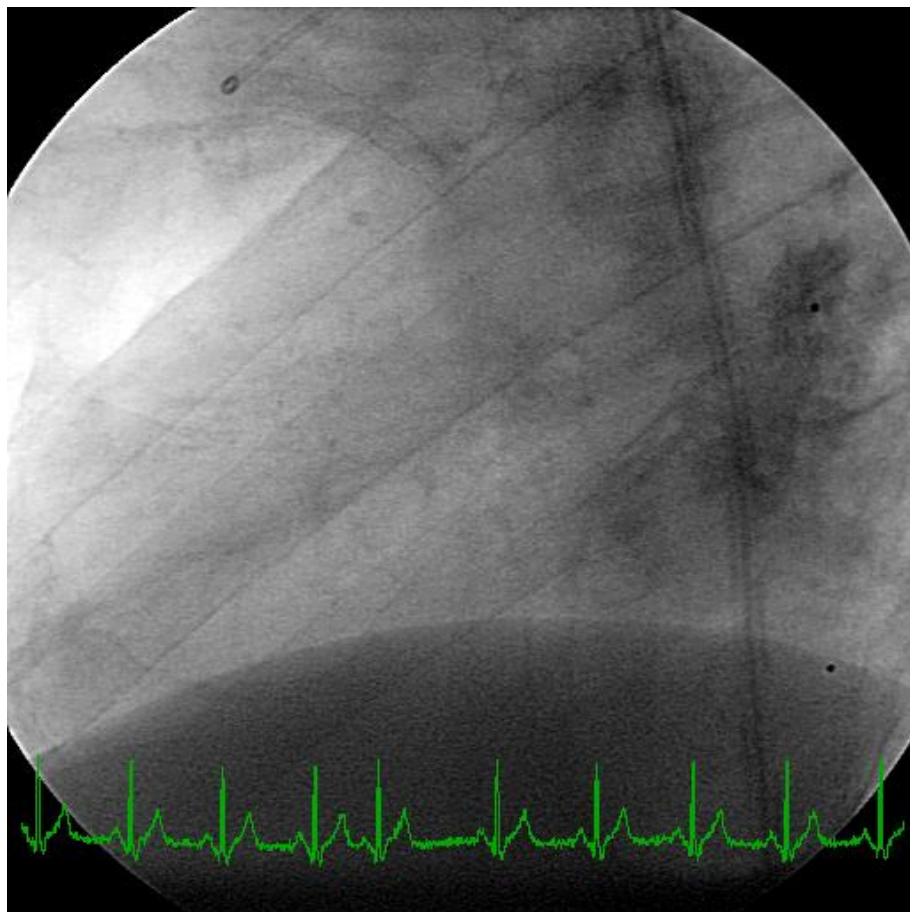
m, 53 y, anterior STEMI

Case 2 – How did I treat ?



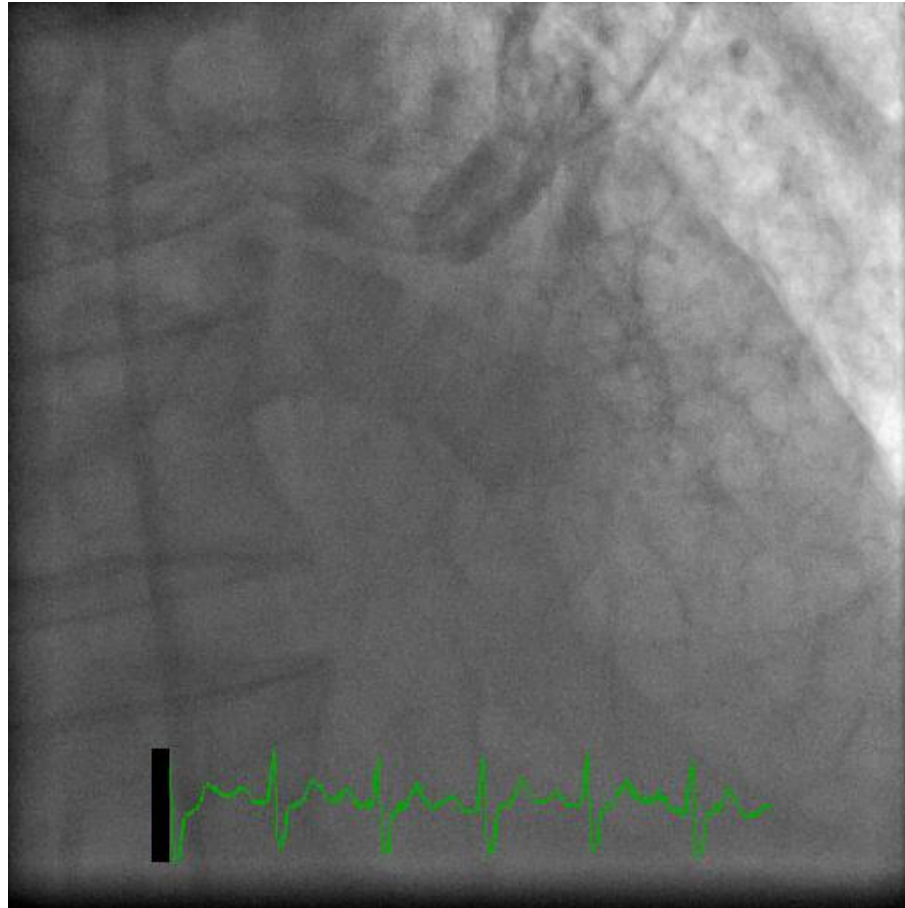
1 manual aspiration, 3 wires & 2 stents later...

