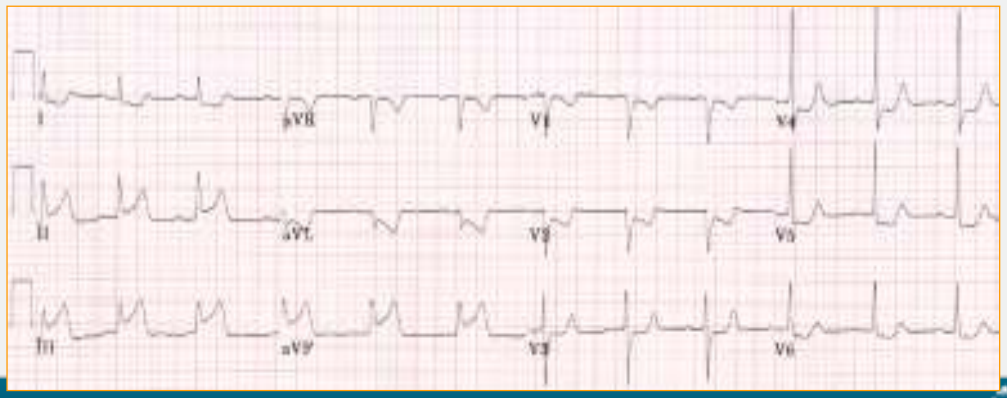
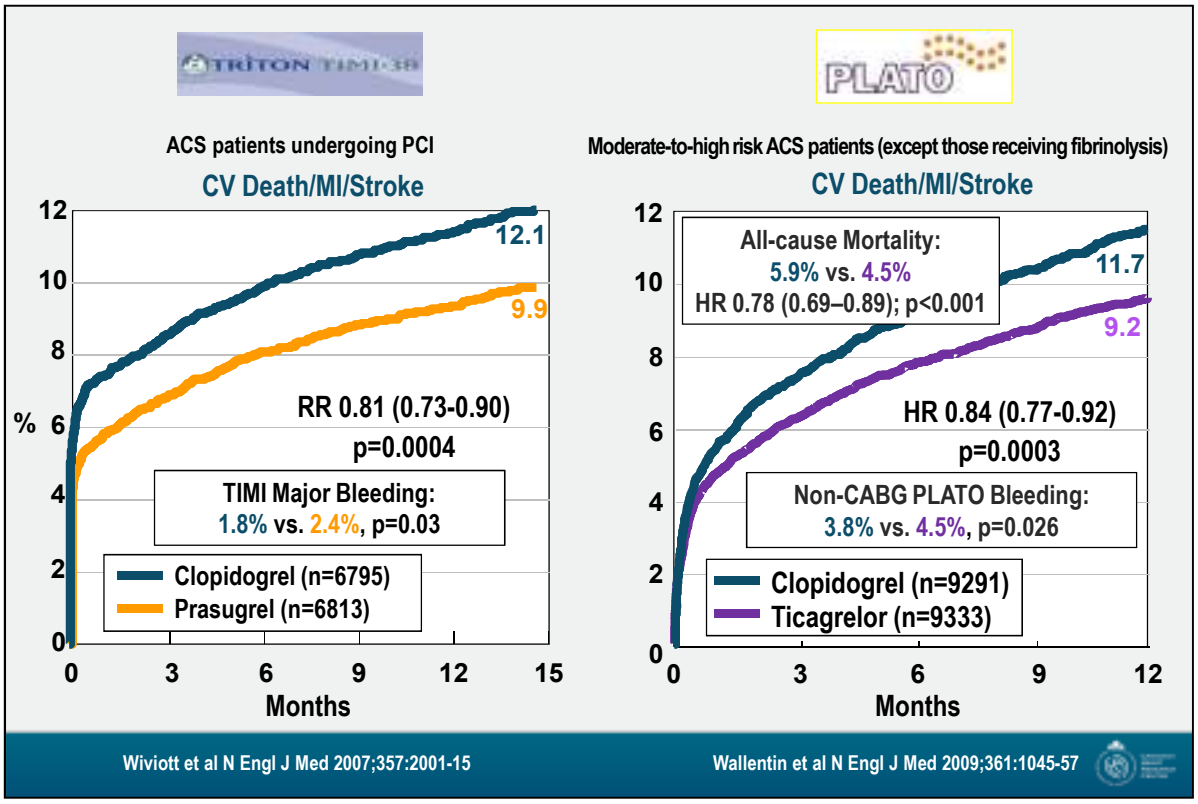
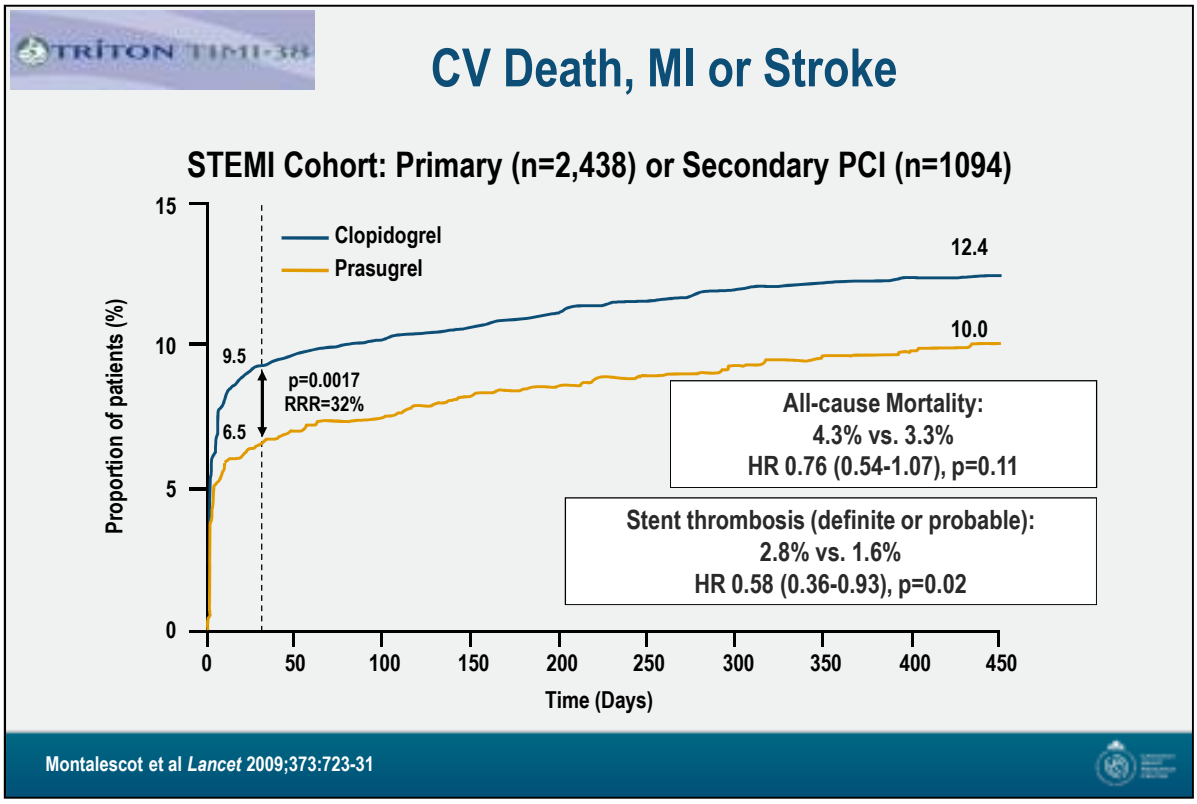
- 64 year old female
- Prior Diabetes Mellitus, Hypertension, Dyslipidemia; Family History of premature CAD
- On Metformin, Sulfonylurea, Ramipril, Rosuvastatin
- New onset central chest pain, dyspnea, and diaphoresis 90 minutes ago
- Heart rate 74/min; BP 168/94 mm Hg, Killip Class I
- ECG = ST elevation inferior, ST depression I, aVL, V1-6



