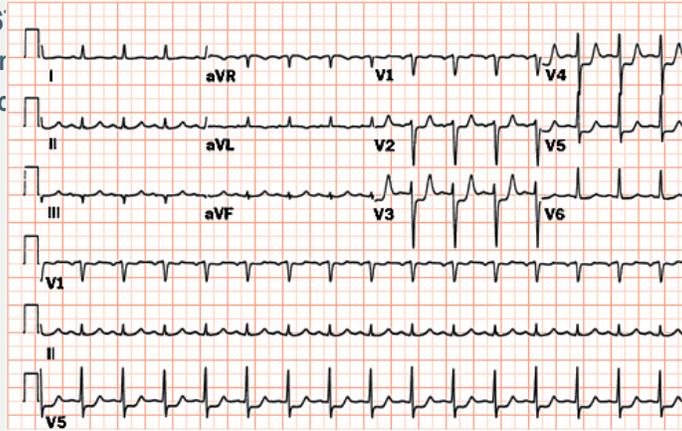


- 76 year old female
- Prior Hypertension, Hyperlipidemia, Smoking
- On Hydrochlorothiazide, Atorvastatin
- New onset chest discomfort; 2 episodes in past 24 hours
- Heart rate 122/min; BP 170/92 mm Hg, Killip Class I
- ECG = S
- Creatinin
- Hemoglc



The case is one of a high risk non-ST-segment elevation myocardial infarction (NSTEMI) patient who presents with ST-segment depression (V_2 - V_6) and an elevated troponin. The choice of dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA; Aspirin®) and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) is raised.

- 76 year old female
- Prior Hypertension, Hyperlipidemia, Smoking
- On Hydrochlorothiazide, Atorvastatin
- New onset chest discomfort; 2 episodes in past 24 hours
- Heart rate 122/min; BP 170/92 mm Hg, Killip Class I
- ECG = ST depression; troponin “positive”
- Creatinine 110 $\mu\text{mol/L}$; eGFR 45 ml/min/1.73m²
- Hemoglobin 124 g/L

What oral antiplatelet therapy would you choose?

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

The patient received ASA and clopidogrel as prescribed by the emergency department (ED) physician.



Antithrombotic Therapies in NSTEMI at Presentation

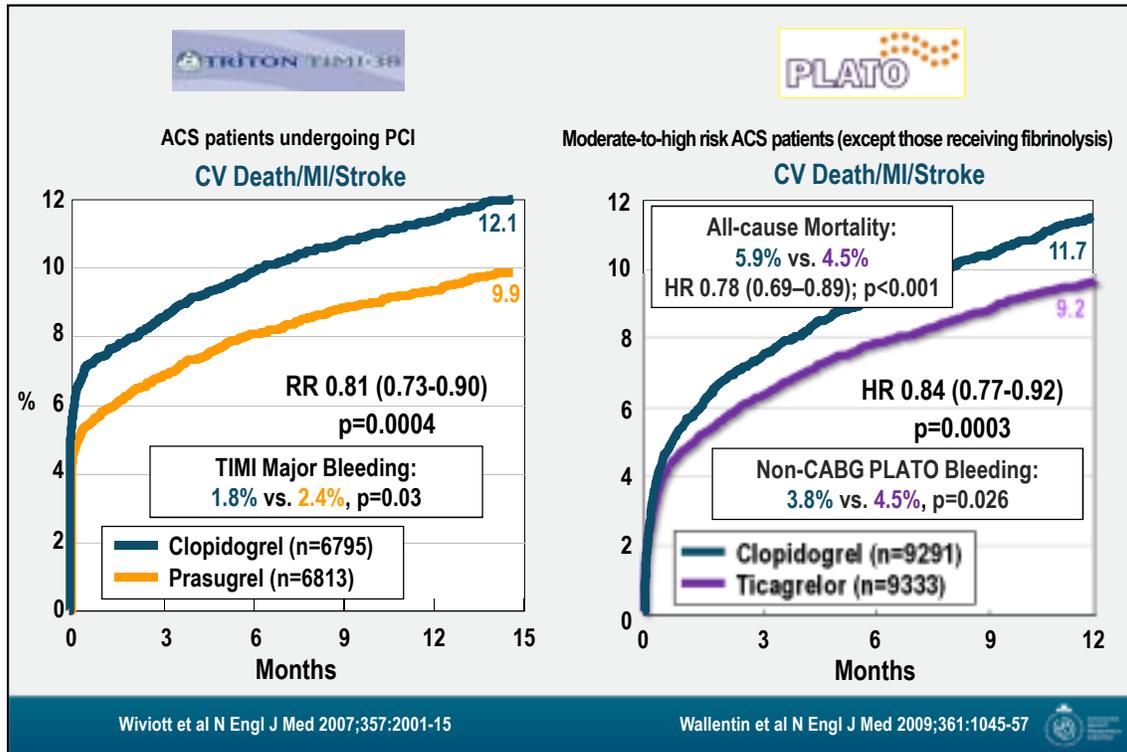
	Present/ 24 hrs (%)
ASA	100
Clopidogrel	44
Prasugrel	2
Ticagrelor	53

Why not ticagrelor?