Case 3 – How would you treat ?



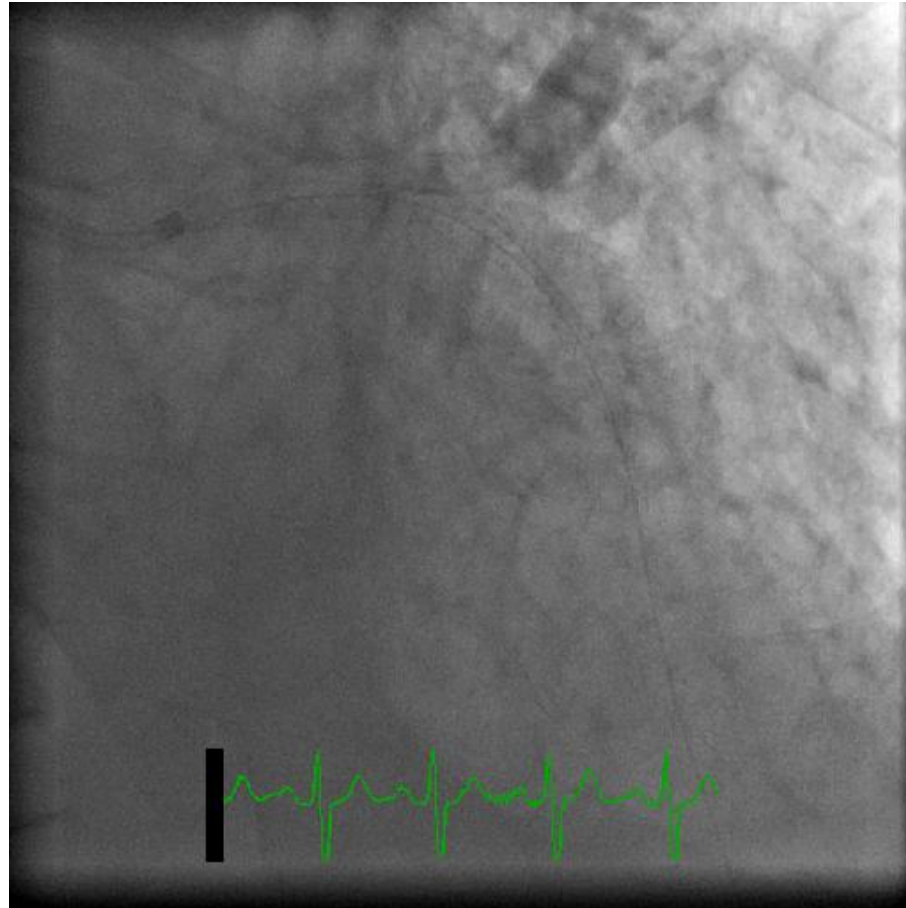
m, 71 y, s/p CABG, NSTEMACS

Case 3 – How would you treat ?



on day 6 – subac. thrombosis...

Case 3 – How did we treat ?



on day 6 – subac. thrombosis, aspiration only...

