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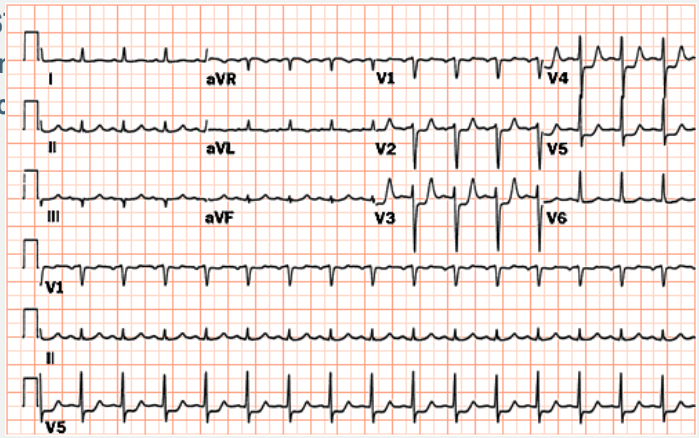

The case is one of a high risk non-ST-segment elevation myocardial infarction (NSTEMI) patient who presents with ST-segment depression (V_2-V_6) and an elevated troponin. The choice of dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA; Aspirin®) and a $P2Y_{12}$ receptor inhibitor (clopidogrel,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

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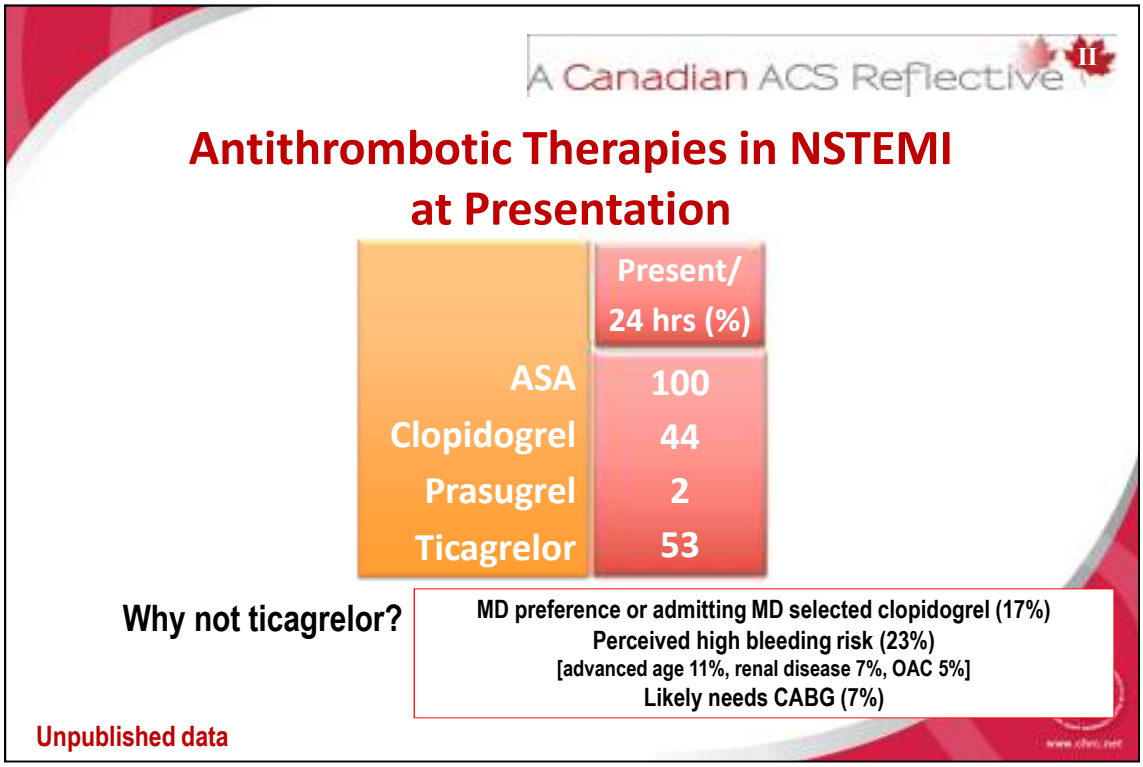
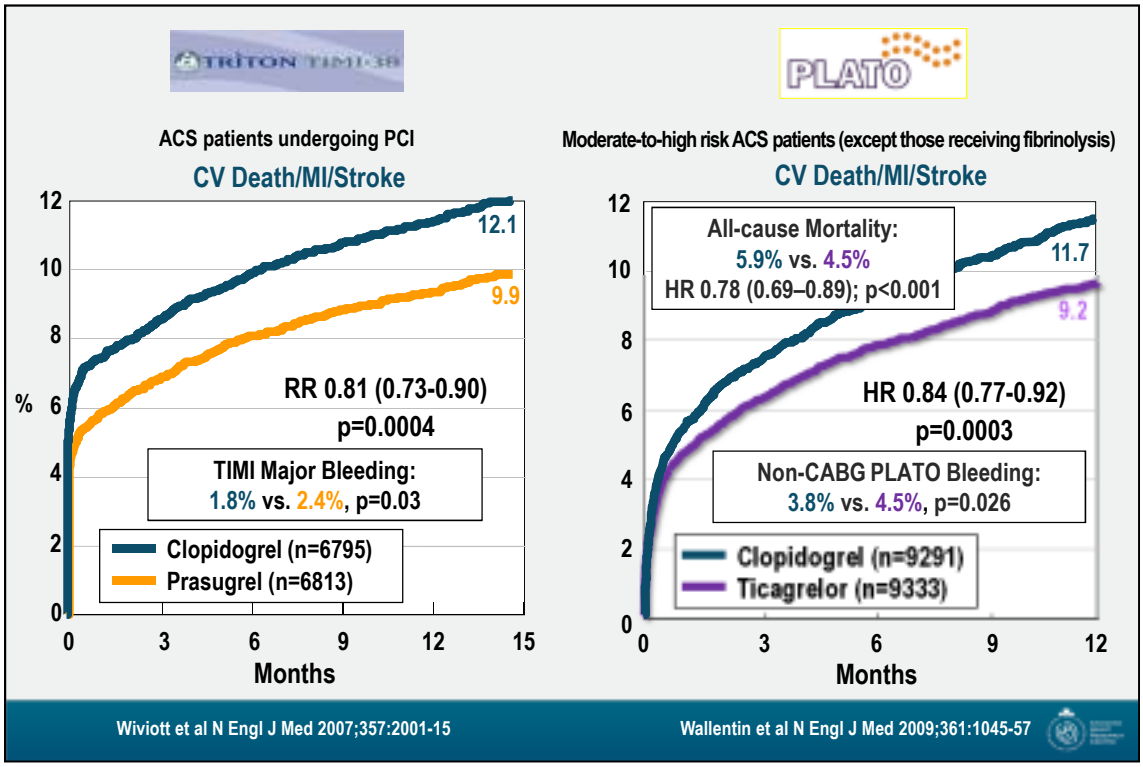
What oral antiplatelet therapy would you choose?

