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NSTEMI Decision-Tree Accelerates Introduction of Evidence-Based Therapies

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Introduction

In patients presenting with an acute coronary syndrome (ACS), early initiation of oral antiplatelet therapy is critical to the prevention of recurrent ischemic events. In a series of large trials, clopidogrel, prasugrel, and ticagrelor have all demonstrated protection against thrombotic events when combined with aspirin in ACS patients. These trials have also demonstrated that the therapeutic window, defined by the distance between a reduced risk of thrombus formation and an unacceptable increase in bleeding events, is narrow, differing for such variables as type of ACS, planned intervention, and time elapsed from onset of symptoms. At the University of Ottawa Heart Institute, an evidence-based decision-tree for ACS patients suspected of a non-ST elevated segment MI (NSTEMI) has been recently revised. Derived from the clinical trials, the decision-tree guides clinicians to initial therapies, including antiplatelet agents, most likely to provide an optimal benefit-to-risk ratio. The goal is to provide a clear decision scheme that will accelerate the time to appropriate therapy.

Guidelines developed by the Canadian Cardiovascular Society (CCS) for the use of antiplatelet therapies in ACS patients have been developed and updated on the basis of large antiplatelet trials.[1,2] These trials demonstrate that available regimens are not interchangeable for relative protection against thrombotic events or for their relative risk of adverse events, including increased risk of minor and major bleeding. The history of these trials traces the effort to improve antiplatelet efficacy to reduce risk of cardiovascular events without provoking an unacceptable rate of minor and major bleeding.

The modern era of dual antiplatelet therapy in ACS patients was initiated with the publication of the CURE trial in 2001.[3] In CURE, patients with a non-ST segment elevated myocardial infarction (NSTEMI) who were randomized to receive clopidogrel in addition to aspirin had a 20% reduction ($P<0.001$) in the risk of a composite endpoint of ischemic events relative to those who received aspirin alone. A similar trial, CLARITY-TIMI 28, showed an even greater relative risk reduction for clopidogrel when administered with aspirin relative to aspirin alone in patients with ST-elevated MI (STEMI).[4]

These trials demonstrated that greater platelet inhibition was associated with greater protection from cardiovascular (CV) events, but it was not clear whether still further risk reductions with acceptable safety were possible with more potent suppression of platelet activation, particularly among patients at highest risk. This was relevant not only to different types of ACS, a term that captures a spectrum of clinical conditions from unstable angina to no-flow thrombotic occlusions, but to ACS patients undergoing invasive procedures, such as percutaneous interventions (PCI), which can induce a counterproductive thrombotic response even as they are applied to restore and sustain blood flow.[5]

The series of antiplatelet ACS trials conducted since CURE and CLARITY-TIMI 28, including those conducted with the newer agents prasugrel and ticagrelor, have established opportunities in which more effective platelet inhibition can provide further reductions in life-threatening CV events. The clinical trials have also yielded a new set of evidence to confirm a narrow gap between lower risk of CV events and greater risk of bleeding. In fact, event reductions from greater antiplatelet effect have not always been judged to warrant the increased risk of bleeding. Current guidelines are designed to identify how current options are best applied to achieve an optimal benefit-to-risk ratio on an evidence basis.

Targeting Platelet Activation

Relative to aspirin, which attenuates platelets by inhibiting cyclooxygenase and other enzymes that mediate activation,[6]

clopidogrel, prasugrel and ticagrelor inhibit P2Y12, a predominant activating receptor on the surface of the platelet.[7] These P2Y12 inhibitors are not interchangeable. Both clopidogrel and prasugrel, which are thienopyridines, achieve inhibition of P2Y12 through a metabolite.[8] For clopidogrel, a prodrug that is dependent on a two-step process mediated through the cytochrome P450 system, antiplatelet effect is delayed several hours after ingestion. Prasugrel is also converted into its active metabolite through hepatic metabolism but this is achieved in a single step. As a result the antiplatelet effect is achieved more quickly after ingestion of prasugrel than clopidogrel, and there appears to be less variability in response. Ticagrelor, a non-thienopyridine, is orally active with direct but reversible binding to the P2Y12 receptor.[9] It also has a rapid onset of action and appears to provide a more predictable antiplatelet effect than clopidogrel.