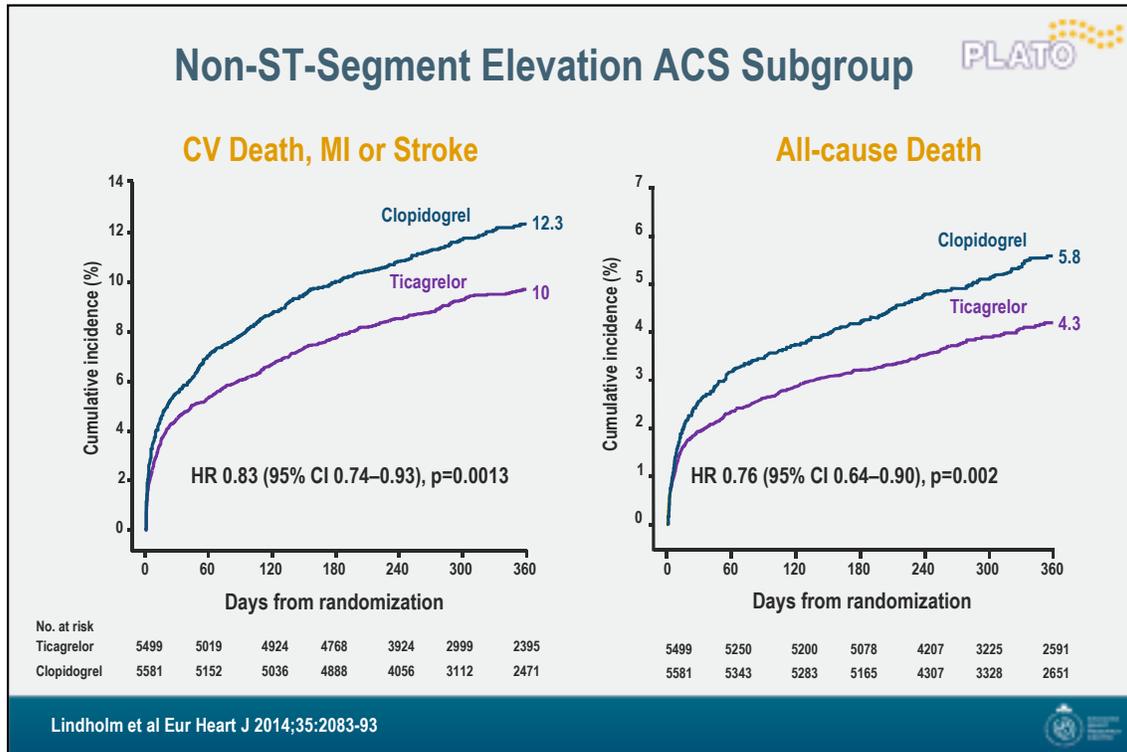
MD preference or admitting MD selected clopidogrel (17%)
 Perceived high bleeding risk (23%)
 [advanced age 11%, renal disease 7%, OAC 5%]
 Likely needs CABG (7%)

Unpublished data

The Canadian ACS Reflective II is an ongoing observational study of NSTEMI patients. Of the approximate 500 patients who have been enrolled thus far, use of DAPT by the frontline physician and/or specialist within the first 24 hours of presentation is appropriately (as per guideline recommendations) quite high. All patients received initial ASA and 99% received a P2Y₁₂ receptor inhibitor, with 53% prescribed ticagrelor, 44% clopidogrel, and 2% prasugrel. Since the Canadian Cardiovascular Society (CCS)/Canadian Association of Interventional Cardiologists (CAIC) 2018 Focused Update recommends preferential use of ticagrelor over clopidogrel, the most responsible physician (MD) was asked why ticagrelor wasn't used in about half of the patients. The reasons, including perceived high bleeding risk (23%; for advanced age, concomitant renal disease, and need for oral anticoagulant [OAC]), potential need for coronary artery bypass grafting surgery (CABG; 7%), and MD preference (or the admitting MD selected clopidogrel), suggests an opportunity in some cases to optimize the choice of P2Y₁₂ receptor inhibitor.