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

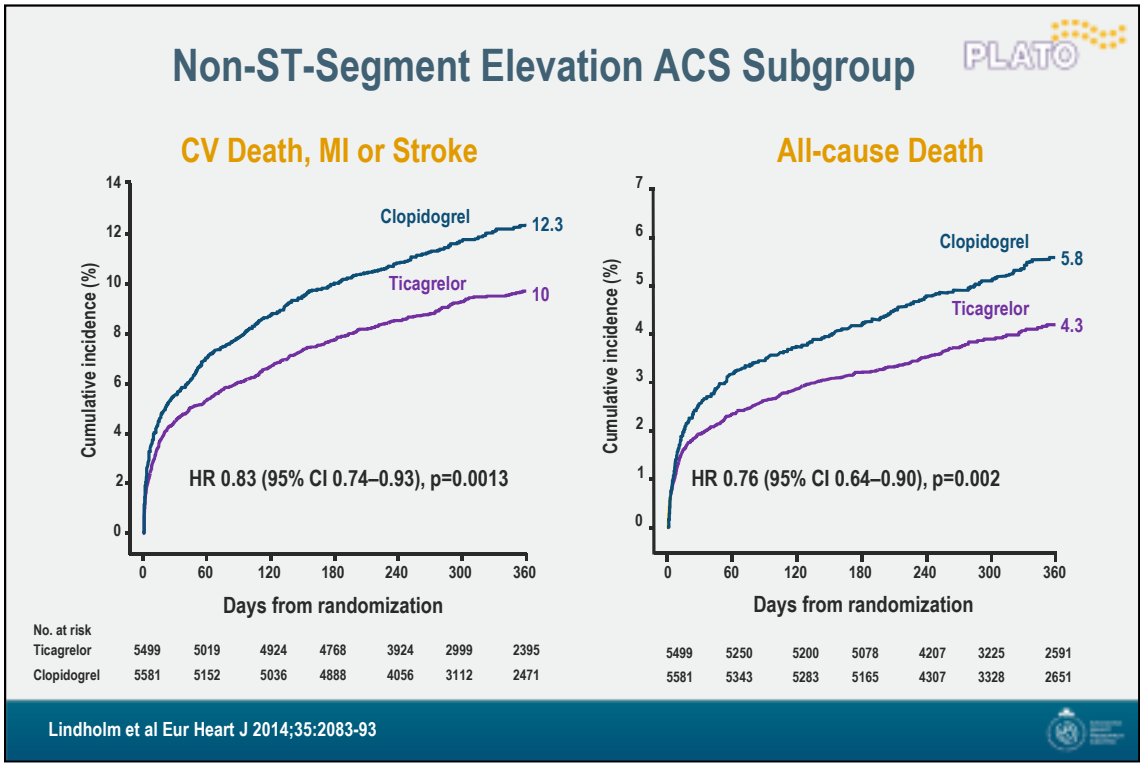
The patient received ASA and clopidogrel as prescribed by the emergency department (ED) physician.



