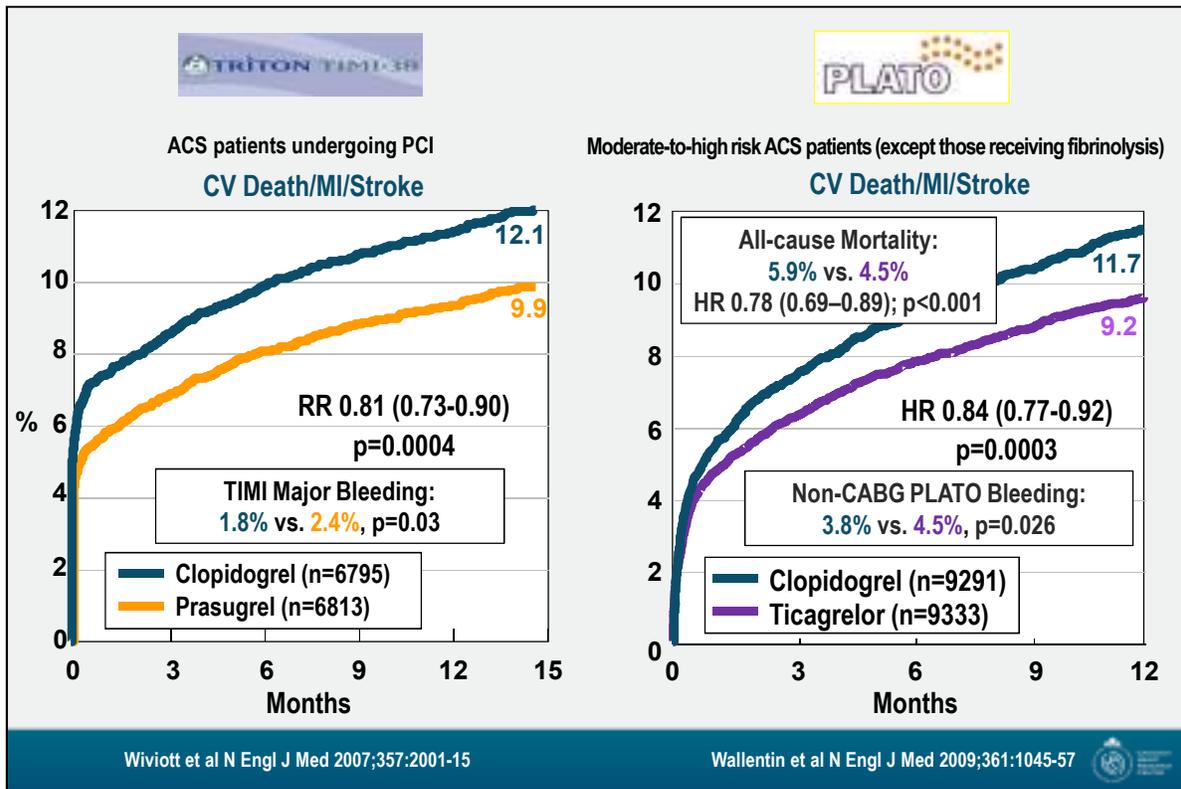


- 64 year old female
- Prior Diabetes Mellitus, Hypertension, Dyslipidemia; Family History of premature CAD
- On Metformin, Sulfonyleurea, Ramipril, Rosuvastatin
- New onset central chest pain, dyspnea, and diaphoresis 90 minutes ago
- Heart rate 74/min; BP 168/94 mm Hg, Killip Class I
- ECG = ST elevation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