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.



Subgroup analysis of the PLATO trial in patients with NSTEMI and unstable angina, demonstrating that the 1-year rates of the primary endpoint (CV death, MI, or stroke; left panel) and all-cause death (right panel) are high amongst this NSTEMI cohort. Further, the relative benefit of ticagrelor over clopidogrel was consistent with the overall trial results across the spectrum of ACS patients, such that the absolute benefit of ticagrelor is numerically greater absolute benefit (with a lower number needed to treat [NNT]) than that observed in the STEMI subgroup (data not shown).



2012 Focused Update on the Canadian Cardiovascular Society Guidelines for the use of Antiplatelet Therapy Antiplatelet Therapy for Secondary Prevention in the First Year Following STEMI and NSTEMI

Strong preference for the new ADP receptor inhibitors over clopidogrel (in addition to ASA 81 mg daily) for 1 year

Values & Preferences: Recommendations place greater emphasis on reduction of major cardiovascular events and stent thrombosis vs. an increase in bleeding complications.

Amongst patients with ACS, including NSTEMI, the CCS 2012 Focused Update includes the recommendation for preferential use of ticagrelor (or prasugrel if the patient has undergone PCI) 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.

SECONDARY PREVENTION POST ACS and BEYOND

LIFESTYLE RECOMMENDATIONS

- Stop smoking
- Weight reduction
- Increased physical activity
- Stress management
- Depression Counseling
- Healthy diet

Recommended	Alternative	Consideration
<ul style="list-style-type: none"> ■ Dual antiplatelet therapy → ASA 81mg + 1 year of Ticagrelor 90mg od 	<ul style="list-style-type: none"> Prasugrel 20mg od Clopidogrel 75mg od 	<ul style="list-style-type: none"> Consider Ticagrelor 90mg BID 1 year post-ACS for high risk
<ul style="list-style-type: none"> ■ ACE inhibition (in absence of heart failure or LVEF <40%) → Ramapril 10mg od or Perindopril 4mg od 	<ul style="list-style-type: none"> Trinitentan 80mg od (if ACE intolerant) 	<ul style="list-style-type: none"> For low risk, consider setting: <ul style="list-style-type: none"> ■ Lisinopril 10mg od and ■ Candesartan 16-32mg od or ■ PCSK9 inhibitor: <ul style="list-style-type: none"> ■ Evolocumab 140 mg q2w ■ Inclisiran 180 mg q2w
<ul style="list-style-type: none"> ■ Beta-blocker (in absence of heart failure or LVEF <40%) → Metoprolol 50mg bid or Carvedilol 12.5-25mg bid or Bisoprolol 50mg od 	<ul style="list-style-type: none"> Bisoprolol 10mg od 	
<ul style="list-style-type: none"> ■ BP Control → CHEP based algorithm using evidence based medications 		<ul style="list-style-type: none"> As needed: DHP CCB = Amlodipine Chlorthalidone/Simvastatin Ezetimibe 10 or 25mg OD
<ul style="list-style-type: none"> ■ Glycemic control → ADA based algorithm using evidence based medications 		

For patients with Heart Failure / LVEF < 40%

- ACEi (Perindopril 4mg OD or Ramapril 5mg BID or Trandolapril 1-4mg OD or Enalapril 5-20mg OD) or ARB (Valsartan 80-160mg BID or Candesartan 16-32mg OD)
- Beta blocker (Bisoprolol 10mg OD or Carvedilol 25mg BID)
- Spironolactone 25-50mg OD or Eplerenone 25-50mg OD
- Sacubitril / Valsartan 200mg BID for symptomatic patients (NYHA II-IV) already on ACEi or ARB

- ICD for EF < 35% and > 40 days post-MI
- CRT for EF < 35% and QRS > 130 msec

Fitchett et al Can J Cardiol 2016;32:S15-34

Similarly, recommendations for DAPT, including the preferential use of ticagrelor, are highlighted in a secondary prevention post-ACS paper from Fitchett et al.