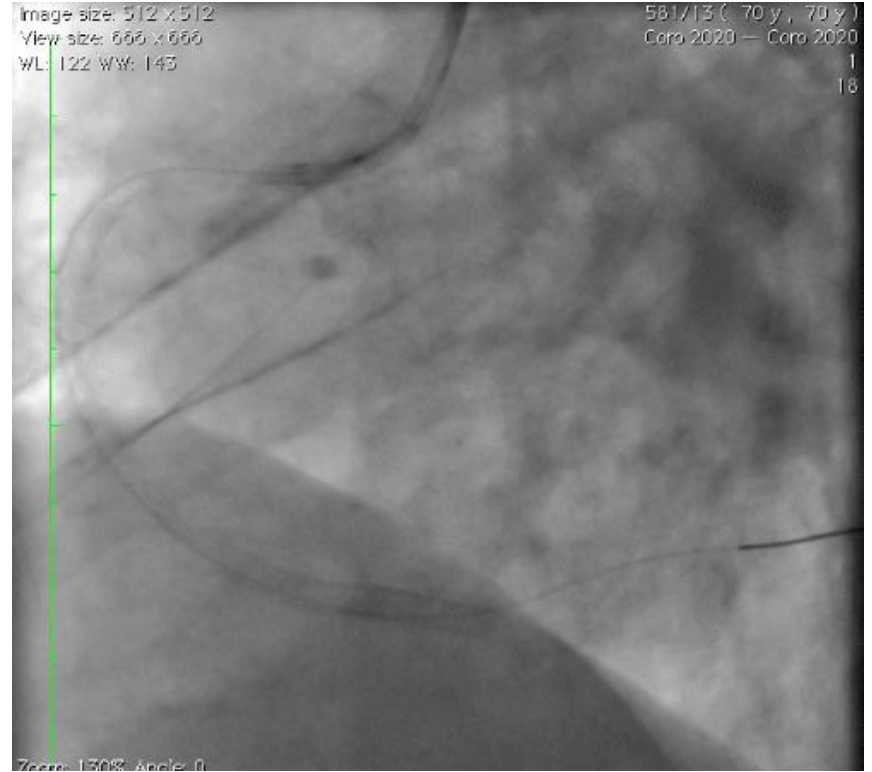
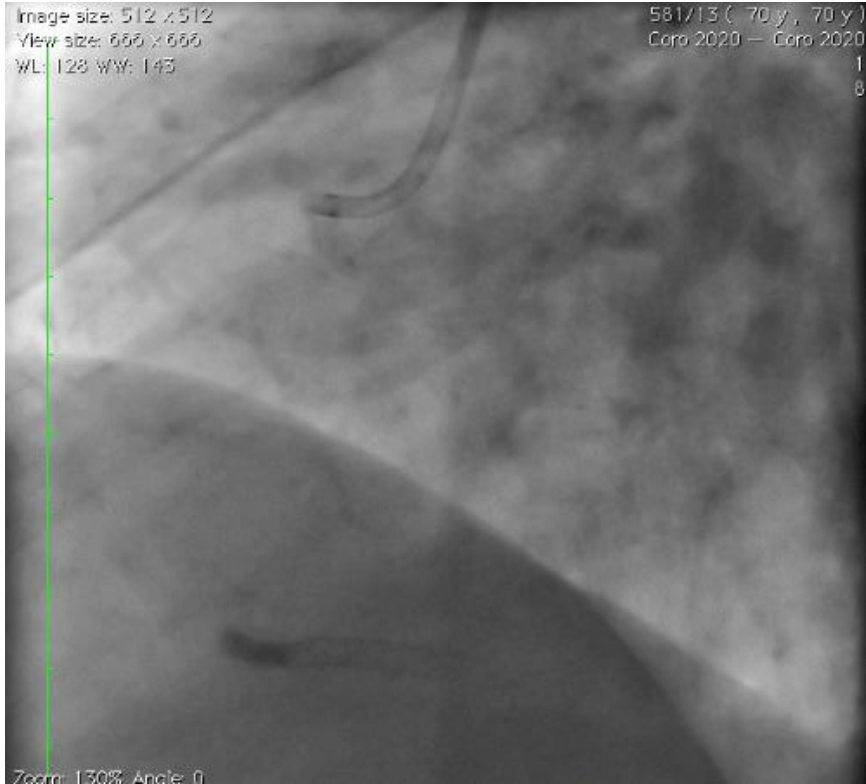
PLATO study: In stent thrombosis

Patients with intent for invasive treatment	Ticagrelor (n=6732)	Clopidogrel (n=6676)	HR for ticagrelor (95% CI)	P value
Stent thrombosis, n (%)				
<i>Definite</i>	71 (1.3)	106 (1.9)	0.67 (0.50-0.91)	0.0091
<i>Probable + Definite</i>	118 (2.1)	158 (2.8)	0.75 (0.59-0.95)	0.0167
<i>Possible + Probable + Definite</i>	155 (2.8)	202 (3.6)	0.77 (0.62-0.95)	0.0131

Second IST

- **20.3.2013. re-re-STEMI inf**
 - **re-re-PCI RCA, good clinical recovery, EHO – EF 40%**
 - **stable angina III st**
-

Second IST



**high risk ACS, potential CABG,
clopidogrel hypo reactor, repeat in
stent thrombosis**

Stable angina 2013: antithrombotic therapy

Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption.