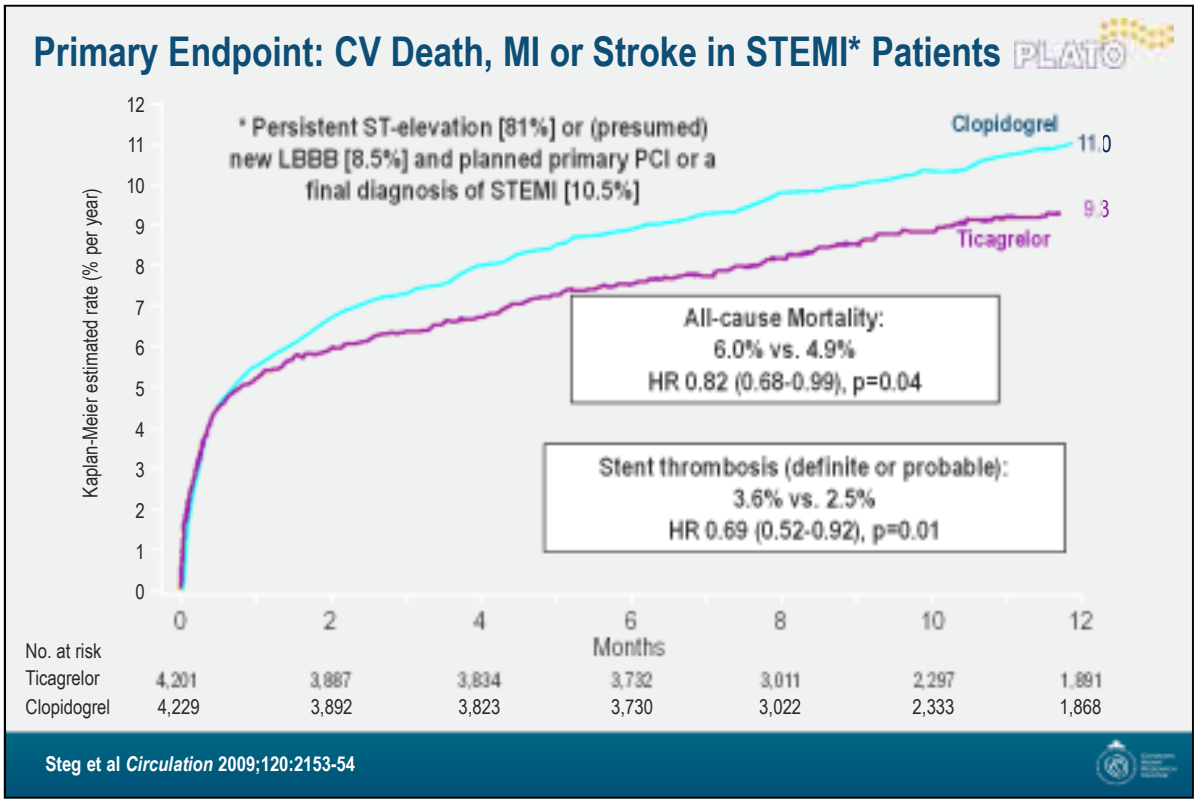
The case is one of an inferior ST-segment elevation myocardial infarction (STEMI) who presents to a percutaneous coronary intervention (PCI)-capable hospital within 90 minutes of symptom onset. Coronary angiography reveals mid-right coronary artery (RCA) occlusion and the patient receives a 2nd generation drug eluting stent (DES). The choice of dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA; Aspirin®) and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) is raised.



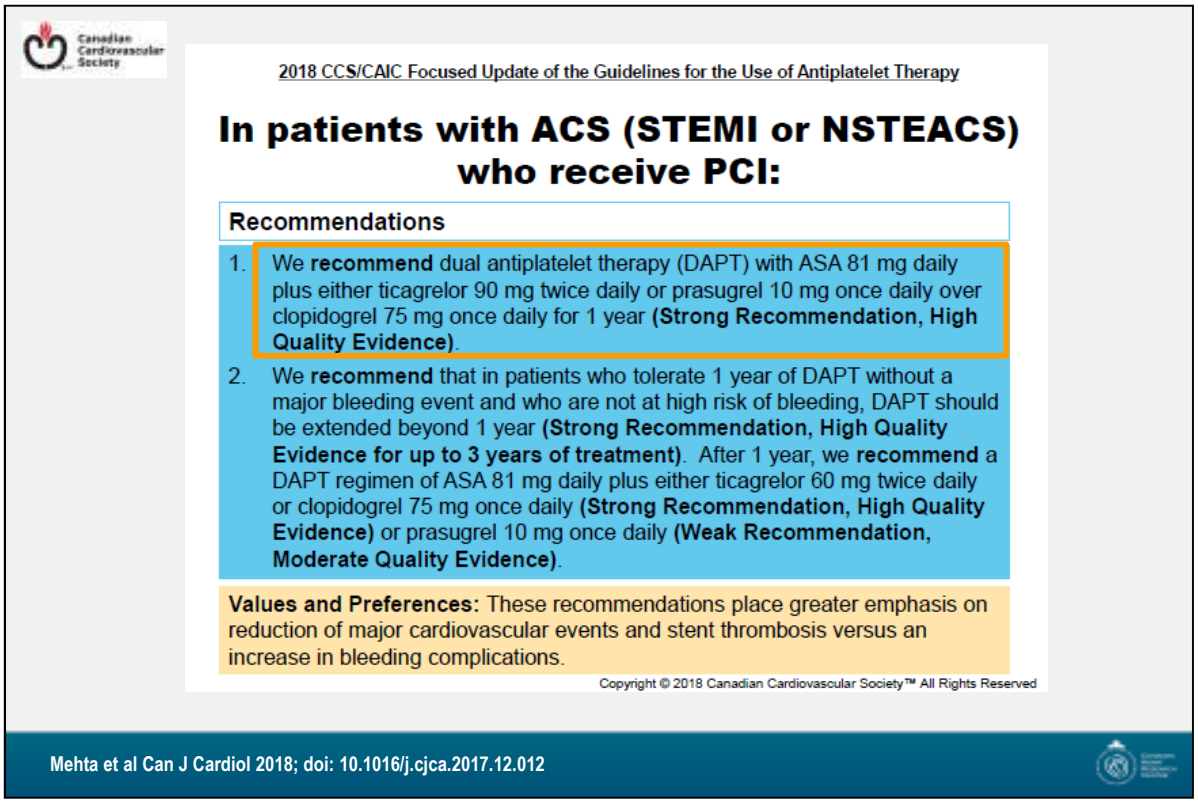
The primary efficacy (time to first cardiovascular [CV] death, myocardial infarction [MI], or stroke) and safety (Major Bleeding) outcomes in the TRITON TIMI-38 (left panel) and PLATO (right panel) trials are presented. In the broad spectrum of ACS patients in the two trials, the more potent $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor, respectively, were significantly more effective than clopidogrel. While these results came at a "cost" of increased major bleeding, this is offset by the reduction in ischemic events and, in the case of ticagrelor vs. clopidogrel in the PLATO trial, all-cause mortality at 1 year was significantly lower.