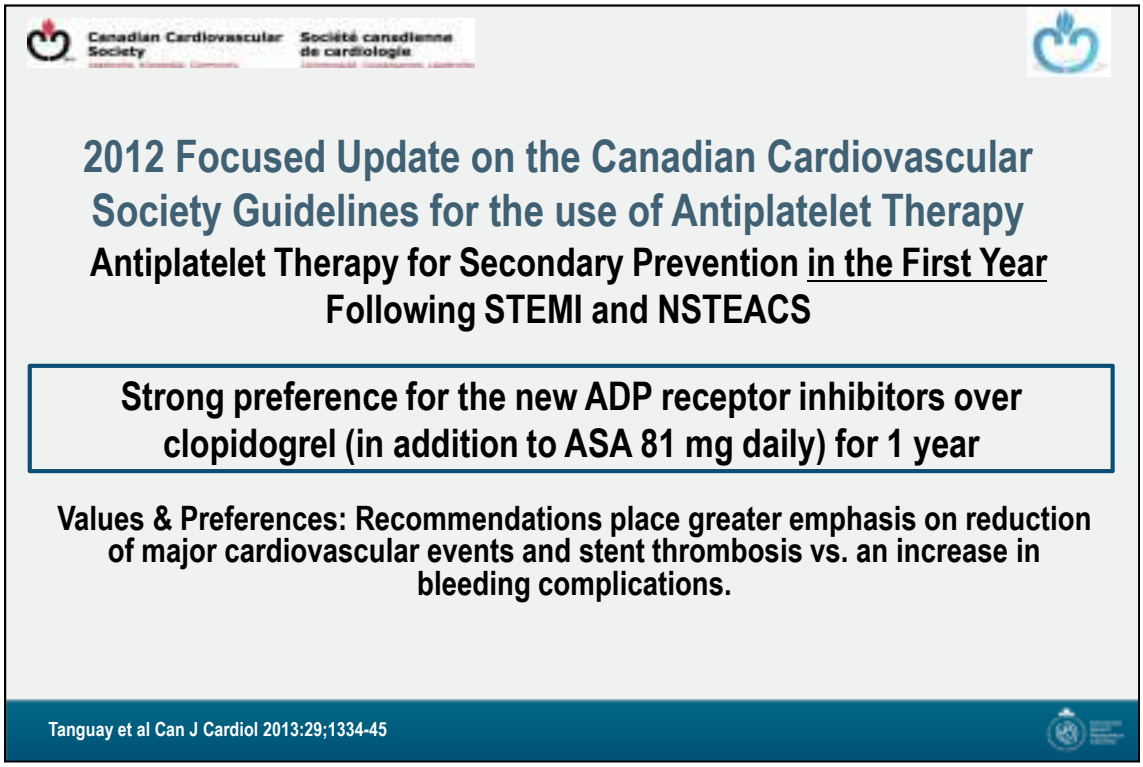
The Canadian ACS Reflective II is an ongoing observational study of NSTEMI patients. Of the approximate 500 patients who have been enrolled thus far, use of DAPT by the frontline physician and/or specialist within the first 24 hours of presentation is appropriately (as per guideline recommendations) quite high. All patients received initial ASA and 99% received a $P2Y_{12}$ 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 $P2Y_{12}$ receptor inhibitor.



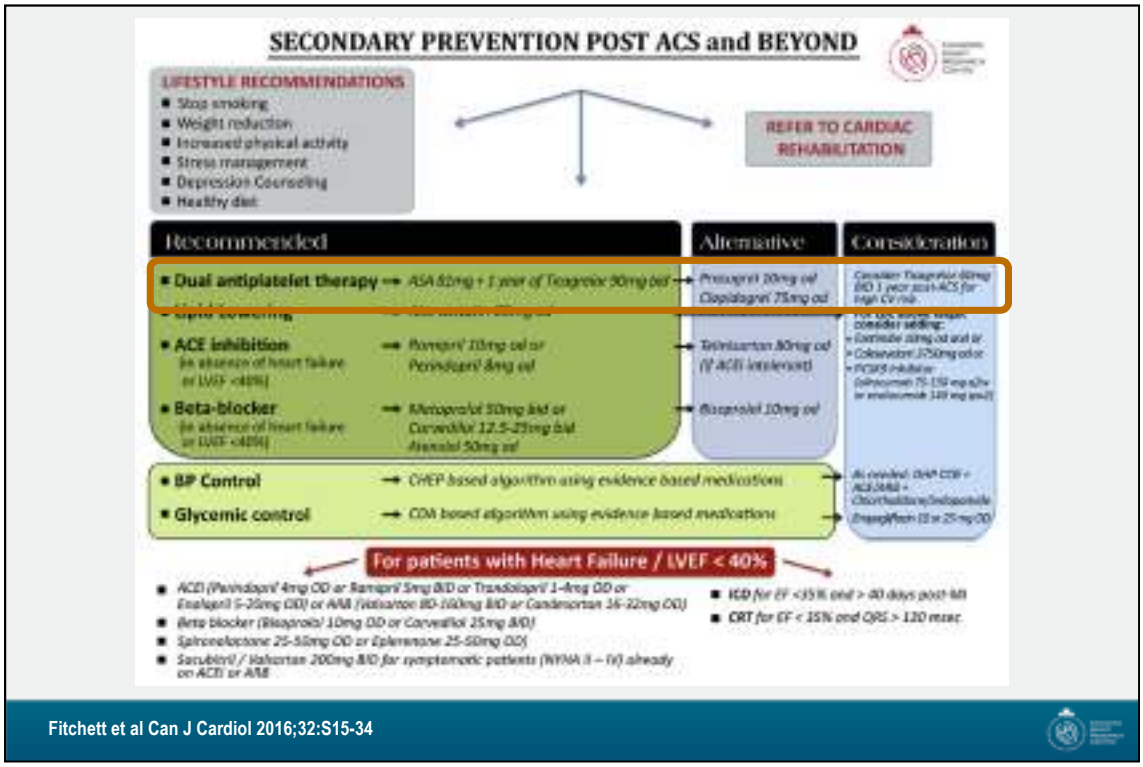
The primary efficacy (time to first cardiovascular [CV] death, myocardial infarction [MI], or stroke) and safety (Major Bleeding) outcomes in the TRITON TIMI-38 (left panel) and PLATO (right panel) trials are presented. In the broad spectrum of ACS patients in the two trials, the more potent $P2Y_{12}$ 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 PLATO trial in patients with NSTE ACS, including NSTEMI and unstable angina, demonstrates that the 1 year rates of the primary endpoint (CV death, MI, or stroke; left panel) and all-cause death (right panel) are high amonst this NSTEACS 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).