IIa

C

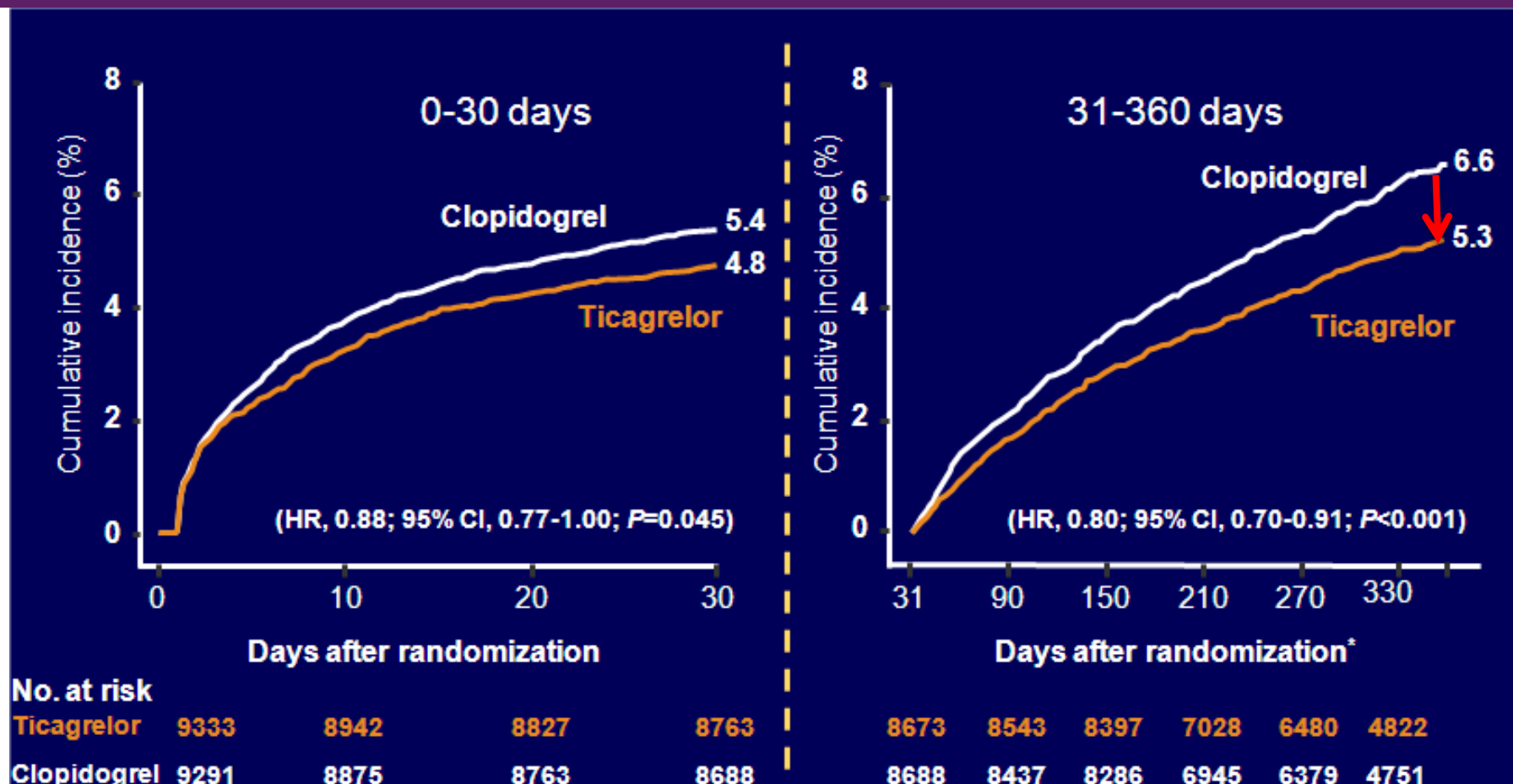
Prasugrel or ticagrelor may be considered in specific high risk situations of elective stenting (e.g. left main stenting; high risk of stent thrombosis; diabetes).