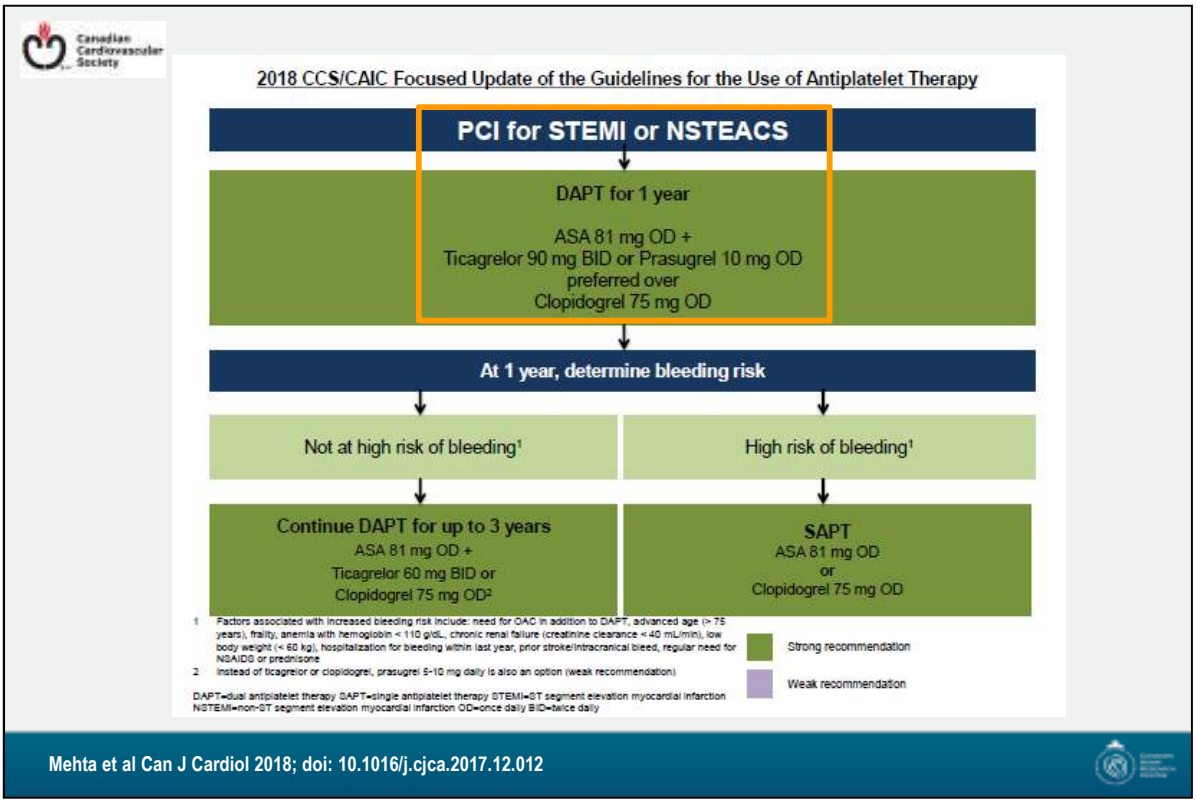
Subgroup analysis of the TRITON TIMI-38 trial in patients with STEMI undergoing primary PCI or "secondary" PCI (PCI in a STEMI patient who didn't undergo primary PCI but later in the course of their STEMI underwent angiography and PCI) showed consistency of benefit of prasugrel over clopidogrel, including for the primary composite endpoint (CV death/MI/stroke) and stent thrombosis. In addition, there was a numeric reduction in all-cause mortality, albeit not statistically significantly different.



Similar findings of the superiority of ticagrelor vs. clopidogrel in the STEMI patients undergoing primary PCI were observed in this subgroup analysis of the PLATO trial. All-cause mortality was significantly lower in this STEMI subgroup with ticagrelor.



Amongst patients with ACS, including STEMI, who receive PCI, the Canadian Cardiovascular Society (CCS)/Canadian Association of Interventional Cardiologists (CAIC) 2018 Focused Update includes the recommendation for preferential use of ticagrelor or prasugrel over clopidogrel for the next year's time. As noted in the Values and Preferences box, this recommendation places relatively greater emphasis on the reduction in major CV events and stent thrombosis vs. the anticipated increase in bleeding complications with the more potent $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor vs. clopidogrel.



These recommendations are depicted graphically.

...But what if...?

- 64 year old female
- Prior Diabetes Mellitus, Hypertension, Dyslipidemia; Family History of premature CAD
- On Metformin, Sulfonylurea, Ramipril, Rosuvastatin
- New onset central chest pain, dyspnea, and diaphoresis 90 minutes ago
- Heart rate 74/min; BP 168/94 mm Hg, Killip Class I
- ECG = ST elevation inferior, ST depression I, aVL, V1-6

Presents to non-PCI-capable hospital and transfer time for primary PCI >2 hours. Receives fibrinolytic therapy (TNK).
What oral antiplatelet therapy would you choose?

a) ASA alone
b) ASA + Clopidogrel
c) ASA + Prasugrel
d) ASA + Ticagrelor

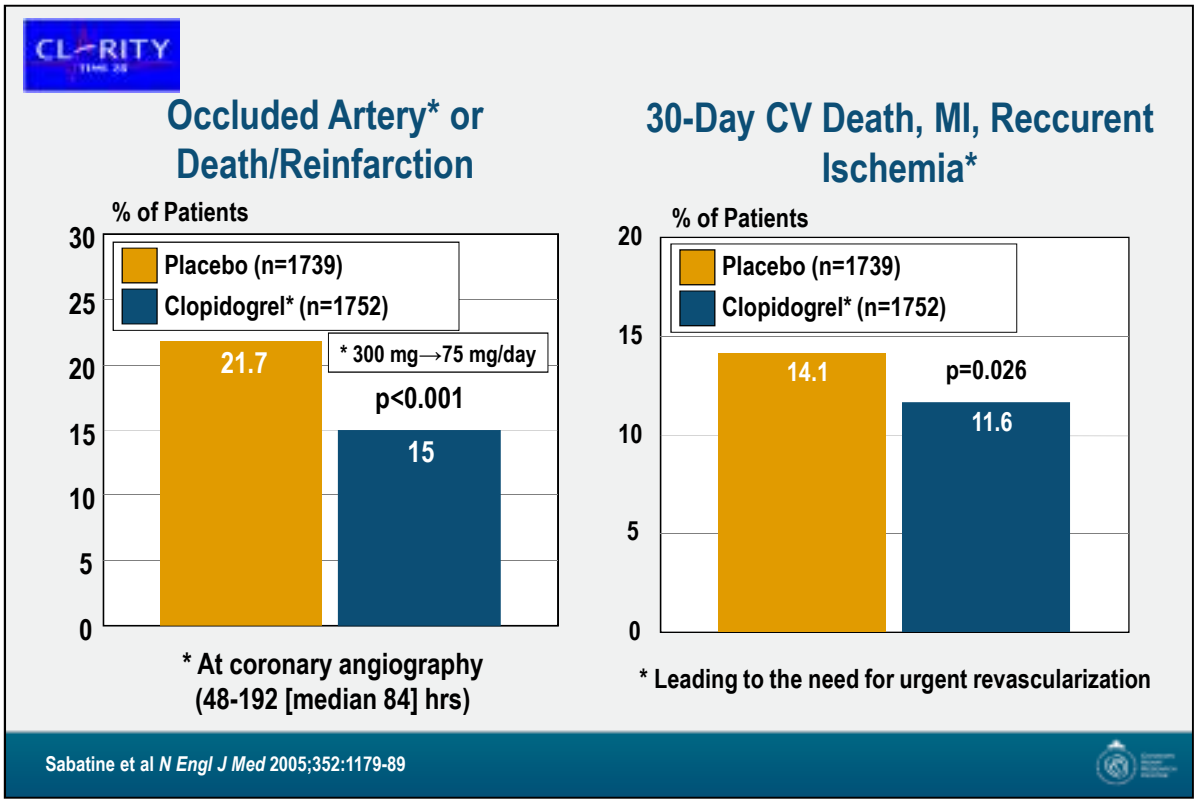
Returning to the case, the choice of oral antiplatelet therapy is now placed in the context of a "what if..." scenario where the patient presents to a non-PCI-capable hospital with lengthy transfer timing anticipated such that the patient receives fibrinolytic therapy instead of primary PCI.