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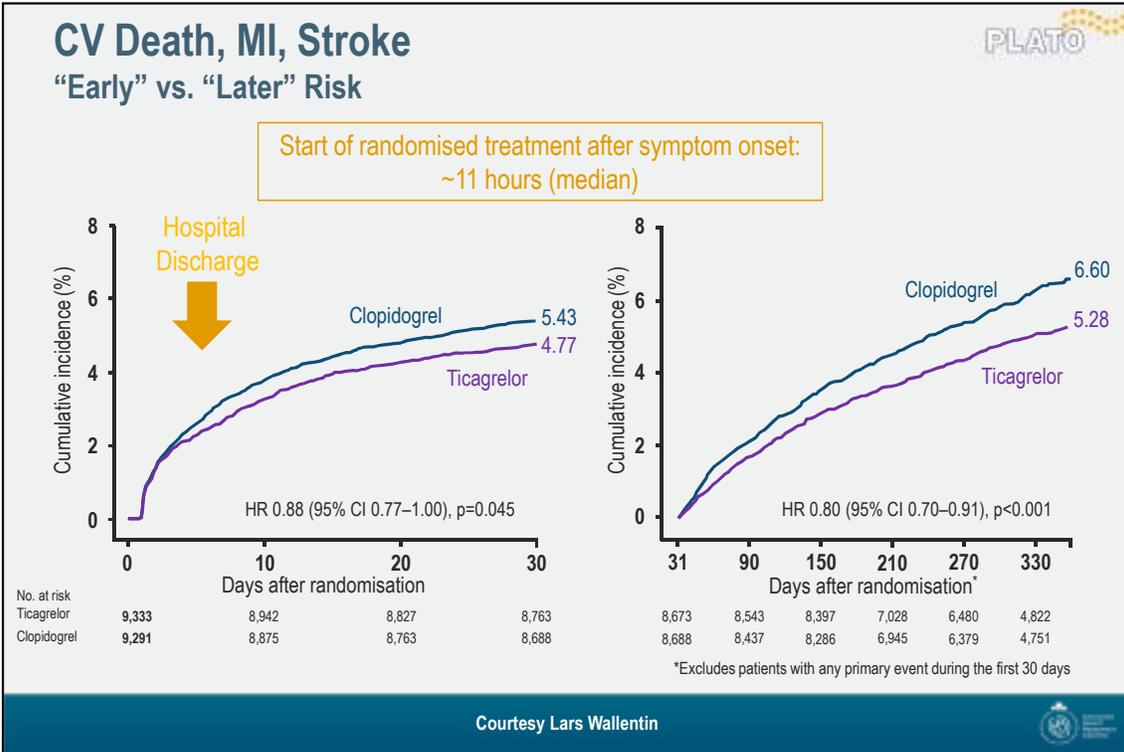
You are asked to consult on this patient the morning after admission (~12 hours after presentation). She is clinically stable; her ECG is now normal; the 2nd troponin level is higher than the first one.

Would you switch this patient’s P2Y₁₂ receptor inhibitor therapy from clopidogrel to ticagrelor?

- a) Yes
- b) No

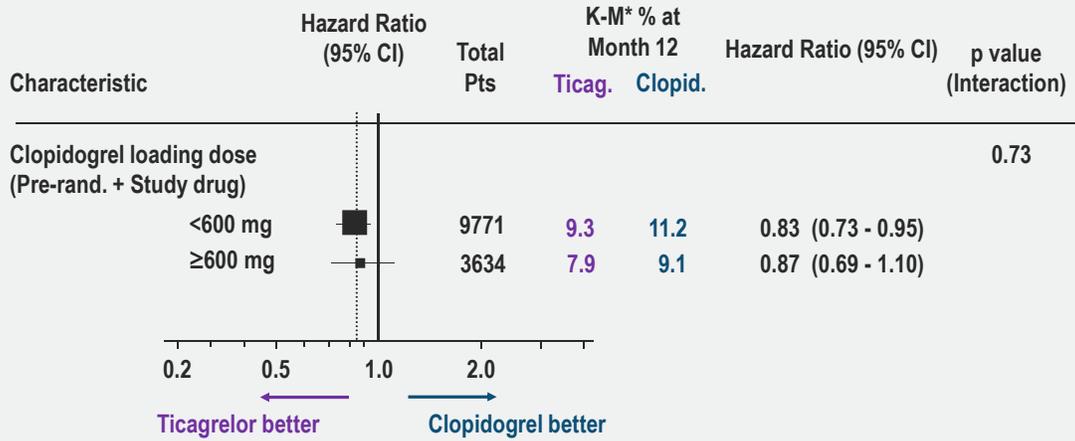


Returning to the NSTEMI case, the choice of either maintaining clopidogrel or switching to ticagrelor is raised for the MD now consulting on the patient’s oral antiplatelet therapy management.