The pharmacological differences between P2Y12 inhibitors have been shown to be clinically meaningful in large clinical trials. Although prasugrel and ticagrelor have not been directly compared, both agents have demonstrated greater protection against major CV events relative to clopidogrel when combined with aspirin in ACS populations. These multinational trials have been instrumental in developing the evidence-based CCS guidelines, which have now been adapted for use at the University of Ottawa Heart Institute.

The first challenge to the standard regimen of clopidogrel and aspirin in ACS patients was produced by the TRITON-TIMI 38 trial.[10] The trial compared prasugrel to clopidogrel in ACS patients scheduled for a PCI after coronary angiography. More than 13,000 patients were randomized. All patients in both arms received aspirin plus an initial loading dose and then a maintenance dose of their assigned therapy. Approximately 75% of patients had NSTEMI and the remainder were STEMI ACS patients.

Relative to clopidogrel, prasugrel was associated with a 20% risk reduction ($P<0.001$) in the composite endpoint of death from CV causes, non-fatal myocardial infarction (MI), and non-fatal stroke. There were also significant reductions in a number of clinically meaningful endpoints, such as urgent target-vessel revascularization, stent thrombosis. However, there was a cost for prasugrel relative to clopidogrel in increased risk of major bleeding ($P=0.03$), life-threatening bleeding ($P=0.01$), and fatal bleeding ($P=0.002$). Overall mortality did not differ between the treatment arms.

In TRITON-TIMI 38, the absolute reduction in risk of CV events exceeded the absolute increase in bleeding, but an effort to improve the benefit-to-risk ratio prompted a series of subsequent analyses that revealed relative bleeding risk to be higher in older patients, patients with a history of stroke or prior transient ischemic attack (TIA), and in patients with low body weight.

A second trial called PLATO evaluated ticagrelor in a much broader ACS population.[11] In that trial, more than 18,000 patients admitted to a hospital for ACS without regard to the planned intervention or pre-hospital antiplatelet therapy were randomized to ticagrelor or clopidogrel. Again, all patients received aspirin and were initiated on their assigned therapy with a loading dose followed by a maintenance regimen. The NSTEMI proportion of the enrolment was slightly lower in PLATO than in TRITON-TIMI 38 at 63%.

Relative to clopidogrel, ticagrelor was associated with a 16% reduction ($P\leq0.001$) in the risk of the same endpoint as that used in TRITON-TIMI 38. Significant reductions in secondary endpoints favouring ticagrelor included death from CV causes ($P=0.005$). In addition, ticagrelor was associated with a significant reduction in all-cause mortality ($P<0.001$). One explanation for this additional advantage is that ticagrelor was associated with a much lower propensity for major bleeding in PLATO than prasugrel in TRITON-TIMI 38. Overall, major bleeding rates did not differ significantly between the ticagrelor and clopidogrel arms. Major bleeding not related to coronary artery bypass grafting (CABG) was higher in the ticagrelor arm, but rates of fatal bleeding were not significantly different.