Dual Oral Antiplatelet Therapy

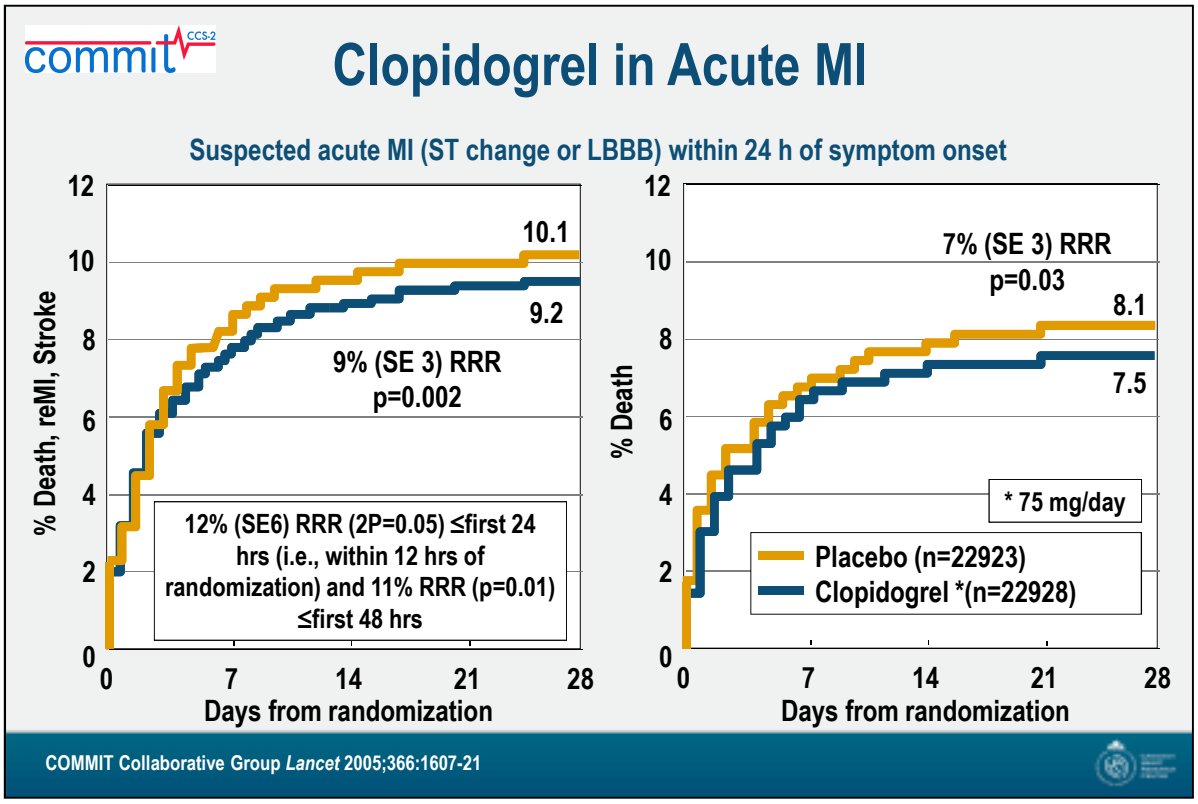
- **Adjunctive antiplatelet therapy with ASA (Aspirin™) and a at the time of fibrinolysis (another class IA recommendation[1]) has been shown to**
  - **improve the patency rate of the infarct-related artery (IRA)[2]**
  - **reduce ischemic complications[2]**
  - **reduce in-hospital mortality[3]**

[1] O'Gara et al *Circulation* 2013;127:e362-425; [2] Sabatine et al *N Engl J Med* 2005;352:1179-89;
[3] Chen et al *Lancet* 2005;366:1607-21

The value of DAPT, specifically with ASA and clopidogrel, as adjunctive therapy with fibrinolysis is highlighted, referencing the American Heart Association (AHA)/American College of Cardiology (ACC) STEMI guideline recommendations based on 2 randomized trials (CLARITY TIMI-28 and COMMIT CCS-2) demonstrating benefit of clopidogrel (including an all-cause mortality reduction vs. placebo in the COMMIT trial).



The benefit of clopidogrel (300 mg load followed by 75 mg daily) vs. placebo on the primary (left panel) and secondary (right panel) outcomes is seen in the CLARITY TIMI-28 trial.



Similarly, in the >45,000 patient clinical outcome trial, the co-primary endpoints (Death, reinfarction, or stroke [left panel] and all-cause death [right panel]) were significantly lower in clopidogrel (75 mg load followed by 75 mg daily) vs. placebo treated patients. The component endpoint (left panel) was statistically significant within the first 24 hours (i.e., within 12 hours of randomization), even though only 75 mg of clopidogrel was given initially.

...But what if...?

- 64 year old female
- Prior Diabetes Mellitus, Hypertension, Dyslipidemia; Family History of premature CAD
- On Metformin, Sulfonylurea, Ramipril, Rosuvastatin
- New onset central chest pain, dyspnea, and diaphoresis 90 minutes ago
- Heart rate 74/min; BP 168/94 mm Hg, Killip Class I
- ECG = ST elevation inferior, ST depression I, aVL, V1-6

Presents to non-PCI-capable hospital and transfer time for primary PCI >2 hours. Receives fibrinolytic therapy (TNK).

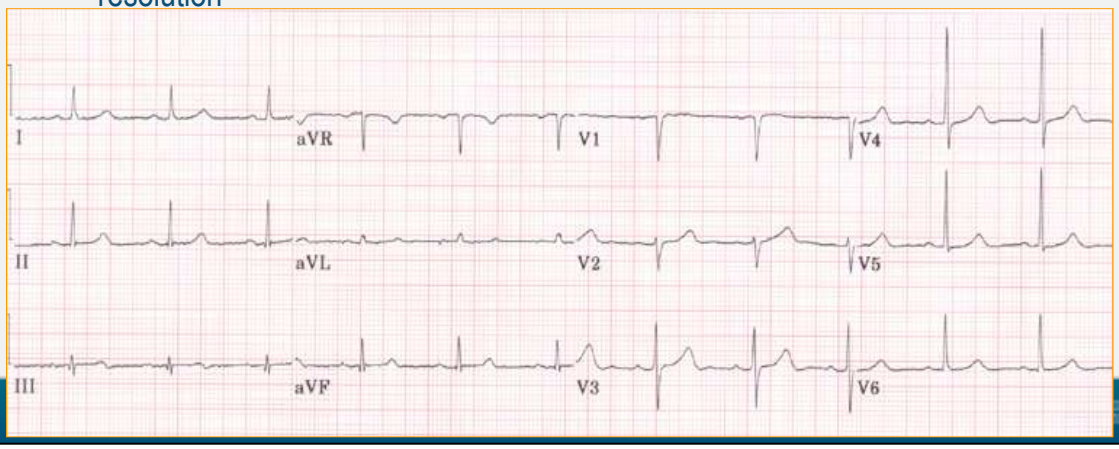
What oral antiplatelet therapy would you choose?

a) ASA alone
b) ASA + Clopidogrel → prescribed by ED physician
c) ASA + Prasugrel
d) ASA + Ticagrelor

The "what if" scenario part of the case is revisited and notes that the patient received ASA and clopidogrel as prescribed by the emergency department (ED) physician.