The value of ticagrelor over clopidogrel in the PLATO trial is further highlighted by this landmark analysis of the primary endpoint (CV Death, MI, or Stroke). Recognizing that approximately half of the patients enrolled in the PLATO trial received clopidogrel initially and that randomization after symptom onset to ticagrelor or “continued” clopidogrel occurred a median of 11 hours later, the early (≤ 30 days; left panel) and later (>30 days-1 year; right panel) benefits of ticagrelor over clopidogrel are demonstrated.

Planned Invasive Strategy: Primary Efficacy Endpoint (CV Death/MI/Stroke) by Clopidogrel Loading Dose



* K-M = Kaplan-Meier estimate



In the PLATO trial, regardless of whether the patient received any clopidogrel, or what dose of clopidogrel administered as part of initial treatment before randomized allocation to ticagrelor or clopidogrel, the benefit of ticagrelor over clopidogrel was consistently observed.

Canadian Cardiovascular Society

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

Examples of common clinical scenarios for P2Y₁₂ inhibitor switching

Intensification from clopidogrel to prasugrel or ticagrelor	Switching between prasugrel and ticagrelor	De-escalation from prasugrel or ticagrelor to clopidogrel
<p>In patients:</p> <ul style="list-style-type: none"> - with ACS, who are initially treated with clopidogrel at presentation - admitted with thrombotic event (e.g., stent thrombosis or ACS), who have been treated with clopidogrel - who are known poor metabolizer of clopidogrel (e.g., CYP2C19 loss-of-function) 	<p>In patients:</p> <ul style="list-style-type: none"> -with intolerance or side effects, who have additional high-risk clinical or angiographic features for thrombotic events warranting completion of the prescribed course of DAPT -admitted with thrombotic event (e.g., stent thrombosis or ACS), who have been treated with the initial P2Y₁₂ receptor inhibitor agent -interactions between CYP3A inducers and ticagrelor which affect its pharmacodynamics 	<p>In patients with:</p> <ul style="list-style-type: none"> -major bleeding complication that has resolved, who have additional high-risk clinical or angiographic features for thrombotic events, warranting completion of the prescribed course of DAPT -clinically relevant nuisance bleeding that interferes with patient's ability to continue with prasugrel or ticagrelor -intolerance or side effects to prasugrel / ticagrelor in patients who do not have additional high-risk clinical or angiographic features for thrombotic events -a new indication for requiring concurrent treatment with an oral anticoagulant

Mehta et al Can J Cardiol 2018; doi: 10.1016/j.cjca.2017.12.012

Thus, the CCS/Canadian Association of Interventional Cardiologists (CAIC) 2018 Focused Update includes the recommendation for intensification of P2Y₁₂ receptor inhibitor therapy from clopidogrel with ticagrelor (or prasugrel if the patient is undergoing PCI), including in ACS patients who are initially treated with clopidogrel at hospital presentation.

Intensification strategies

Switching from clopidogrel to ticagrelor

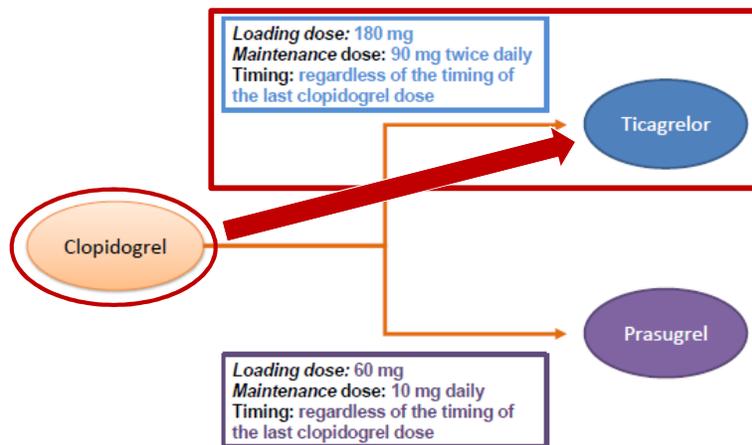
16. For patients requiring a switch from clopidogrel to ticagrelor, we **recommend** a ticagrelor loading dose of 180 mg followed by 90 mg twice daily, regardless of the timing of the last clopidogrel dose (**Strong Recommendation, Moderate Quality Evidence**).

Switching from clopidogrel to prasugrel

17. For patients requiring a switch from clopidogrel to prasugrel, we **recommend** a prasugrel loading dose of 60 mg followed by 10 mg daily, regardless of the timing of the last clopidogrel dose (**Strong Recommendation, Moderate Quality Evidence**).