Amongst patients with ACS, including NSTEACS, 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 $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor vs. clopidogrel.



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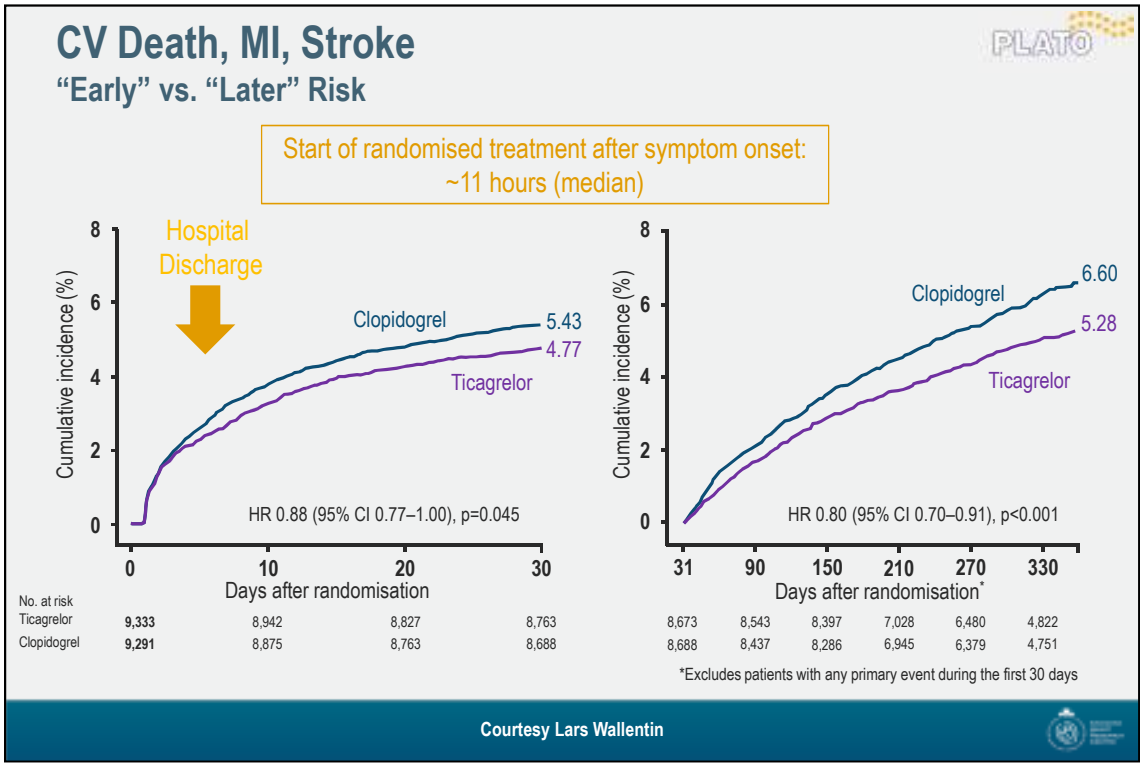
You are asked to consult on this patient the morning after admission (~12 hours after presentation). She is clinically stable; her ECG is now normal; the 2nd troponin level is higher than the first one.

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

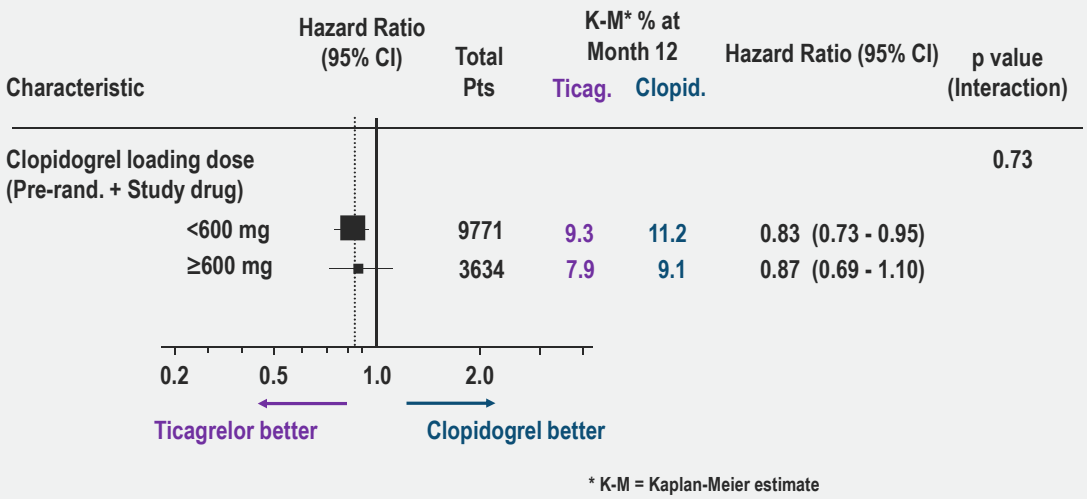
a) Yes
b) No

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.