...But what if...?

- 64 year old female
- Chest pain and dyspnea resolve post-lysis
- Hemodynamically stable
- 2nd ECG 60 minutes post-lysis = ST elevation (and ST depression) resolution



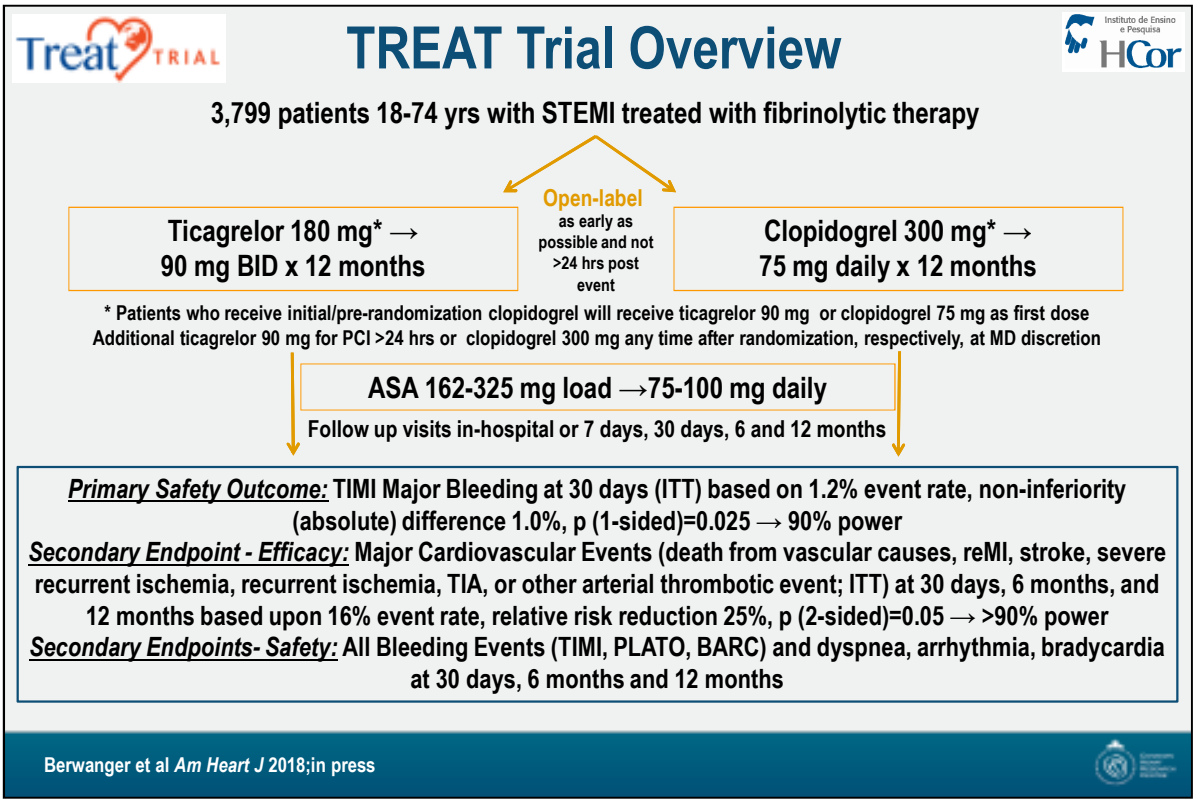
The case evolves with ECG-demonstrated ST-segment elevation resolution post-lysis and raises the question of whether the $P2Y_{12}$ receptor inhibitor choice should be revisited.

Prasugrel or Ticagrelor Post-Lysis?

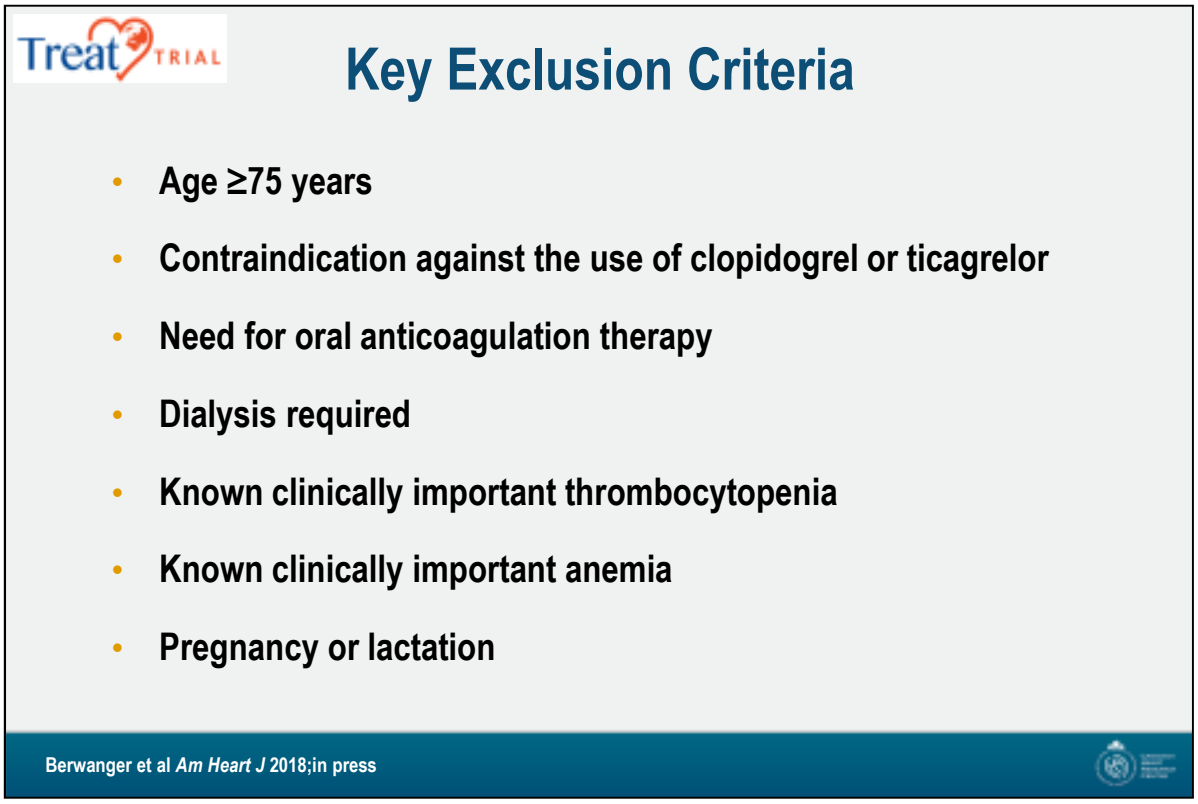
- **Despite superiority over clopidogrel with**
  - **Prasugrel[1]**
  - **Ticagrelor[3]**
  - **including in STEMI patients undergoing primary[2,4] or secondary PCI[2]**
- ***Patients who received fibrinolytic therapy within 24[1-4]-48[1-2] hours of randomization were excluded***
- **Use of more potent P2Y12 receptor inhibitors early after lysis + clopidogrel in clinical practice:**
  - **COAPT:[4] 94% initially received clopidogrel → 21% subsequently switched to a novel P2Y12ri ≤24 hours of lysis and PCI**
  - **unadjusted MACE and bleeding rates were numerically lower with switching vs. maintaining clopidogrel**