The CCS/CAIC Guidelines specifically recommend a loading dose of ticagrelor (180 mg PO) followed by a maintenance dose (90 mg PO BID), regardless of the timing of the last clopidogrel dose.

Intensification strategies



The CCS/CAIC Guidelines specifically recommend a loading dose of ticagrelor (180 mg PO) followed by a maintenance dose (90 mg PO BID), regardless of the timing of the last clopidogrel dose.

- 76 year old female
- Prior Hypertension, Hyperlipidemia, Smoking
- On Hydrochlorothiazide, Atorvastatin
- New onset chest discomfort; 2 episodes in past 24 hours
- Heart rate 122/min; BP 170/92 mm Hg, Killip Class I
- ECG = ST depression; troponin “positive”
- Creatinine 110 $\mu\text{mol/L}$; eGFR 45 ml/min/1.73m²
- Hemoglobin 124 g/L

You are asked to consult on this patient the morning after admission (~12 hours after presentation). She is clinically stable; her ECG is now normal; the 2nd troponin level is higher than the first one.

Would you switch this patient’s P2Y₁₂ receptor inhibitor therapy from clopidogrel to ticagrelor?

- a) Yes → 180 mg load followed by 90 mg BID
- b) No



According to the CCS/CAIC Guideline recommendations, the consulting MD switched the case patient’s clopidogrel to ticagrelor.

- 76 year old female
- Prior Hypertension, Hyperlipidemia, Smoking
- On Hydrochlorothiazide, Atorvastatin
- New onset chest discomfort; 2 episodes in past 24 hours
- Heart rate 122/min; BP 170/92 mm Hg, Killip Class I
- ECG = ST depression; troponin “positive”
- Creatinine 110 $\mu\text{mol/L}$; eGFR 45 ml/min/1.73m²
- Hemoglobin 124 g/L

Would you refer this patient to coronary angiography?

- a) Yes
- b) No



Returning to the case, the consulting MD is asked whether the high risk NSTEMI patient should be referred for coronary angiography. The patient is transferred on day 3 and undergoes coronary angiography. This reveals multivessel coronary artery disease with the presumed culprits (based on the presenting ECG and the angiographic characteristics) in the proximal left anterior descending (LAD) artery and mid-right coronary artery (RCA). The patient receives 2nd generation drug eluting stents (DES) and, consistent with the approach recommended in the PLATO trial, the patient received additional P2Y₁₂ receptor inhibitor therapy peri-PCI.

- 76 year old female
- Prior Hypertension, Hyperlipidemia, Smoking
- On Hydrochlorothiazide, Atorvastatin
- New onset chest discomfort; 2 episodes in past 24 hours
- Heart rate 122/min; BP 170/92 mm Hg, Killip Class I
- ECG = ST depression; troponin “positive”
- Creatinine 110 $\mu\text{mol/L}$; eGFR 45 ml/min/1.73m²
- Hemoglobin 124 g/L

Transferred on day 3 for coronary angiography:

90% proximal LAD, 50% proximal Circumflex and 80% OM₁, 90% mid- and 60% distal RCA stenoses

2nd generation DES placed in the proximal LAD and mid-RCA

Patients in PLATO undergoing PCI >24 hours after randomization were given an additional dose of study drug (i.e. 90 mg ticagrelor or 300 mg ASA and ticagrelor 90 mg BID clopidogrel)

Returning to the case, the consulting MD is asked whether the high risk NSTEMI patient should be referred for coronary angiography. The patient is transferred on day 3 and undergoes coronary angiography. This reveals multivessel coronary artery disease with the presumed culprits (based on the presenting ECG and the angiographic characteristics) in the proximal left anterior descending (LAD) artery and mid-right coronary artery (RCA). The patient receives 2nd generation drug eluting stents (DES) and, consistent with the approach recommended in the PLATO trial, the patient received additional P2Y₁₂ receptor inhibitor therapy peri-PCI.