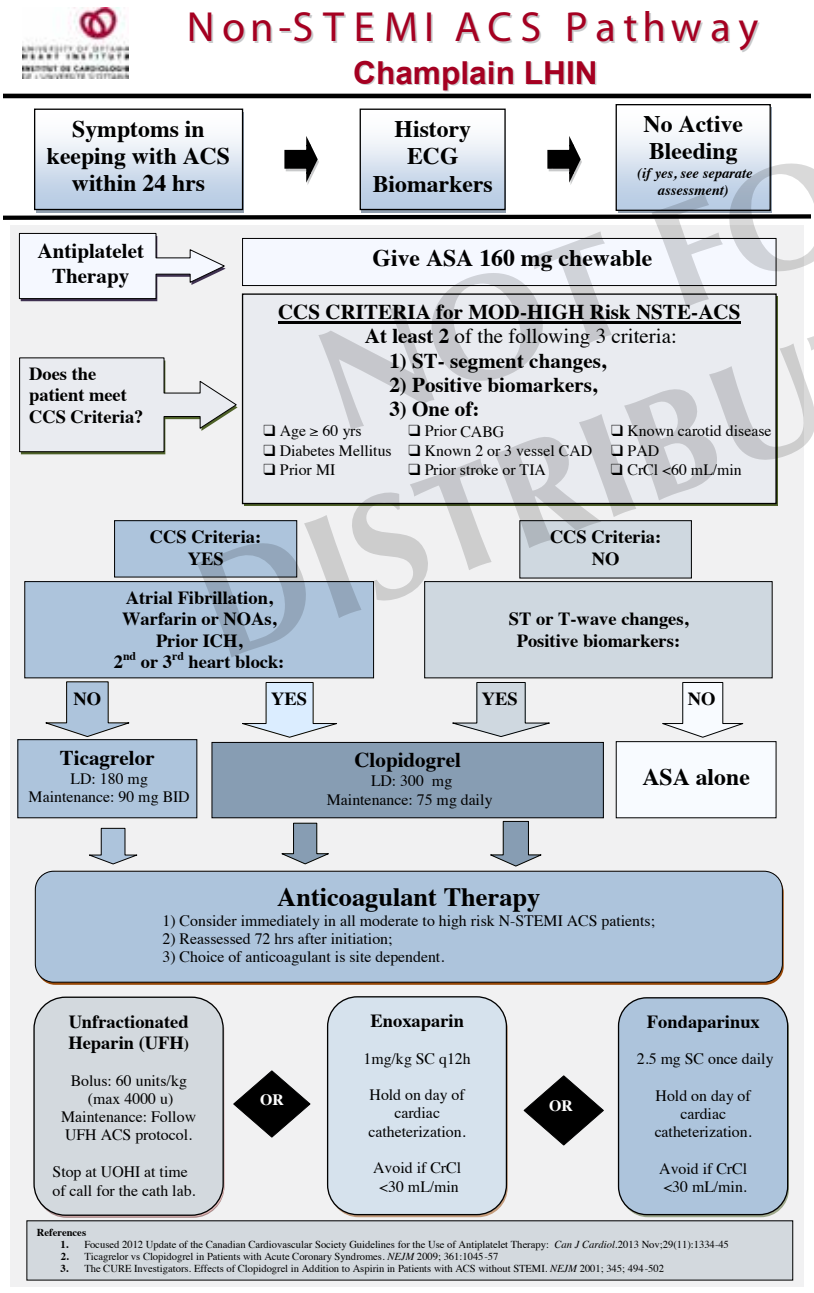
Both TRITON-TIMI 38 and PLATO demonstrate that greater CV risk reductions can be achieved with newer antiplatelet agents relative to clopidogrel when combined with aspirin. While greater antiplatelet effect may be important, speed of onset may also play a role. It is noteworthy that double-the-dose versus standard-dose clopidogrel did not provide an advantage for CV endpoints in the CURRENT OASIS-7 trial overall,[12] although a 14% reduction ($P=0.039$) in a composite endpoint of CV events was achieved by the higher dose in the subpopulation of PCI patients.[13] CURRENT OASIS-7 and a previous study, PCI-CURE,[14] also found no advantage but increased risk for high-dose aspirin.

Antiplatelet ACS Guidelines

The large antiplatelet trials conducted over the past 15 years have informed treatment guidelines, identifying opportunities where risk of CV events can be lowered with a net benefit relative to the potential for increased bleeding. These trials demonstrate that antiplatelet therapies are not interchangeable, particularly in patients at high risk of a CV event. In the most recent CCS guidelines, four algorithms have been provided to address different levels of thrombotic risk in ACS populations. These are NSTEMI patients receiving immediate antiplatelet therapy, NSTEMI patients with a planned PCI who have not yet received a P2Y12 inhibitor, STEMI patients, and ACS patients undergoing CABG.

When combined with aspirin, ticagrelor or prasugrel are preferred over clopidogrel in most pathways outlined in the CCS guidelines, but there are exceptions. This includes STEMI patients who do not proceed to PCI and are managed with fibrinolytic therapy. In this group, clopidogrel is preferred due to concern over increased risk of bleeding and lack of trial data showing an advantage for newer agents. When prasugrel is an option, such as in NSTEMI patients with a planned PCI, the guidelines recommend a reduced dose in older patients and patients weighing <60 kg. A history of stroke or TIA is a contraindication for prasugrel. Antiplatelet therapy is maintained for 12 months after the ACS admission.