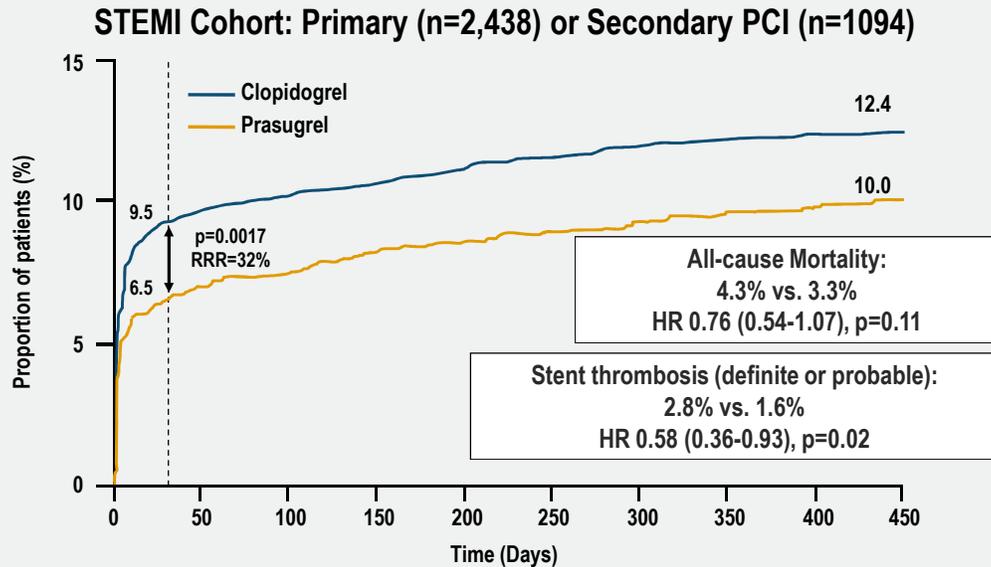


The case is one of an inferior ST-segment elevation myocardial infarction (STEMI) who presents to a percutaneous coronary intervention (PCI)-capable hospital within 90 minutes of symptom onset. Coronary angiography reveals mid-right coronary artery (RCA) occlusion and the patient receives a 2nd generation drug eluting stent (DES). The choice of dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA; Aspirin®) and a P2Y₁₂ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) is raised.