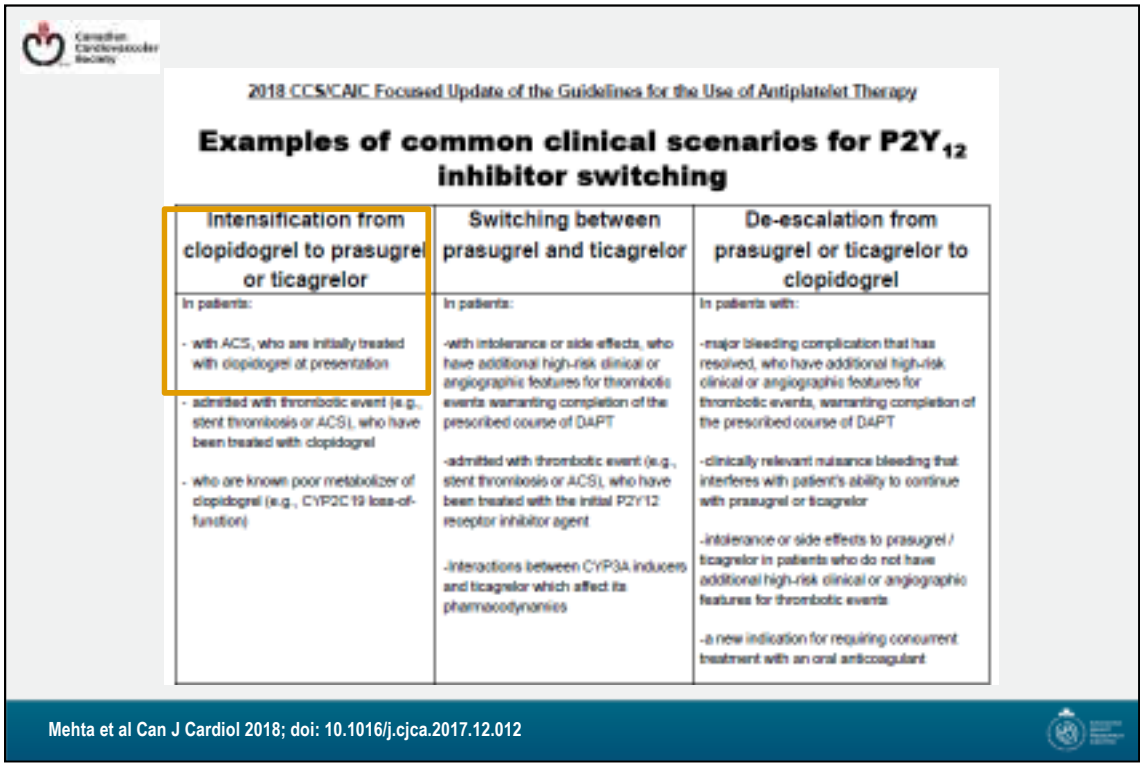
The value of ticagrelor over clopidogrel in the PLATO trial is further highlighted by this landmark analysis of the primary endpoint (CV Death, MI, or Stroke). Recognizing that approximately half of the patients enrolled in the PLATO trial received clopidogrel initially and that randomization after symptom 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 Stragey: Primary Efficacy Endpoint (CV Death/MI/Stroke) by Clopidogrel Loading Dose