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

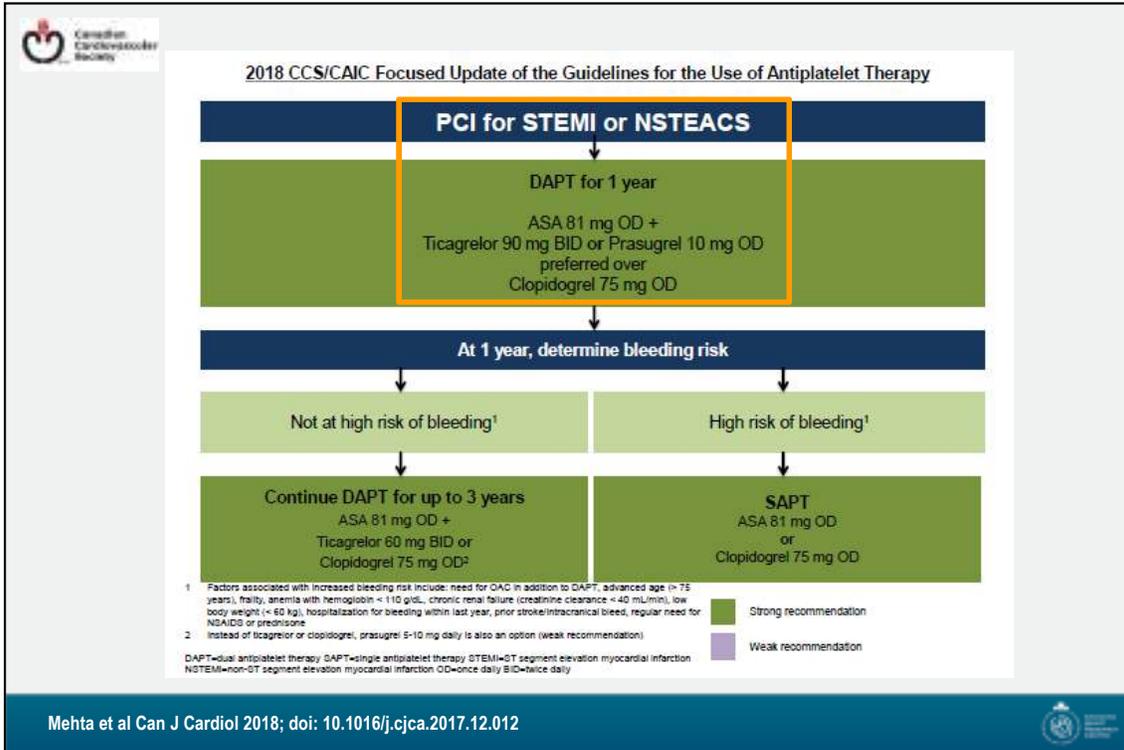
Recommendations

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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According to the CCS/CAIC Guideline recommendations, this NSTEMI patient who has undergone PCI should continue to receive ticagrelor for the next year.



According to the CCS/CAIC Guideline recommendations, this NSTEMACS patient who has undergone PCI should continue to receive ticagrelor for the next year.

...But what if...?

- 76 year old female
- Prior Hypertension, Hyperlipidemia, Smoking
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- New onset chest discomfort; 2 episodes in past 24 hours
- Heart rate 122/min; BP 170/92 mm Hg, Killip Class I
- ECG = ST depression; troponin “positive”
- Creatinine 110 $\mu\text{mol/L}$; eGFR 45 ml/min/1.73m²
- Hemoglobin 124 g/L

Transferred on day 3 for coronary angiography:

40% proximal LAD, multiple 30-40% proximal and mid Circumflex, 30-50% proximal, mid, and distal RCA stenoses



The case is revisited and asks “what if” the coronary angiogram revealed no significant ($\geq 50-70\%$) obstructive stenoses but demonstrates mild multivessel CAD such that the interventional cardiologist’s opinion is that PCI *not* be undertaken and that the patient should be treated medically? Would that medical management approach include continuation of DAPT post-discharge?

- 76 year old female
- Prior Hypertension, Hyperlipidemia, Smoking
- On Hydrochlorothiazide, Atorvastatin
- New onset chest discomfort; 2 episodes in past 24 hours
- Heart rate 122/min; BP 170/92 mm Hg, Killip Class I
- ECG = ST depression; troponin “positive”
- Creatinine 110 $\mu\text{mol/L}$; eGFR 45 ml/min/1.73m²
- Hemoglobin 124 g/L

Interventional cardiologists opinion: Treat medically

Would you recommend continuing DAPT post-discharge?