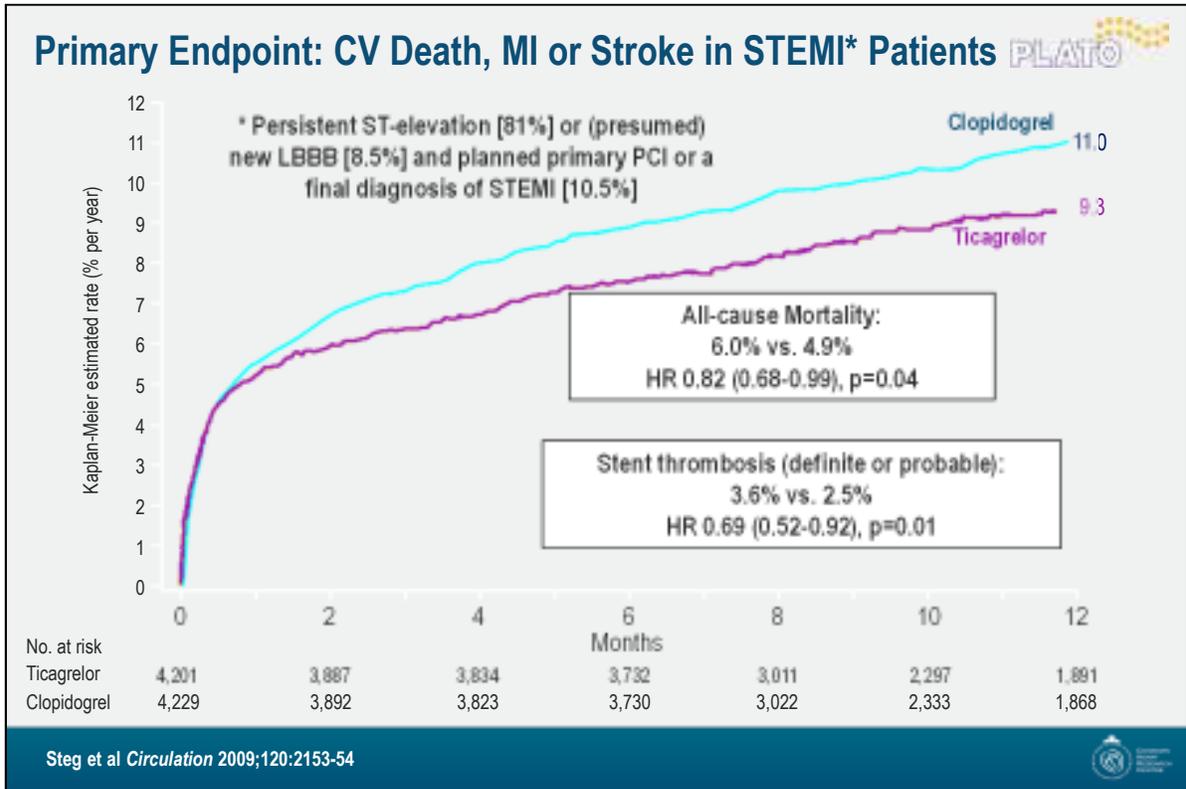


The primary efficacy (time to first cardiovascular [CV] death, myocardial infarction [MI], or stroke) and safety (Major Bleeding) outcomes in the TRITON TIMI-38 (left panel) and PLATO (right panel) trials are presented. In the broad spectrum of ACS patients in the two trials, the more potent P2Y₁₂ receptor 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.

CV Death, MI or Stroke



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.

In patients with ACS (STEMI or NSTEMI) who receive PCI:

Recommendations

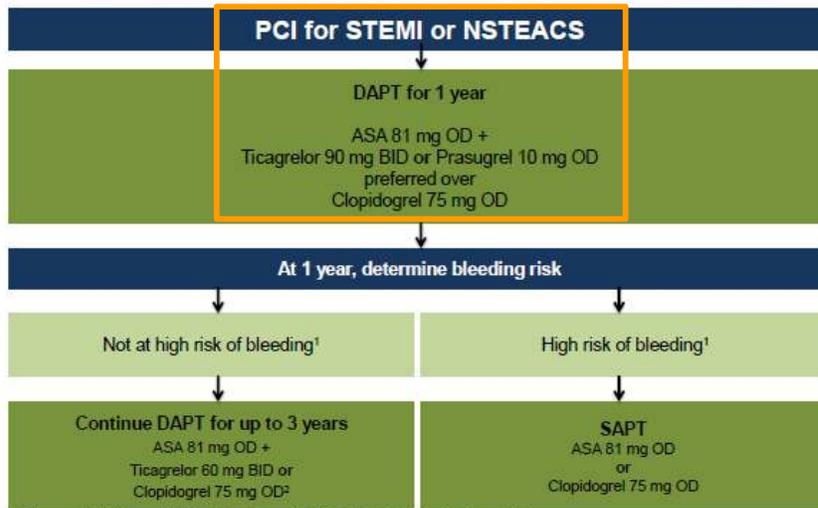
1. We **recommend** dual antiplatelet therapy (DAPT) with ASA 81 mg daily plus either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily over clopidogrel 75 mg once daily for 1 year (**Strong Recommendation, High Quality Evidence**).
2. We **recommend** that in patients who tolerate 1 year of DAPT without a major bleeding event and who are not at high risk of bleeding, DAPT should be extended beyond 1 year (**Strong Recommendation, High Quality Evidence for up to 3 years of treatment**). After 1 year, we **recommend** a DAPT regimen of ASA 81 mg daily plus either ticagrelor 60 mg twice daily or clopidogrel 75 mg once daily (**Strong Recommendation, High Quality Evidence**) or prasugrel 10 mg once daily (**Weak Recommendation, Moderate Quality Evidence**).

Values and Preferences: These recommendations place greater emphasis on reduction of major cardiovascular events and stent thrombosis versus an increase in bleeding complications.

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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 P2Y₁₂ receptor inhibitors prasugrel and ticagrelor vs. clopidogrel.

2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy



¹ Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/L, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior stroke/intracranial bleed, regular need for NSAIDs or prednisone.

² Instead of ticagrelor or clopidogrel, prasugrel 5-10 mg daily is also an option (weak recommendation).

DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy; STEMI=ST segment elevation myocardial infarction; NSTEMI=non-ST segment elevation myocardial infarction; OD=once daily; BID=twice daily.

Strong recommendation

Weak recommendation

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 P2Y₁₂ inhibitor at the time of fibrinolysis (another class IA recommendation¹) has been shown to**
 - improve the patency rate of the infarct-related artery (IRA)²
 - reduce ischemic complications²
 - reduce in-hospital mortality³

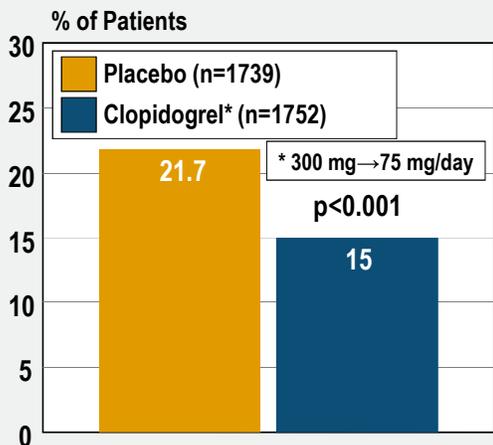
¹ O'Gara et al *Circulation* 2013;127:e362-425; ² Sabatine et al *N Engl J Med* 2005;352:1179-89;

³ Chen et al *Lancet* 2005;366:1607-21



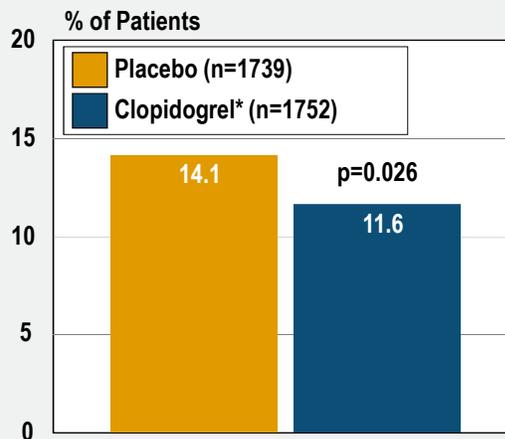
The value of DAPT, specifically with ASA and clopidogrel, as adjunctive therapy with fibrinolysis is highlighted, referencing the American Heart Association (AHA)/American College of Cardiology (ACC) STEMI guideline recommendations based on 2 randomized trials (CLARITY TIMI-28 and COMMIT CCS-2) demonstrating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

Occluded Artery* or Death/Reinfarction



* At coronary angiography (48-192 [median 84] hrs)