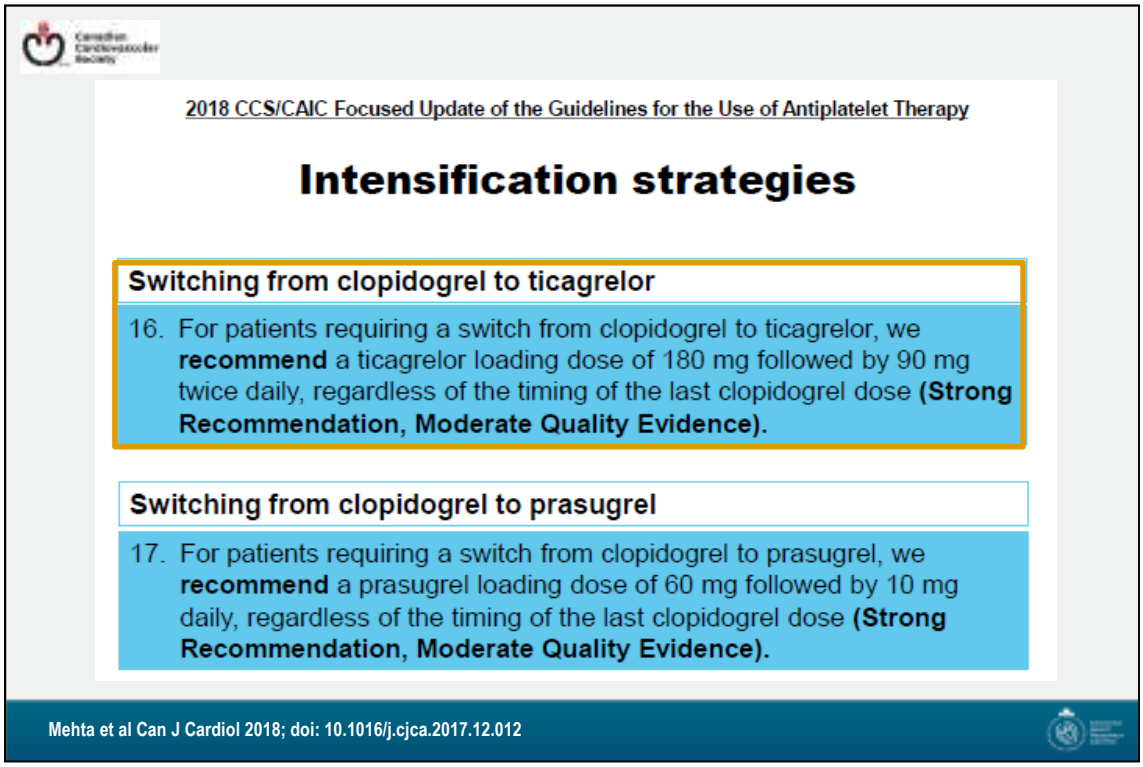


Cannon et al Lancet 2010: 375;283-93

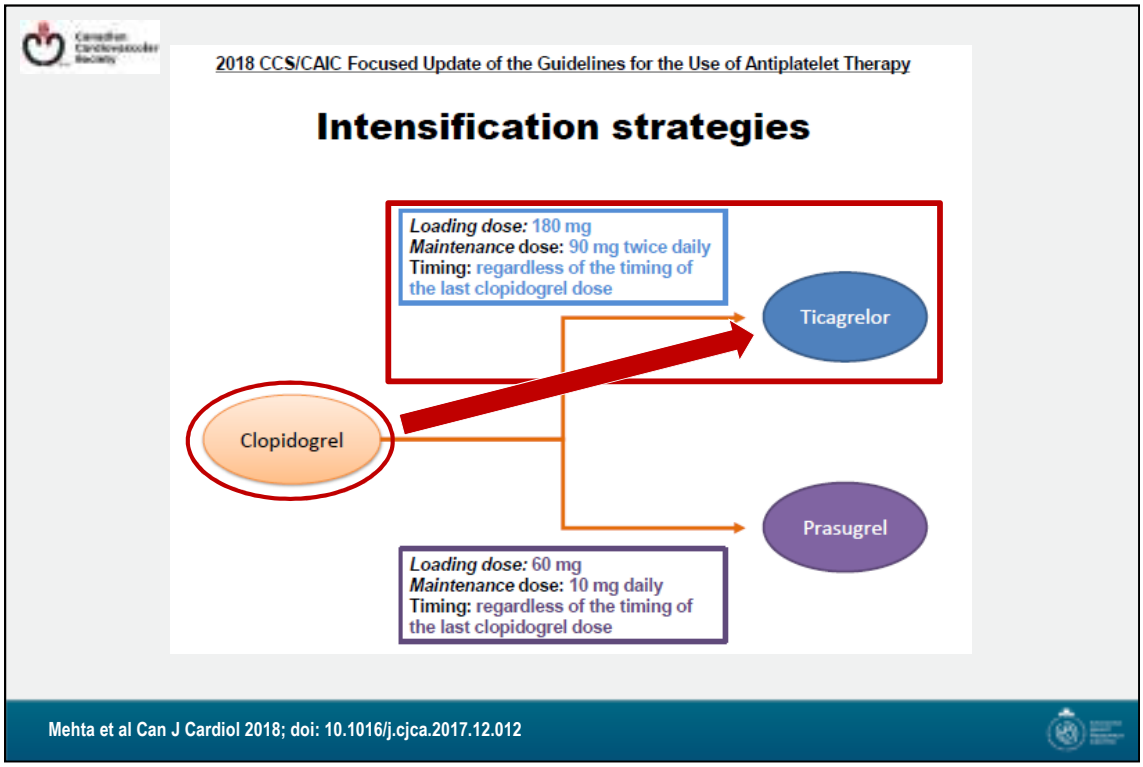
In the PLATO trial, regardless of whether the patient received any clopidogrel, or what dose of clopidogrel administered as part of initial treatment before randomized allocation to ticagrelor or clopidogrel, the benefit of ticagrelor over clopidogrel was consistently observed.



Thus, the CCS/Canadian Association of Interventional Cardiologists (CAIC) 2018 Focused Update includes the recommendation for intensification of $P2Y_{12}$ 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.



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.



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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 →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.