- a) Yes
- b) No

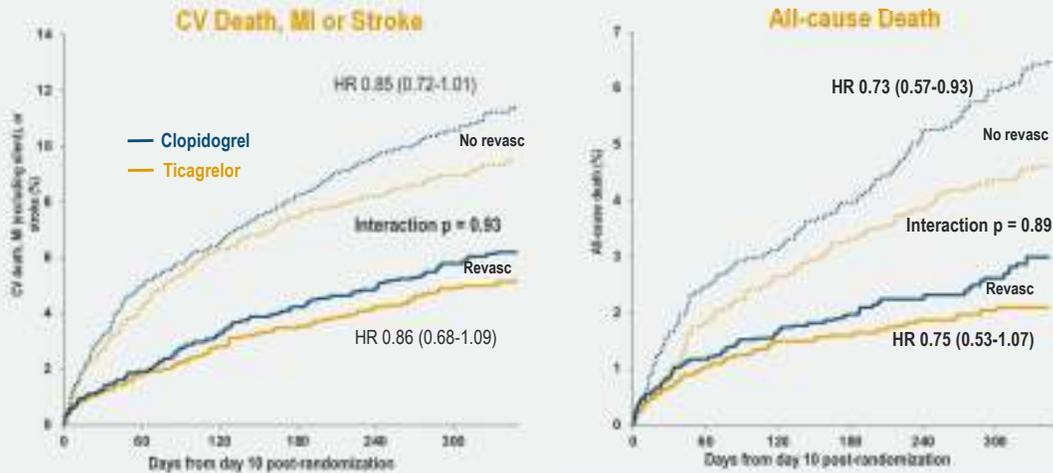


The case is revisited and asks “what if” the coronary angiogram revealed no significant ($\geq 50\text{-}70\%$) obstructive stenoses but demonstrates mild multivessel CAD such that the interventional cardiologist’s opinion is that PCI *not* be undertaken and that the patient should be treated medically? Would that medical management approach include continuation of DAPT post-discharge?

Non-ST-Segment Elevation ACS Subgroup



During the initial 10 days: 74% had angiography, 46% PCI, and 5% CABG*



*Regardless of revascularization or not, ticagrelor consistently reduced the primary outcome (HR 0.86 vs. 0.85, $P_{\text{int}}=0.93$), and all-cause death (HR 0.75 vs. 0.73, $P_{\text{int}}=0.89$)

Subgroup analysis of the PLATO trial in patients with NSTEMI and unstable angina, demonstrating that the 1 year rates of the primary endpoint (CV death, MI, or stroke; left panel) and all-cause death (right panel) are high amongst this NSTEMI cohort. Further, the relative benefit of ticagrelor over clopidogrel was consistent with the overall trial results across the spectrum of ACS patients, such that the absolute benefit of ticagrelor is numerically greater absolute benefit (with a lower number needed to treat [NNT]) than that observed in the STEMI subgroup (data not shown). In addition, while 74% of these patients underwent coronary angiography and 51% underwent revascularization (with PCI or CABG), those who were medically managed had even higher event rates. However, the relative benefit of ticagrelor over clopidogrel was maintained, regardless of whether revascularization was performed, such that the absolute benefit of ticagrelor was greatest in the medically managed cohort.

Non-ST-Segment Elevation ACS Subgroup



	Significant disease				No significant disease				Interaction p
	N	Ticagrelor KM rate	Clopidogrel KM rate	HR (95% CI)	N	Ticagrelor KM rate	Clopidogrel KM rate	HR (95% CI)	
CV death / MI (excluding silent) / Stroke	6911	6.34	7.46	0.87 (0.73, 1.05)	810	1.78	4.10	0.46 (0.18, 1.16)	0.1843
All cause death	7153	2.59	3.41	0.80 (0.61, 1.06)	816	0.74	3.11	0.26 (0.07, 0.93)	0.0906
Major bleeding (study criteria)	6419	10.32	9.33	1.11 (0.94, 1.31)	700	2.37	3.73	0.78 (0.28, 2.14)	0.4963

Regardless of angiographic severity of disease, ticagrelor consistently reduced the primary outcome (HR 0.87 vs. 0.46, $P_{int}=0.18$) and all-cause death (HR 0.80 vs. 0.26, $P_{int}=0.09$) with similar risk of major bleeding (HR 1.11 vs. 0.78, $P_{int}=0.50$)

Greatest relative (HR 0.81 [0.65, 0.99]) AND absolute benefit of ticagrelor observed in NSTEMI patients who did NOT undergo revascularization (i.e., medically managed)

Further, regardless of angiographic severity of disease, ticagrelor consistently reduced the primary outcome and all-cause death with similar risk of major bleeding. Indeed, the greatest relative and absolute benefit of ticagrelor was observed in the NSTEMI patients who were medically managed.

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Interventional cardiologists opinion: Treat medically

Would you recommend continuing DAPT post-discharge?

- a) Yes → Ticagrelor 90 mg BID
- b) No



Thus, even though the patient did not undergo PCI and was managed medically, the consulting MD appropriately recommended continuation of ticagrelor 90 mg PO twice daily for the next year.