30-Day CV Death, MI, Recurrent Ischemia*

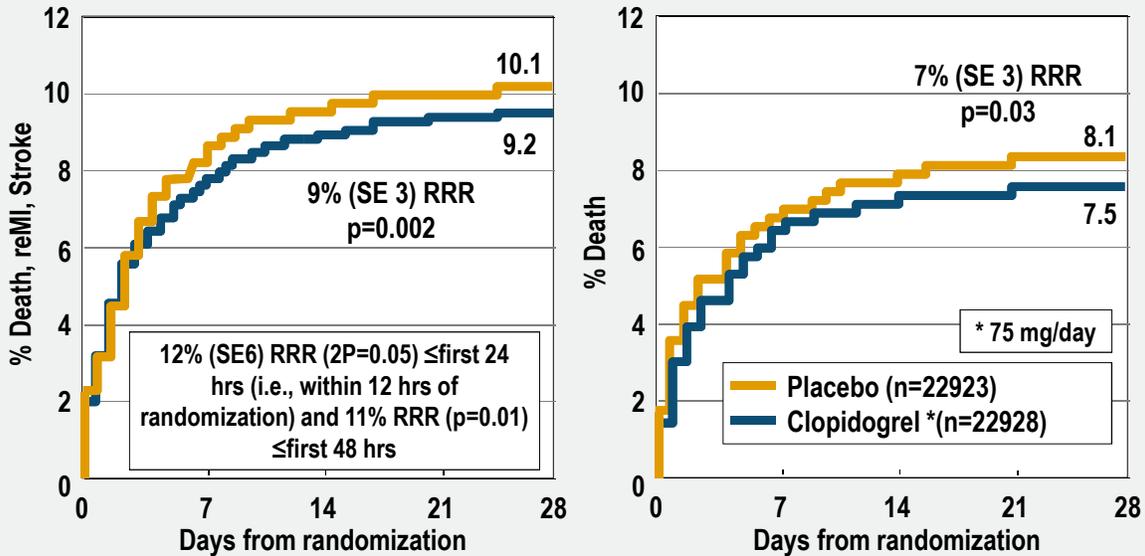


* Leading to the need for urgent revascularization

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.

Clopidogrel in Acute MI

Suspected acute MI (ST change or LBBB) within 24 h of symptom onset



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?

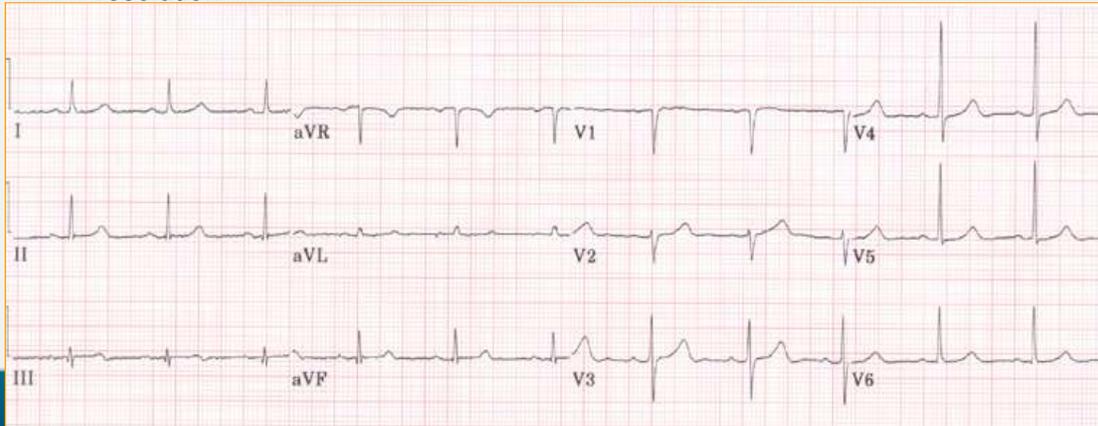
- a) ASA alone
- b) **ASA + Clopidogrel** → prescribed by ED physician
- c) ASA + Prasugrel
- d) ASA + Ticagrelor

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 P2Y₁₂ receptor inhibitor choice should be revisited.

Prasugrel or Ticagrelor Post-Lysis?

- Despite superiority over clopidogrel with
 - Prasugrel¹
 - Ticagrelor³
 - including in STEMI patients undergoing primary^{2,4} or secondary PCI²
- **Patients who received fibrinolytic therapy within 24¹⁻⁴-48¹⁻² 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

¹Wiviott et al *N Engl J Med* 2007;357:2001-15; ²Montalescot et al *Lancet* 2009;373:723-31; ³Wallentin et al *N Engl J Med* 2009;361:1045-57; ⁴Steg et al *Circulation* 2009;120:2153-54; ⁵Dehghani 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 P2Y₁₂ 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.