[1]Wiviott et al *N Engl J Med* 2007;357:2001-15; [2]Montalescot et al *Lancet* 2009;373:723-31; [3]Wallentin et al *N Engl J Med* 2009;361:1045-57; [4]Steg et al *Circulation* 2009;120:2153-54; [5]Dehghani et al *Can J Cardiol* 2016;32:S116-7

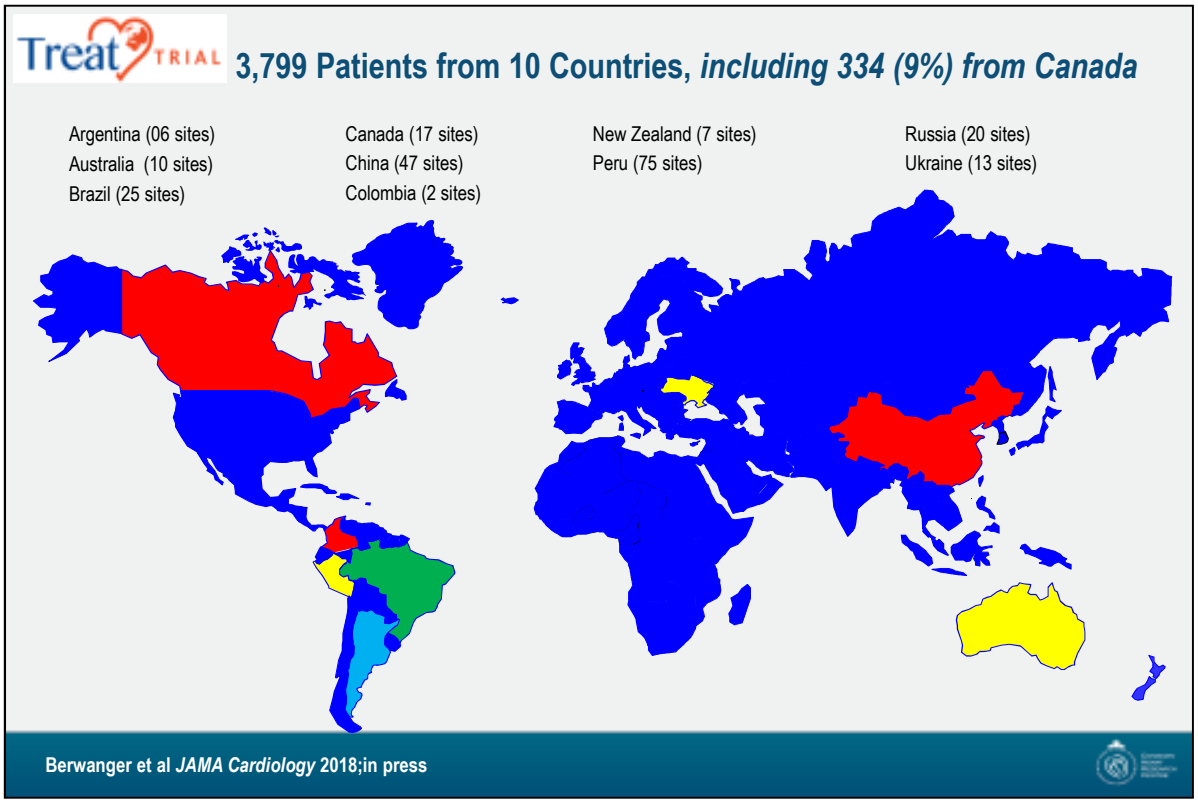
Despite the demonstrated superiority of either prasugrel or ticagrelor over clopidogrel, it is important to recognize that STEMI patients who received fibrinolytic therapy within the first 24-48 hours were excluded from the TRITON TIMI-38 and PLATO trials. A Canadian observational (Canadian Oral AntipLatelet [COAPT]) study abstract described that the vast majority (94%) of lytic-treated patients receive clopidogrel; however, 21% were subsequently switched within 24 hours of having received lysis when they went on to PCI. The unadjusted major adverse CV events (MACE) and bleeding rates were numerically lower with those who were switched to a more potent $P2Y_{12}$ receptor inhibitors (ticagrelor or prasugrel) vs. maintaining clopidogrel. However, this is a relatively small, non-randomized observation that shouldn't be used to guide clinical practice, but raises the hypothesis that the use of ticagrelor (instead of continuing clopidogrel) in STEMI fibrinolytic-treated patients may be a safe and effective approach.



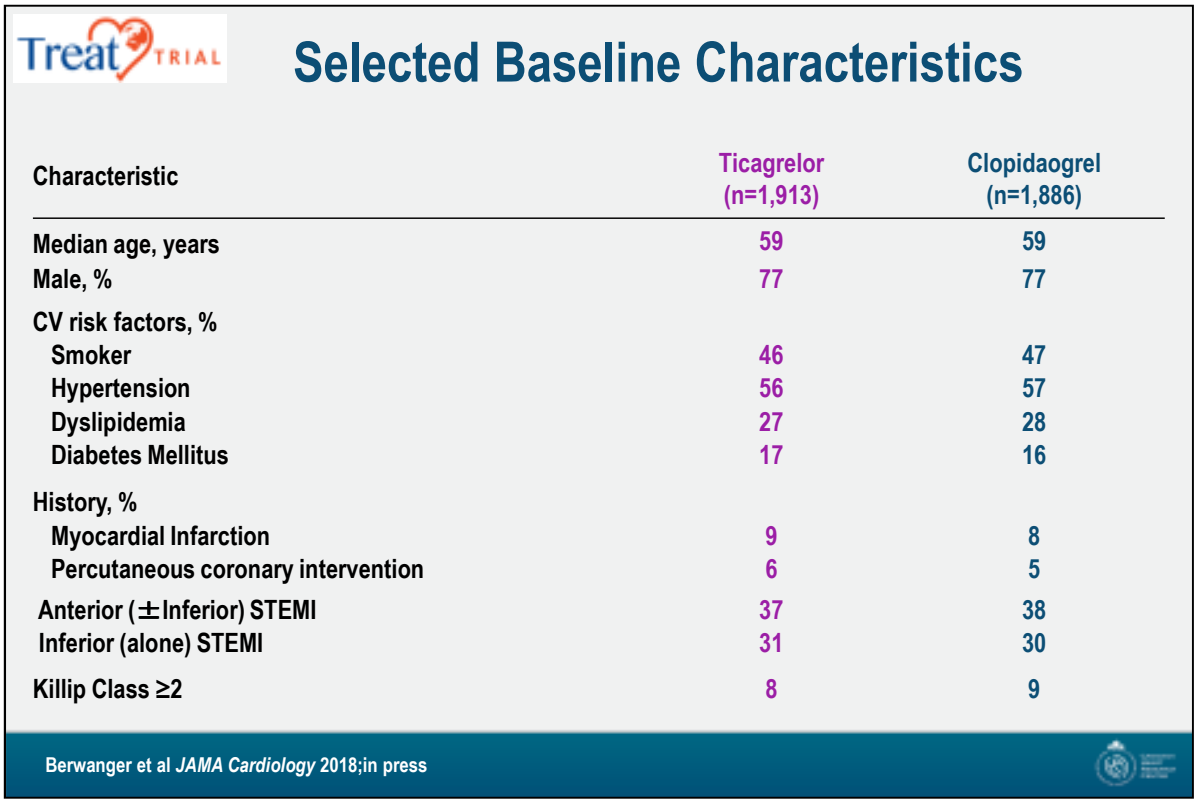
The Administration of TicagREIor in pAtients with ST elevation myocardial infarction treated with pharmacological Thrombolysis (TREAT) trial is an investigator-initiated trial (supported at arms length by AstraZeneca) led by Dr. Otavio Berwanger and the not-for-profit academic research organization (ARO) HCor. The design and key endpoints of this open-label comparison of ticagrelor vs. clopidogrel within 24 hours of symptom onset are presented.