At the University of Ottawa Heart Institute, these guidelines have been adapted to streamline decisions for time-sensitive initiation of therapy in NSTEMI patients. These focus on pathways most likely to rapidly restore or sustain perfusion while minimizing bleeding risk. In an effort to achieve the greatest benefit-to-risk ratio of care, complex decision-trees are avoided. Evidence-based, ticagrelor is preferred among patients who would have met the entry criteria for the PLATO trial. In others, such as those on warfarin or with a history of atrial fibrillation, clopidogrel remains the standard. Prasugrel has not been included in the algorithm in NSTEMI because the TRITON-TIMI 38 trial only enrolled patients with a planned PCI. The decision-tree is for NSTEMI patients prior to catheterization, when the treatment plan is uncertain. Moreover, in an unselected ACS population, up to one third of patients have relative contraindications to prasugrel, such as low body weight, age over 75 years, or history of stroke. Following selection of an antiplatelet regimen, anticoagulation is an integral part of thrombotic risk reduction.



In all settings, clear pathways of intervention can be useful in developing reproducible and rapid quality of care. At our centre and at regional hospitals that refer to our centre, an effort to adapt decision-making to the available resources and expertise has been undertaken within an evidence-based context. In the NSTEMI algorithm, the specific recommendations for antiplatelet therapy are evidence-based but practical, incorporating the concept that the optimal benefit-to-risk ratio will be derived from choices associated with low risk of increased bleeding and can be implemented rapidly.

Conclusion

Large clinical trials demonstrate that currently available antiplatelet therapies are not interchangeable. Relative to clopidogrel, both ticagrelor and prasugrel have demonstrated a reduced risk of ischemic events in selected ACS populations. These data are useful but require translation into practical patient management pathways that are clear and sufficiently simple to minimize delays. The guidelines developed at the Ottawa Heart Institute have been adopted from the CCS guidelines in an effort to introduce opportunities for improved outcome in the context of local practice.

Questions & Answers

Q: In the past, essentially all ACS patients were initiated on dual antiplatelet therapy with clopidogrel and aspirin. Now, there is a decision-tree introducing choices. Is there a risk this will delay care?

Dr. Le May: I think the opposite is true. We now have choices with the potential of improving the benefit-to-risk ratio of antiplatelet therapy, but we want clinicians to make these choices quickly. The decision-tree employs evidence-based guidance to streamline the process. For those clinicians without the time or interest to review and know this literature, these recommendations should eliminate confusion.

Q: The inhibition of platelets includes an inherent risk of increased bleeding. Are you confident that the algorithm achieves the optimal benefit-to-risk ratio?

Dr. Le May: There is certainly the potential for greater risk of bleeding with more effective inhibition of platelet activity, but PLATO demonstrated an overall mortality reduction with a neutral effect for major bleeding across the overall study population. To reproduce this favourable benefit-to-risk ratio, it is essential to apply inclusion and exclusion criteria similar to those employed in the trial. We have, for example, continued to recommend clopidogrel over ticagrelor in patients on warfarin or who are in atrial fibrillation. To the extent that greater inhibition of platelets carries an increased risk of bleeding, the data that underlie the decision-tree demonstrate that the risk of bleeding does not override the reduction in the risk of thrombotic events whereas thrombotic events will be increased without the most effective therapy.

Q: Prasugrel has also been shown to be more effective than clopidogrel in a large trial, but it was not included in your NSTEMI guidelines. Why?

Dr. Le May: The TRITON-TIMI 38 trial involved a cath-lab approach in which the anatomy had already been evaluated and a PCI scheduled. The immediate referral to a cath lab without a waiting period is not a standard of care in Canada. As a result, the data from the trial are not relevant to NSTEMI during initial therapy. In TRITON-TIMI 38, prasugrel was also compared to a 300-mg rather than a 600-mg loading dose of clopidogrel, so there has been some debate about how to interpret the results. Our decision-tree was designed to apply clear evidence to support rapid decisions in NSTEMI patients.

Q: Do you think there is further room for risk reduction by employing even more aggressive antiplatelet therapy in patients at highest risk?

Dr. Le May: In ACS patients, we are constantly looking for the PRU [P2Y12 reactivity unit] sweet spot, which is the level of platelet inhibition that provides the greatest reduction in thrombotic events at the lowest risk of clinically significant bleeding. For patients in the highest risk groups, we are probably not there. There are many strategies to consider even with existing antiplatelet drugs, such as higher or more frequent doses or initiating an antiplatelet therapy even in a patient already on a thrombolytic. There is certainly room to improve outcomes, but trials are essential to demonstrate benefit over risk. □

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