3,799 patients 18-74 yrs with STEMI treated with fibrinolytic therapy



* Patients who receive initial/pre-randomization clopidogrel will receive ticagrelor 90 mg or clopidogrel 75 mg as first dose
Additional ticagrelor 90 mg for PCI >24 hrs or clopidogrel 300 mg any time after randomization, respectively, at MD discretion

ASA 162-325 mg load → 75-100 mg daily

Follow up visits in-hospital or 7 days, 30 days, 6 and 12 months

Primary Safety Outcome: TIMI Major Bleeding at 30 days (ITT) based on 1.2% event rate, non-inferiority (absolute) difference 1.0%, p (1-sided)=0.025 → 90% power
Secondary Endpoint - Efficacy: Major Cardiovascular Events (death from vascular causes, reMI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event; ITT) at 30 days, 6 months, and 12 months based upon 16% event rate, relative risk reduction 25%, p (2-sided)=0.05 → >90% power
Secondary Endpoints- Safety: All Bleeding Events (TIMI, PLATO, BARC) and dyspnea, arrhythmia, bradycardia at 30 days, 6 months and 12 months

The Administration of TicagRElor 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.

Key Exclusion Criteria

- **Age \geq 75 years**
- **Contraindication against the use of clopidogrel or ticagrelor**
- **Need for oral anticoagulation therapy**
- **Dialysis required**
- **Known clinically important thrombocytopenia**
- **Known clinically important anemia**
- **Pregnancy or lactation**

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



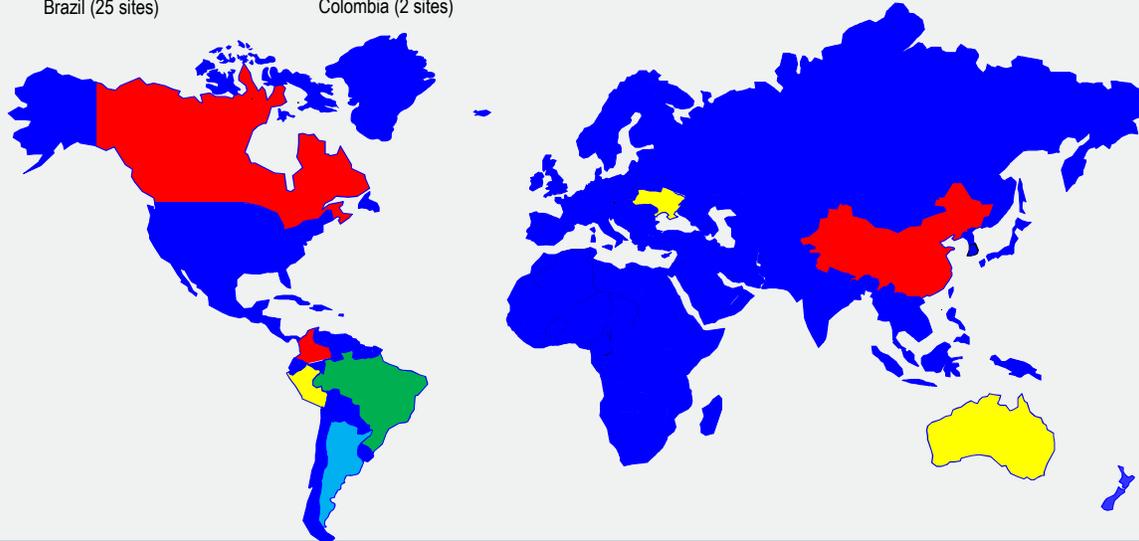
3,799 Patients from 10 Countries, including 334 (9%) from Canada

Argentina (06 sites)
Australia (10 sites)
Brazil (25 sites)

Canada (17 sites)
China (47 sites)
Colombia (2 sites)

New Zealand (7 sites)
Peru (75 sites)

Russia (20 sites)
Ukraine (13 sites)



Berwanger et al *JAMA Cardiology* 2018;in press



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

Selected Baseline Characteristics

| Characteristic | Ticagrelor (n=1,913) | Clopidogrel (n=1,886) |
|------------------------------------|-------------------------|--------------------------|
| Median age, years | 59 | 59 |
| Male, % | 77 | 77 |
| CV risk factors, % | | |
| Smoker | 46 | 47 |
| Hypertension | 56 | 57 |
| Dyslipidemia | 27 | 28 |
| Diabetes Mellitus | 17 | 16 |
| History, % | | |
| Myocardial Infarction | 9 | 8 |
| Percutaneous coronary intervention | 6 | 5 |
| Anterior (\pm Inferior) STEMI | 37 | 38 |
| Inferior (alone) STEMI | 31 | 30 |
| Killip Class ≥ 2 | 8 | 9 |