IIb

C

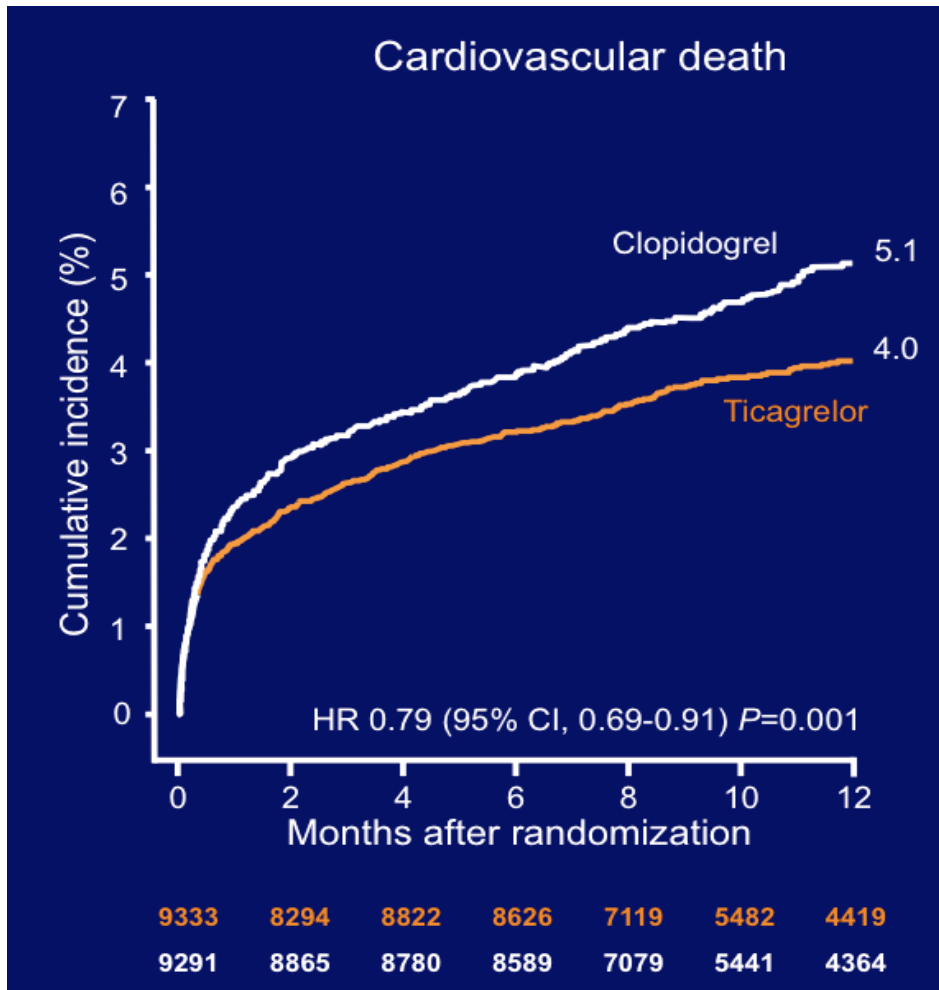
Ticagrelor should or may be considered in some stable patients after PCI

PLATO outcomes (early and late period)



MACE reduction benefite increase by time.

PLATO study



- Significant reduction of cardiovascular death (4,0 to 5,1% in 12 months)
- Treating 1000 patients with ticagrelor, 14 lives can be saved

