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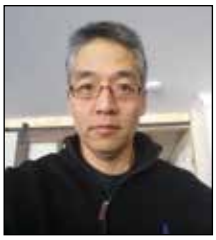
A Regional Perspective on the Evidence and Resulting Changes



Guest Editor:

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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. Evidence-based guidelines, derived from the clinical trials, have been developed to lead to selection of the antiplatelet regimen most likely to provide an optimal benefit-to-risk ratio. At St. Mary's General Hospital, an antiplatelet protocol for ACS patients has been adapted from current guidelines to 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.

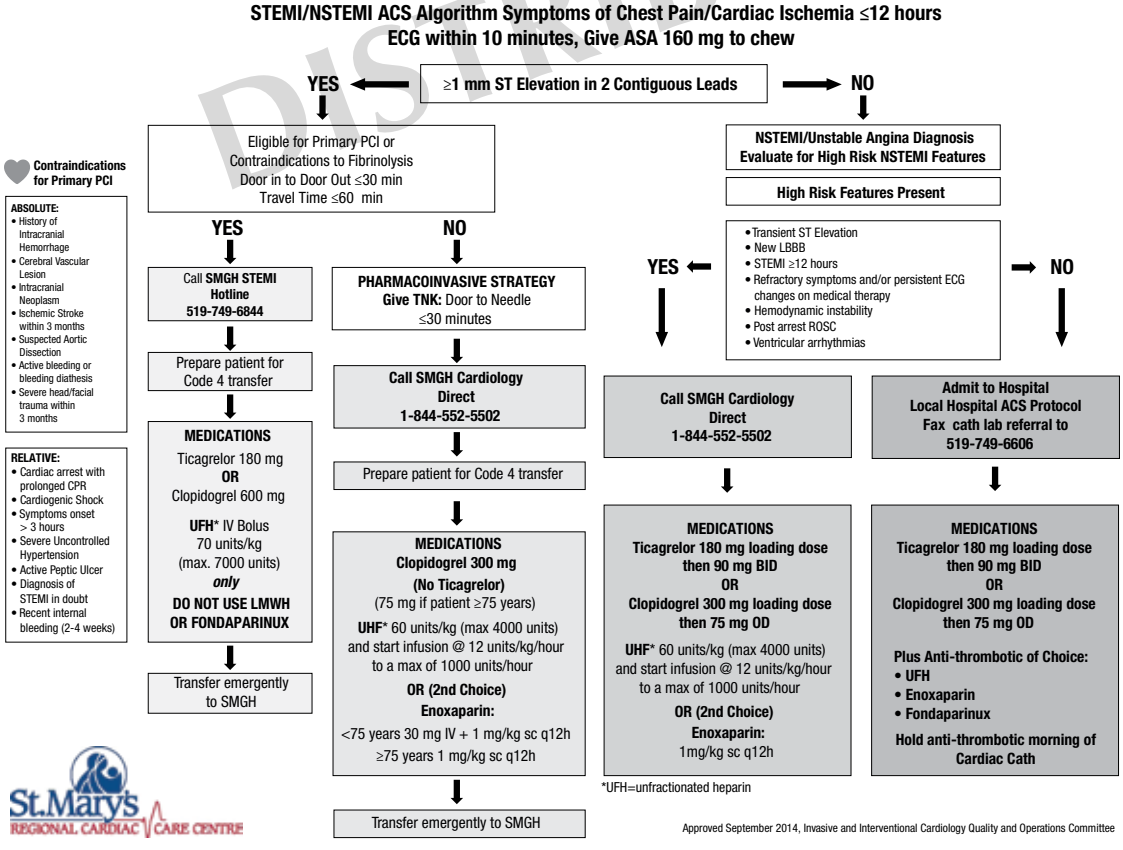
Targeting Platelet Activation

Relative to aspirin, which attenuates platelets by inhibiting cyclooxygenase and other enzymes that mediate activation,[6] clopidogrel, prasugrel and ticagrelor inhibit $P2Y_{12}$, a predominant activating receptor on the surface of the platelet.[7] These $P2Y_{12}$ inhibitors are not interchangeable. Both clopidogrel and prasugrel, which are thienopyridines, achieve inhibition of $P2Y_{12}$ 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. Prasgurel 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-theinopyridine, is orally active with direct and reversible binding to the $P2Y_{12}$ 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 $P2Y_{12}$ 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.