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 |
| Retepase | 17 | 17 |
| Non-fibrin specific (e.g., Streptokinase) | 23 | 24 |

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 | | |
| Within 24 hours after randomization | 57 | 56 |
| Cardiac surgery | 42 | 42 |
| | 2 | 2 |

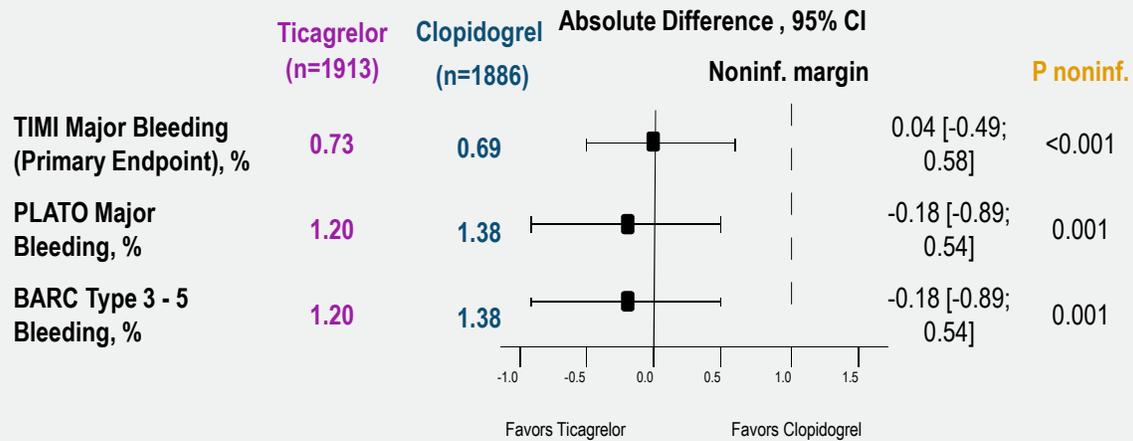
90% of patients had received clopidogrel prior to randomization. PCI was undertaken in 57% of patients, including 42% within 24 hours of randomization.

In-Hospital Treatments

| Medication | Ticagrelor (n=1,913) | Clopidogrel (n=1,886) |
|----------------------------------|-------------------------|--------------------------|
| In-hospital treatment , % | | |
| Aspirin | 99 | 99 |
| Unfractionated 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 |