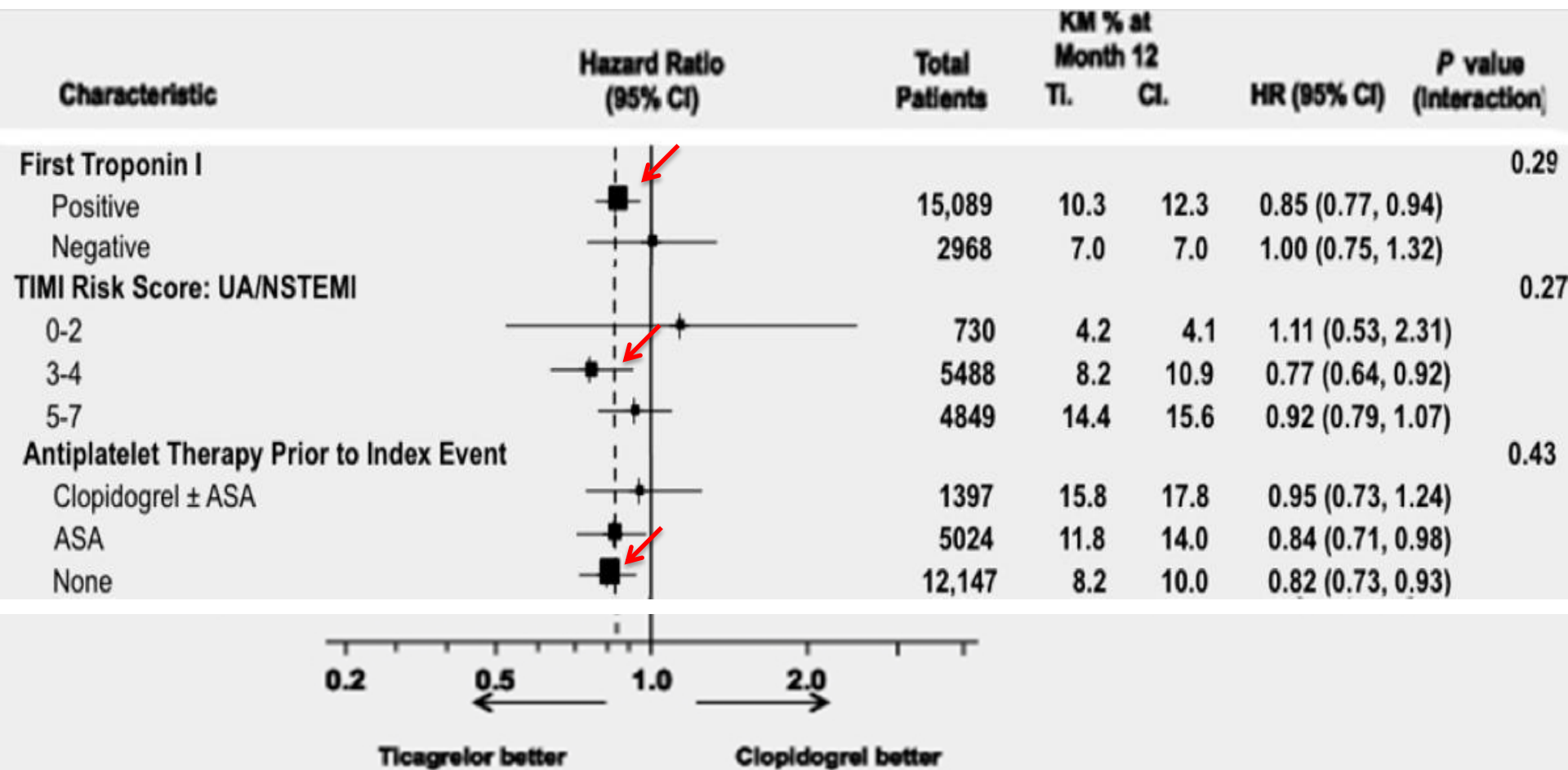
My questions after PLATO

Study has shown superiority of the new drug. Considering the price, can we give it to all ACS patients?