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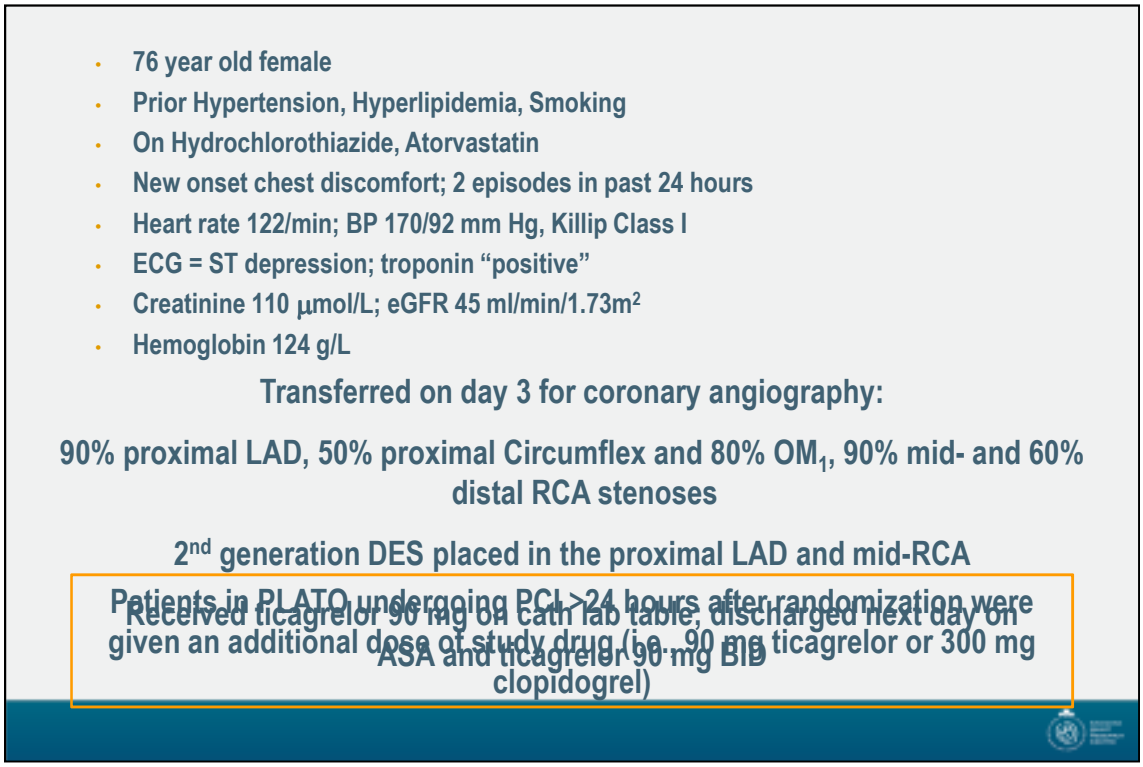
Would you refer this patient to coronary angiography?

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 $P2Y_{12}$ receptor inhibitor therapy peri-PCI.



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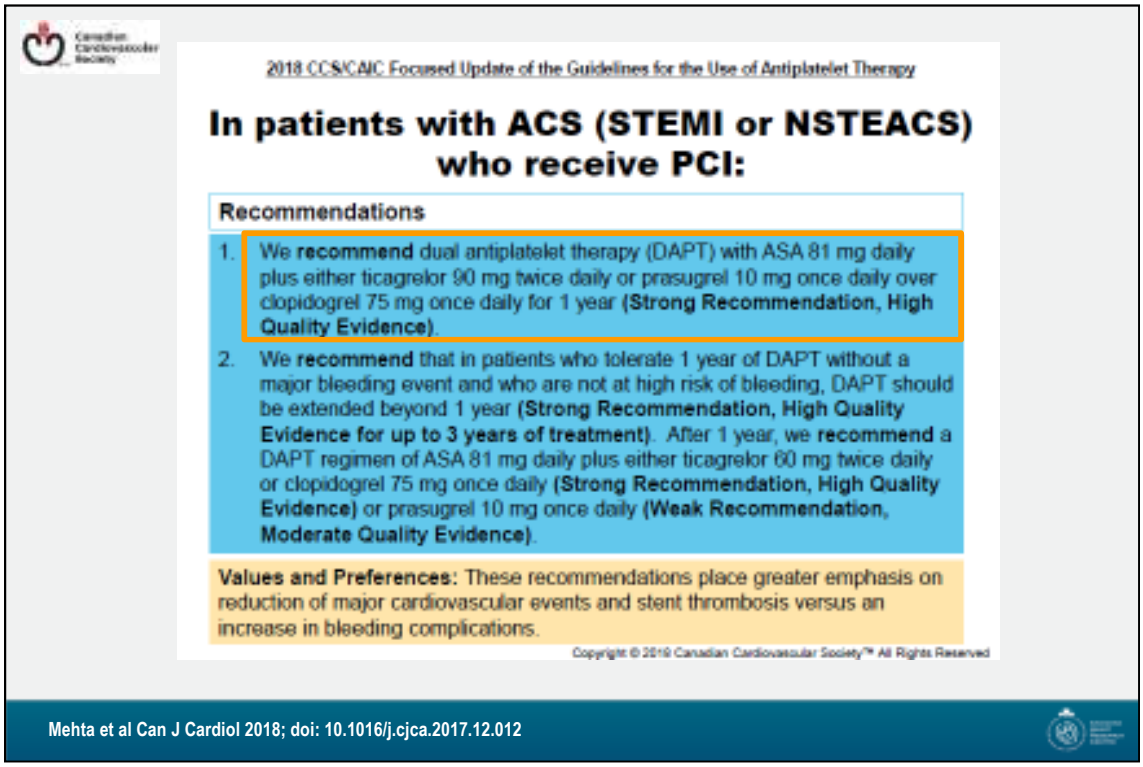
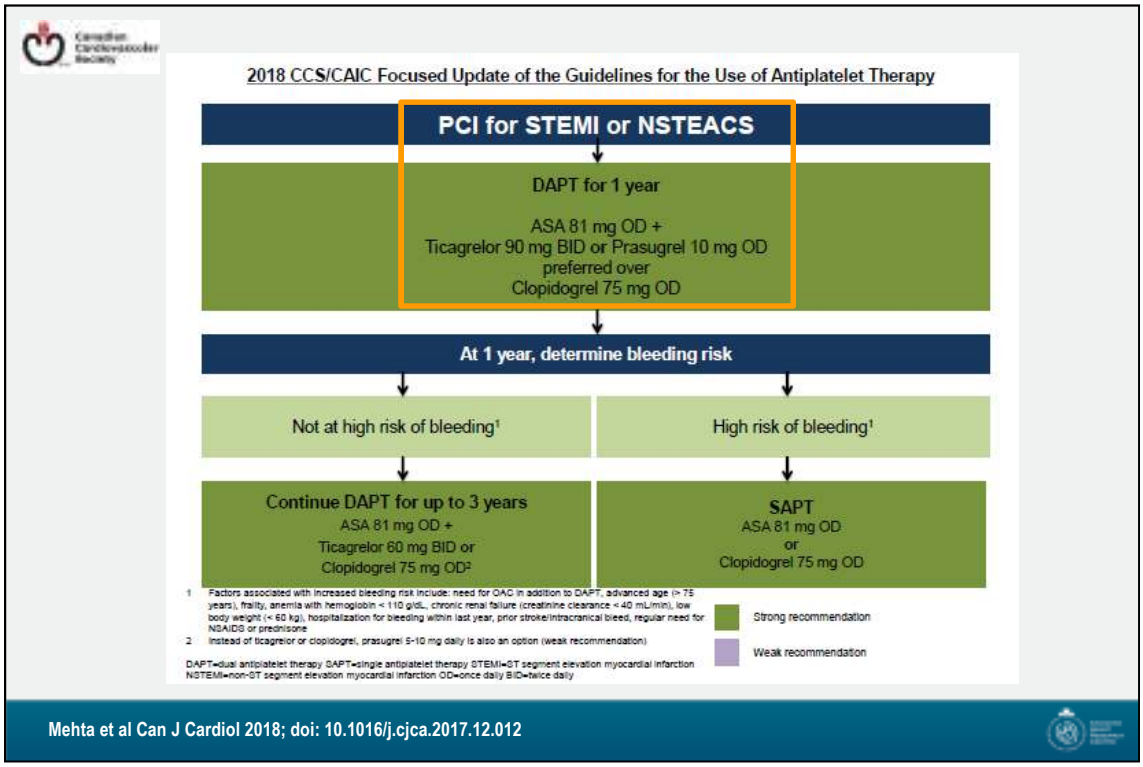