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

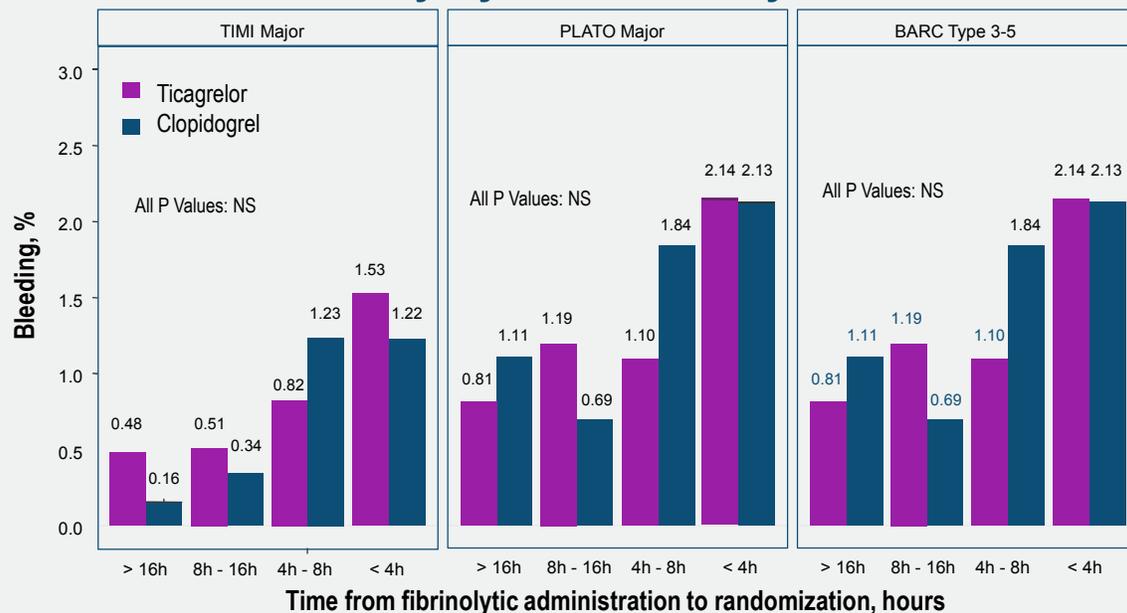


* Absolute difference (in percentage) presented as bilateral 95% confidence interval.

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

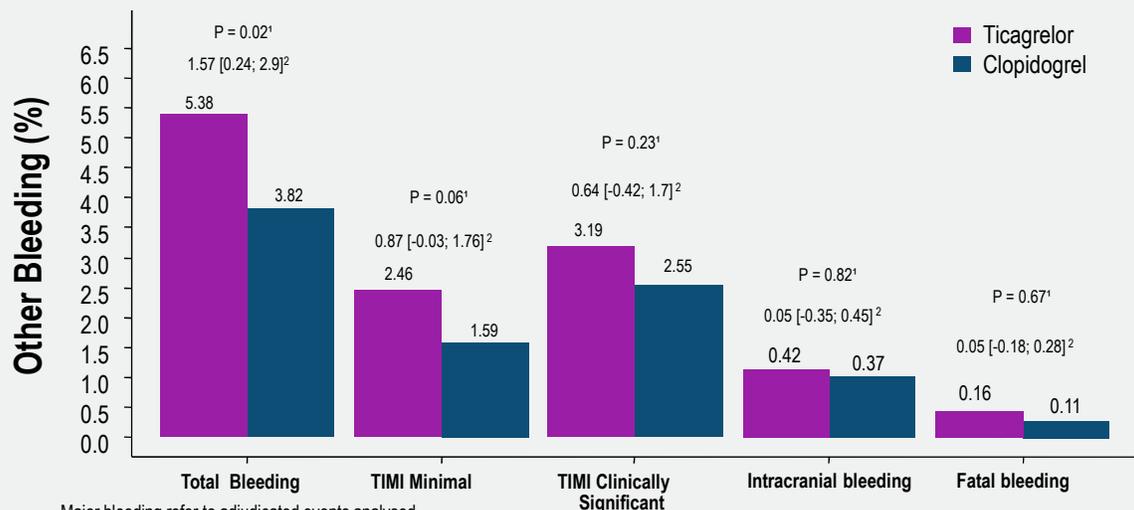
The primary outcome of TREAT is major bleeding (according to the TIMI definition) at 30 days; major bleeding rates by TIMI, PLATO, and BARC (Type 3-5) definitions were very low in both treatment groups. The absolute difference between ticagrelor and clopidogrel was -0.04%. All of the upper 95% confidence 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.

Safety by Time from Lysis



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.

Other Bleeding Outcomes



Major bleeding refer to adjudicated events analysed.
¹Proportion of patients (%)
¹ two-sided proportions
² Absolute difference (%), 95% CI = confidence interval

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 P2Y₁₂ receptor inhibitor compared to clopidogrel. However, intracranial and fatal bleeding were infrequent and not substantially different.

Conclusions and Implications

- In patients aged <75 years with STEMI and initial treatment with clopidogrel, administration of ticagrelor after fibrinolytic therapy was noninferior to clopidogrel for TIMI, PLATO, and BARC major bleeding at 30 days
- Total bleeding was increased with ticagrelor but no differences in intracranial or fatal bleeding were observed
- Ticagrelor is a reasonable option for patients <75 years who have received fibrinolytic therapy (and concomitant clopidogrel in ~90%) within the past 24 hours, with comparable safety compared to clopidogrel

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.