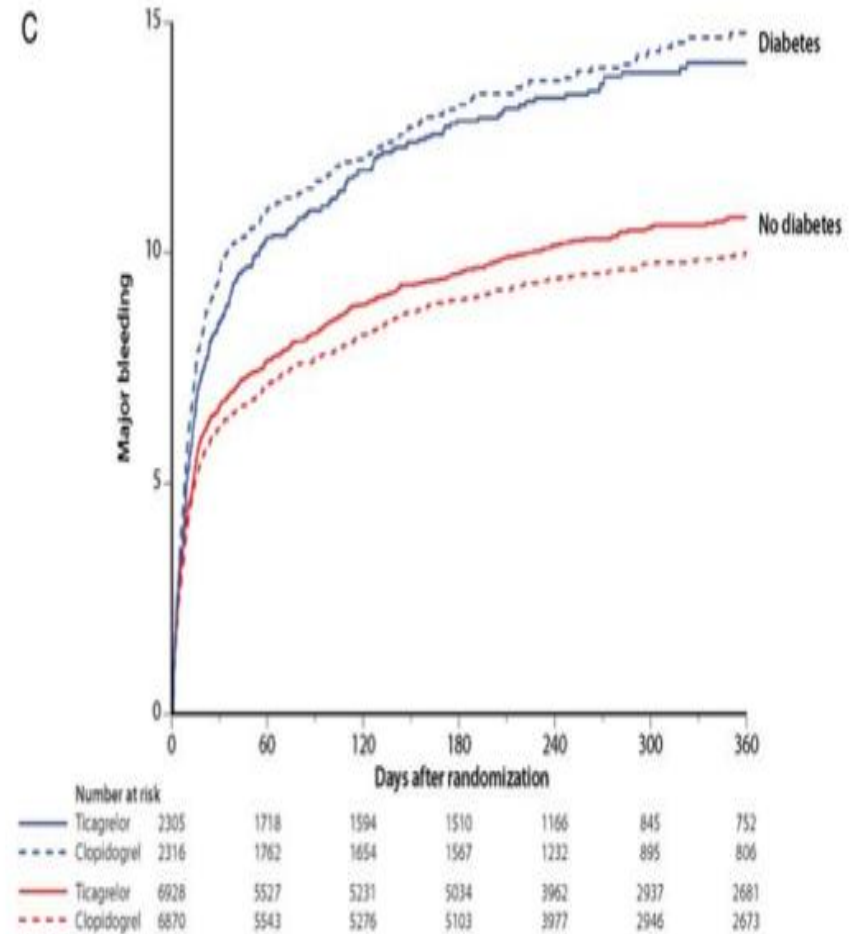
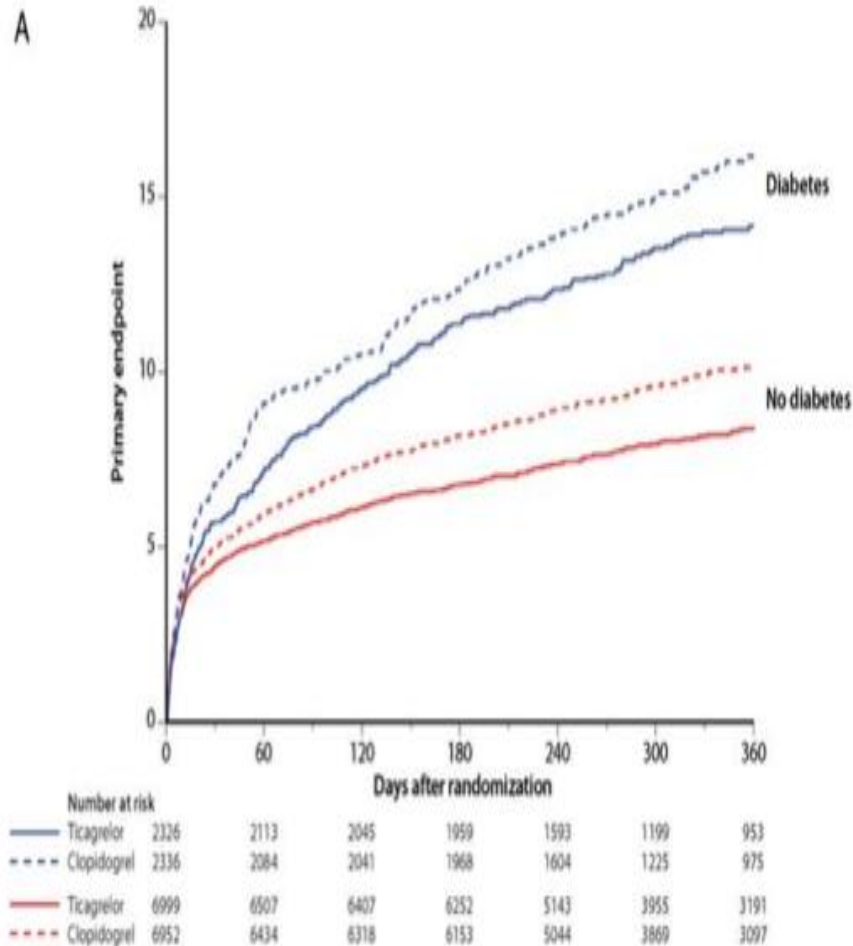
Probably not

Can we identify a group of patients who would benefit most from ticagrelor therapy?