The key exclusion criteria for TREAT are listed, including patients 75 years of age and older and/or those requiring oral anticoagulation therapy.



TREAT was an international study, including 334 (9%) Canadian patients from 17 hospitals in 8 provinces.



Selected baseline characteristics are outlined and were similar in the randomized ticagrelor vs. clopidogrel groups.

Fibrinolytic Therapy

Medication	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
Start of randomised treatment		
Time from symptom to fibrinolytic administration, median hours	2.6	2.6
Time from fibrinolytic administration to randomization, median hours	11.4	11.5
Fibrinolytic Therapy , %		
Tenecteplase	40	40
Alteplase	20	19
Reteplase	17	17
Non-fibrin specific (e.g., Streptokinase)	23	24

Berwanger et al *JAMA Cardiology* 2018;in press

Time from symptom onset to fibrinolytic administration was approximately 2½ hours and time from fibrinolytic administration to randomization was approximately 11-2 hours. 75% of the patients in TREAT received a fibrin-specific lytic, including tenecteplase (TNK) in 40%.

Co-Interventions and Procedures

	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
Clopidogrel before randomization , %		
None (or <300 mg)	10	11
300 mg	87	86
>300 mg	3	3
Invasive procedure performed during index hospitalization , %		
PCI	57	56
Within 24 hours after randomization	42	42
Cardiac surgery	2	2

Berwanger et al *JAMA Cardiology* 2018;in press

90% of patients had received clopidogrel prior to randomization. PCI was undertaken in 57% of patients, including 42% within 24 hours of randomization.

In-Hospital Treatments

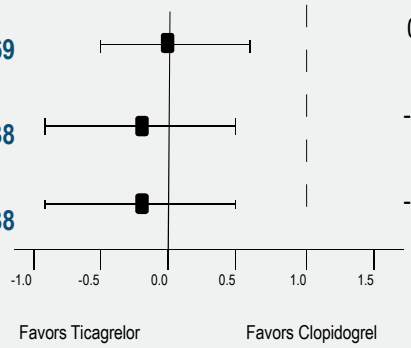
Medication	Ticagrelor (n=1,913)	Clopidogrel (n=1,886)
In-hospital treatment , %		
Aspirin	99	99
Unfractioned heparin	40	39
Low- molecular-weight heparin	69	69
Fondaparinux	4	4
Bivalirudin	1	1
Glycoprotein IIb/IIIa inhibitor	5	5
Beta-blocker	74	74
ACE inhibitor or ARB	70	68
Statin	93	93
Proton pump-inhibitor	55	57

Berwanger et al *JAMA Cardiology* 2018;in press

In-hospital treatment with ASA (Aspirin®), parenteral antithrombotic therapies, and secondary prevention therapies was high. 56% received a proton pump-inhibitor.

Major Bleeding at 30 Days

	Ticagrelor (n=1913)	Clopidogrel (n=1886)	Absolute Difference , 95% CI	P noninf.
			Noninf. margin	
TIMI Major Bleeding (Primary Endpoint), %	0.73	0.69	0.04 [-0.49; 0.58]	<0.001
PLATO Major Bleeding, %	1.20	1.38	-0.18 [-0.89; 0.54]	0.001
BARC Type 3 - 5 Bleeding, %	1.20	1.38	-0.18 [-0.89; 0.54]	0.001

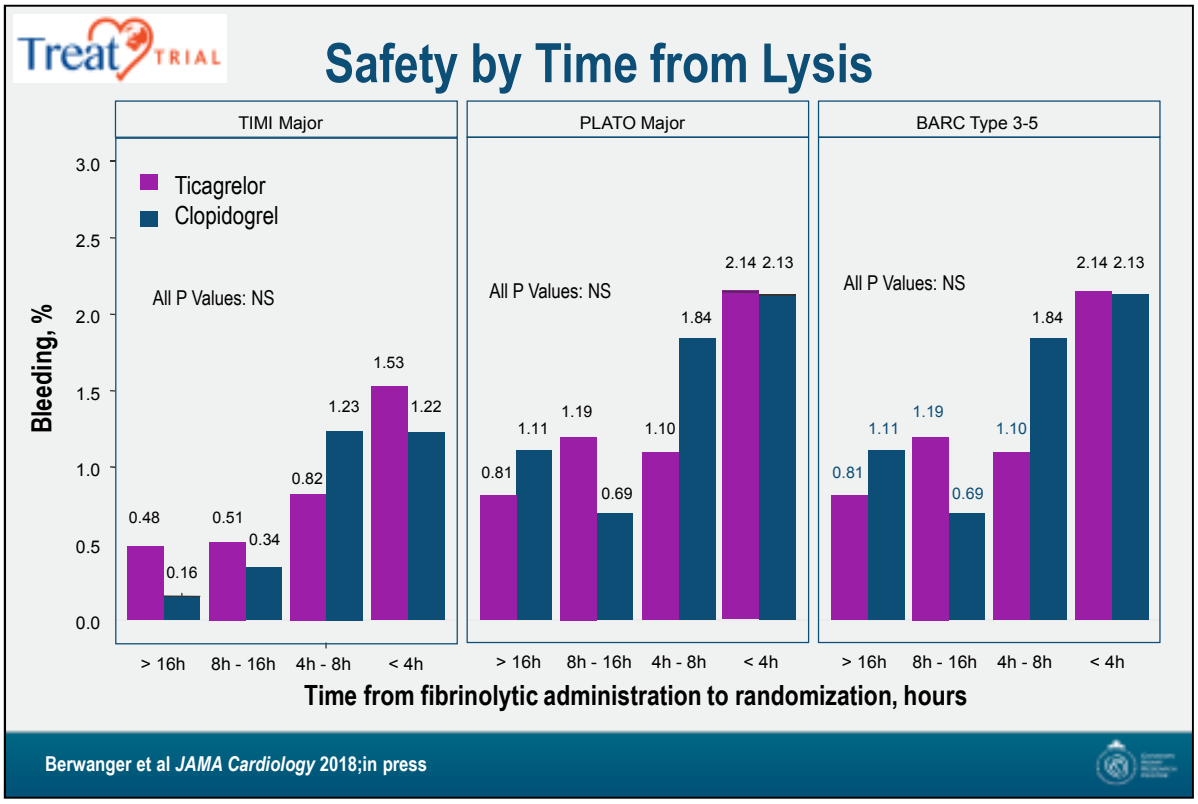


* Absolute difference (in percentage) presented as bilateral 95% confidence interval.