According to the CCS/CAIC Guideline recommendations, this NSTEACS patient who has undergone PCI should continue to receive ticagrelor for the next year.



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...But what if...?

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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 (≥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?

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Interventional cardiologists opinion: Treat medically

Would you recommend continuing DAPT post-discharge?

a) Yes
b) No

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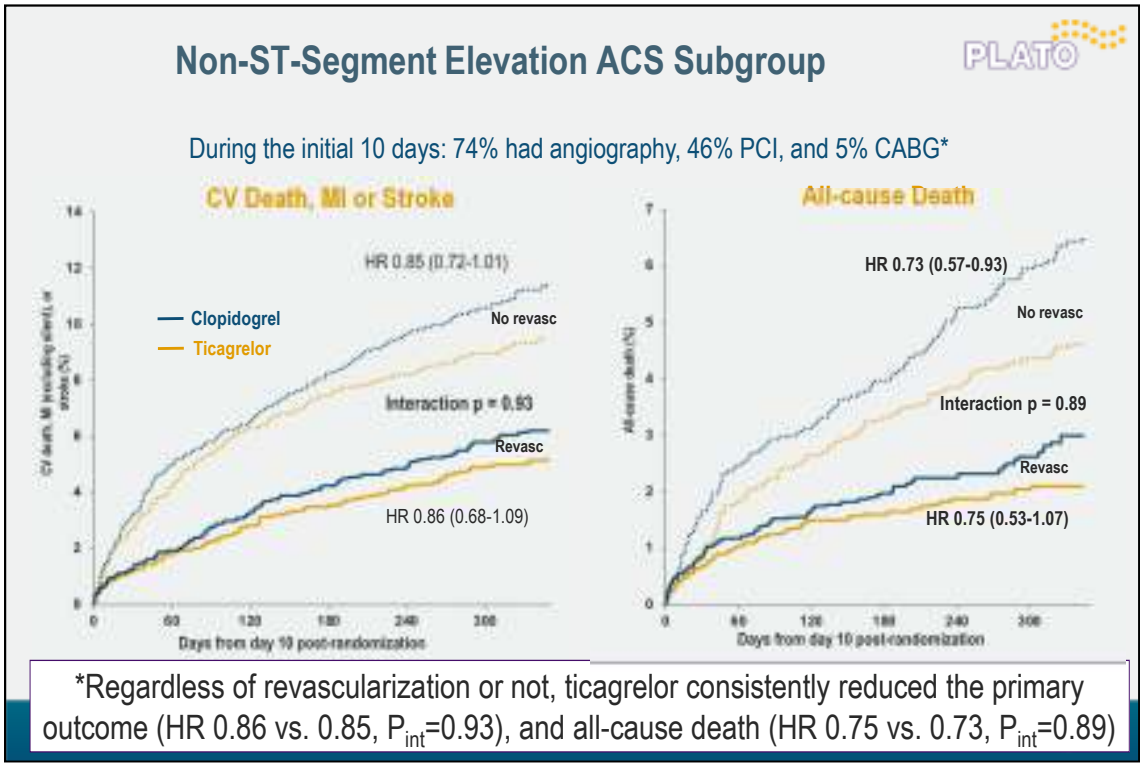

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Non-ST-Segment Elevation ACS Subgroup

	Significant disease				No significant disease				
	N	Ticagrelor KM rate	Clopidogrel KM rate	HR (95% CI)	N	Ticagrelor KM rate	Clopidogrel KM rate	HR (95% CI)	Interaction p
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)

Lindholm et al Eur Heart J 2014;35:2083-93

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 NSTEACS 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.