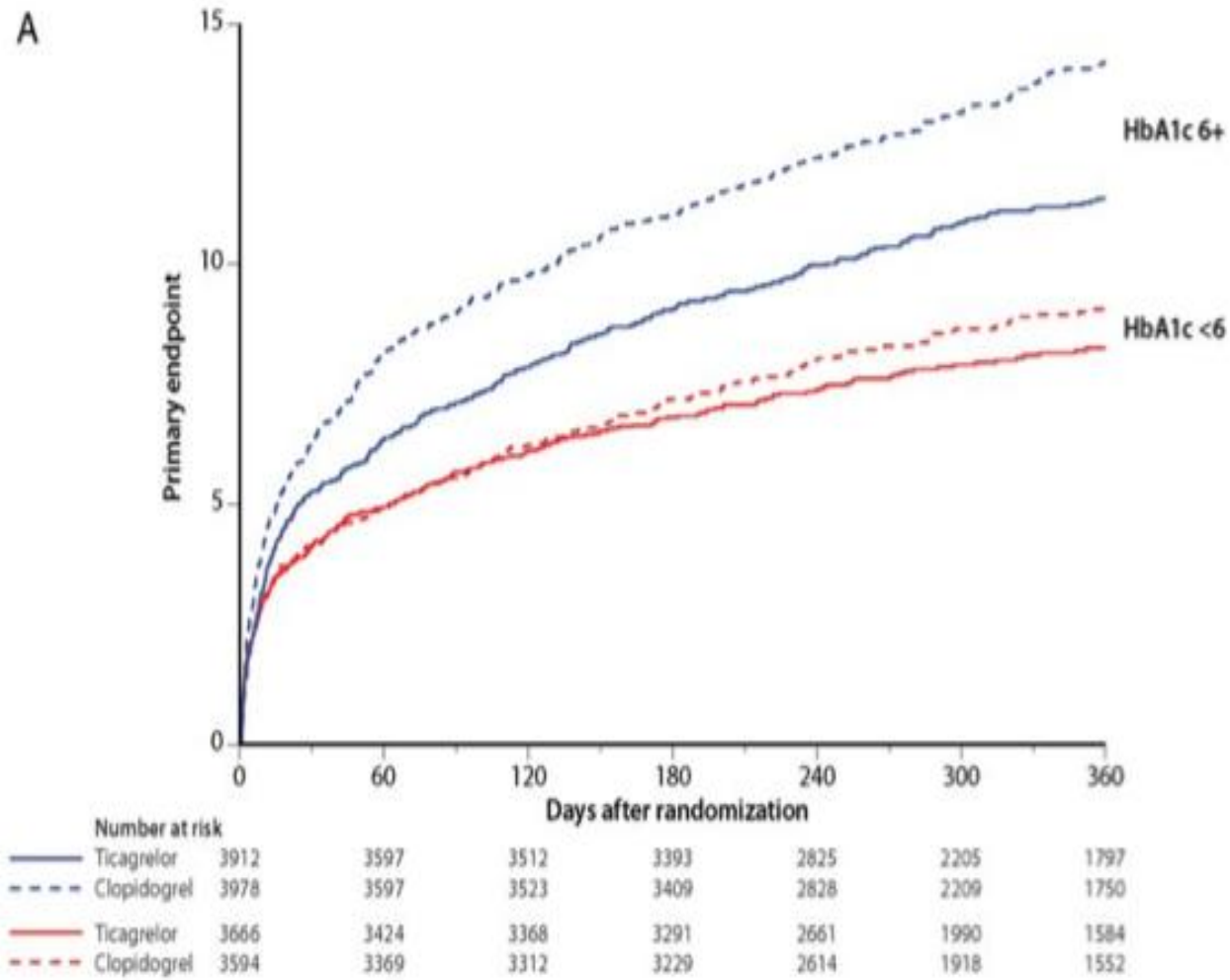
Subgroup analysis



ACS patients with diabetes



ACS patients with diabetes



Who would benefit most?

- ◆ Patients with ACS and planned early invasive strategy (less than 2 hours) because **fast and consistent blockade** of P2Y₁₂ receptors
 - ◆ PCI patients with high potential for thrombotic events because of **significant reduction of in stent thrombosis** (large thrombus burden, suboptimal PCI result, slow TIMI flow, long stent segment etc.) or clinical characteristic like diabetes, renal failure etc.
 - ◆ Patients with stent thrombosis and documented **clopidogrel resistance**.
 - ◆ It would be reasonable for all ACS because of **significant mortality reduction** in 1 year follow up
-



OH.

WHEN THEY SAY "COST-BENEFIT", THEY DON'T USUALLY MEAN OUR BENEFIT.

HERE, PROCESS THIS.

Ticagrelor for all patients with ACS?

- ◆ It would be difficult to achieve that, due to current economic situation
 - ◆ Individual patient selection, what I prefer, would be difficult to apply
 - ◆ We proposed Ticagrelor in all patient undergoing urgent PCI for acute myocardial infarction included in the "**Croatian PCI network**"
 - ◆ Patients with in **stent thrombosis** and known **clopidogrel resistance** are implied
-

Thank you.