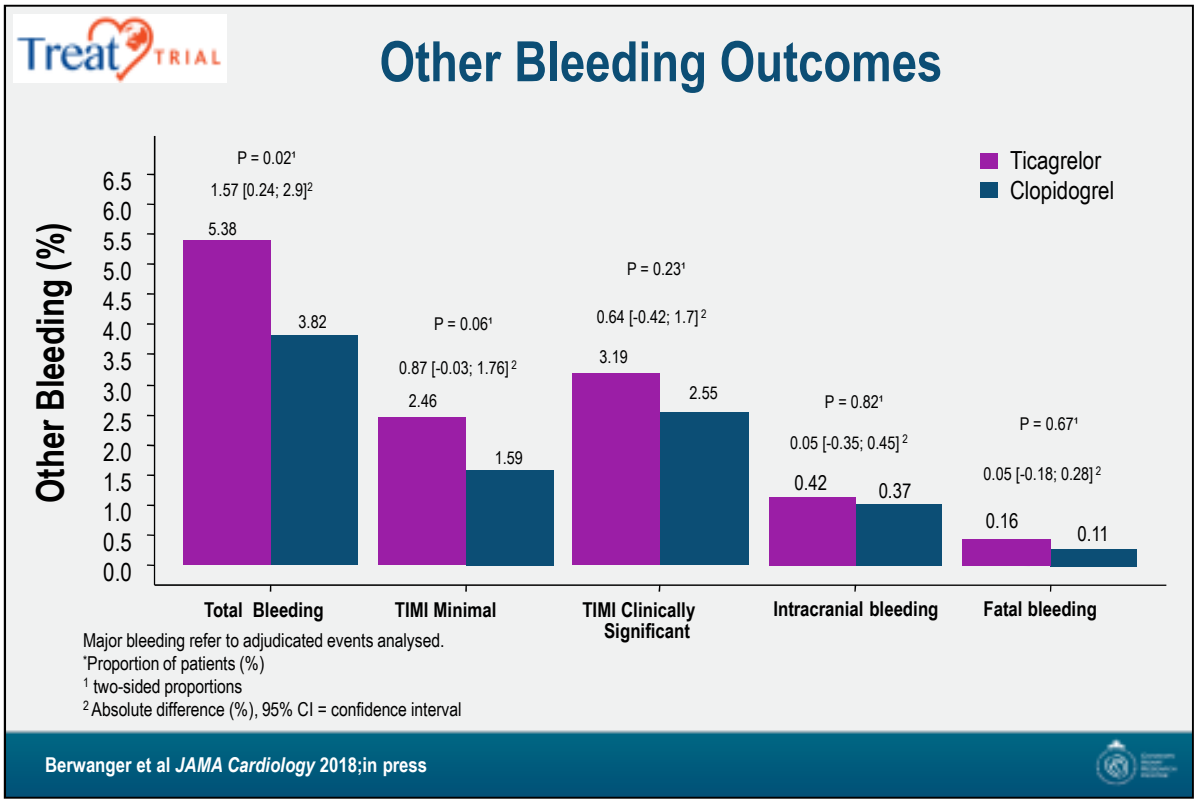
† 1% absolute difference margin non inferiority test. Non-inferiority test was done considering an one sided test.

Berwanger et al *JAMA Cardiology* 2018;in press

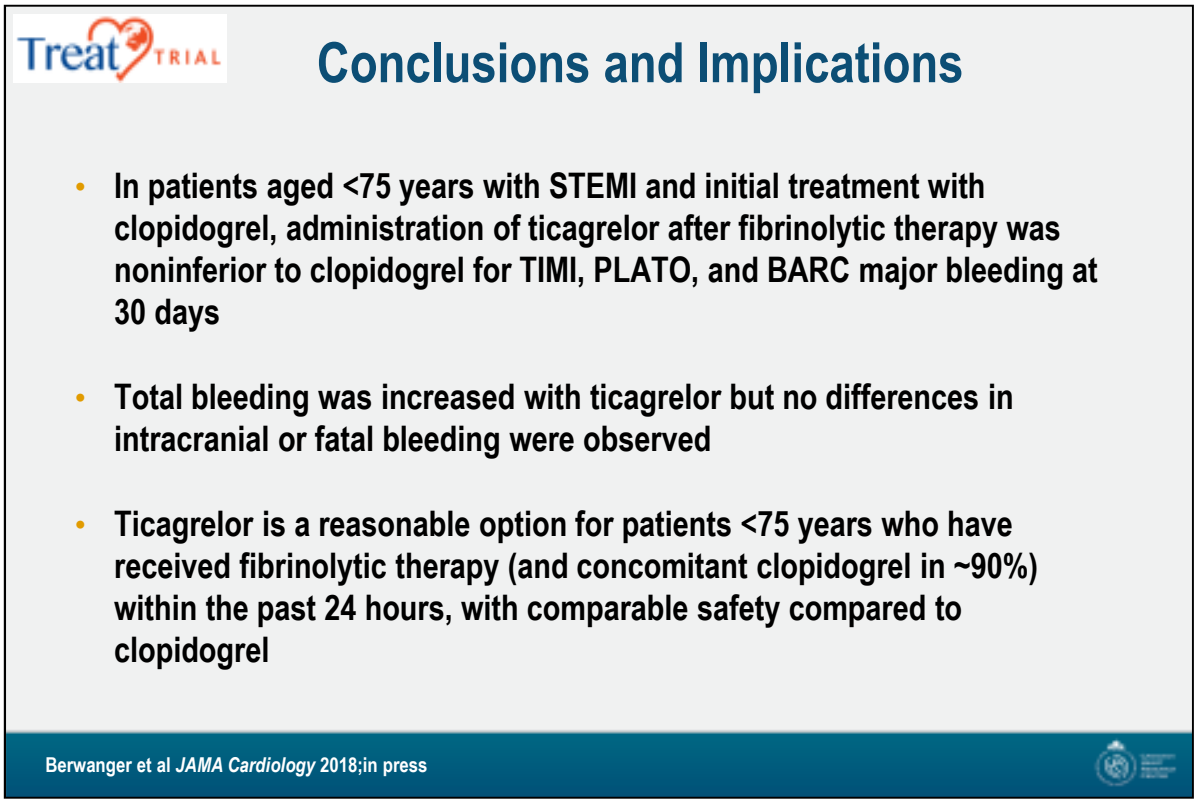
The primary outcome of TREAT is major bleeding (according to the TIMI definition) at 30 days; major bleeding rates by TIMI, PLATO, and BARC (Type 3-5) definitions were very low in both treatment groups. The absolute difference between ticagrelor and clopidogrel was -0.04%. All of the upper 95% confidence intervals (for each major bleeding definition) fell well below the pre-specified, non-inferiority margin of 1%. Thus, ticagrelor was non-inferior to clopidogrel with respect to major bleeding.



Subgroup analysis of different time windows from fibrinolytic administration to administration and related bleeding events are presented. In general, the earlier the time from lysis to randomization (e.g., <4 hours), the higher the rates of major bleeding. However, there are no significant differences in the absolute rates of bleeding in the ticagrelor vs. clopidogrel-treated groups. While the study is underpowered to look at outcomes within subgroups, there at least does not appear to be any important difference between ticagrelor and clopidogrel with respect to major bleeding, regardless of how soon after lysis was administered before study therapy was administered.



30-day total bleeding, TIMI minimal, and TIMI Clinically significant bleeding were numerically higher with ticagrelor vs. clopidogrel, consistent with the PLATO trial results and the fact that ticagrelor is a more potent $P2Y_{12}$ receptor inhibitor compared to clopidogrel. However, intracranial and fatal bleeding were infrequent and not substantially different.



The main findings and clinical implications (i.e., ticagrelor is a reasonable option for STEMI, lytic-treated patients, including those who received clopidogrel initially) are listed.

...But what if...?

- 64 year old female
- Chest pain and dyspnea resolve post-lysis
- Hemodynamically stable
- 2nd ECG 60 minutes post-lysis = ST elevation (and ST depression) resolution

Patient awaiting transfer to PCI-capable hospital.
Received ASA 162 mg and clopidogrel 300 mg together with lysis.

What would you change the current oral antiplatelet therapy prescribed by the ED physician to?

a) **No change—continue ASA + Clopidogrel**
b) **ASA + Prasugrel**
c) **ASA + Ticagrelor**

Returning to the case, the TREAT trial results suggest that ASA and ticagrelor would be a good option for ongoing DAPT.