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. It is due to this bleeding risk that prasugrel

is not featured on our ACS algorithm. In addition, prasugrel was compared to clopidogrel in the TRITON TIMI-38 trial only after the coronary anatomy had been defined and a PCI was scheduled. This decision point for initiating dual antiplatelet therapy is not consistent with practice at our center.

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 TRITON TIMI-38 at 63%.

Relative to clopidogrel, ticagrelor was associated with a 16% reduction ($P \leq 0.001$) 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.

Antiplatelet ACS Guidelines

The large antiplatelet trials conducted over the past 15 years have formed 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 $P2Y_{12}$ 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. Clopidogrel is also the preferred antiplatelet partner with aspirin in patients undergoing CABG. 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 St. Mary's General Hospital, these guidelines have been adapted into a STEMI/NSTEMI algorithm that is designed to streamline decisions for time-sensitive care. In an effort to achieve the greatest benefit-to-risk ratio of care, complex decision trees are avoided. Ticagrelor is now the preferred agent in the setting of primary PCI and NSTEMI. Clopidogrel is preserved as a treatment option even in those with high-risk features because it is readily available and may be the most expedient choice. Prasugrel has not been included in the algorithm even in STEMI patients eligible for PCI because of the previously mentioned relative contraindications that complicate the decision tree. Importantly, no antiplatelet therapy is offered to patients who have received thombolysis as initial therapy.

In all settings, clear pathways of intervention can be useful in developing reproducible and rapid quality of care. In regional hospitals, such as St. Mary's General Hospital, an effort to adapt decision-making to the available resources and expertise has been undertaken within an evidence-based context. In the STEMI/NSTEMI algorithm, the specific recommendations for antiplatelet therapy are practical, evidence-based and aim for the optimal benefit-to-risk ratio.

Conclusion

Large clinical trials demonstrate that both ticagrelor and prasugrel have demonstrated a reduced risk of ischemic events relative to clopidogrel 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 ACS treatment guidelines developed at St Mary's General Hospital have been adapted from the CCS guidelines in an effort to optimize clinical outcomes.

Questions & Answers

Q: Now that there is an algorithm requiring choices for dual antiplatelet therapy rather than giving all patients clopidogrel and aspirin, are you concerned that these decisions will delay care?

Dr. Kim: Whenever there is a change in any treatment protocol, there is the possibility that more time may be spent in contemplation prior to choosing and administering therapy. However, as first-line caregivers familiarize themselves with the distinctions between clopidogrel and ticagrelor, aided by the clarity of the algorithm, this time will be minimized. In the end, any potential delay in care will be negligible and should not have a significant effect on outcome.

Q: For the clinician who fears causing a bleeding event more than failing to prevent a recurrent thrombotic event, what would you say in defense of the new treatment algorithm?

Dr. Kim: The new algorithm advocates the use of ticagrelor over clopidogrel in ACS patients who have not received thrombolysis. In PLATO, the use of ticagrelor did not result in any higher major or fatal bleeding events over clopidogrel. While ticagrelor admittedly comes with a higher (non-CABG) bleeding risk, I think that this risk is outweighed by its significant benefits in preventing major cardiac adverse events (MACE) and death.

The treatment of ACS is a double-edged sword, balancing prevention of thrombosis versus risk of bleeding. Even though bleeding risk should not be ignored, I believe that the primary focus of ACS treatment should be the prevention of MACE, which ultimately has a significant effect on overall prognosis. The risk of bleeding can be managed by close monitoring of high-risk patients, gastric protection, and with prompt adjustment of antiplatelet/antithrombotic regimens in those cases where hemoglobin levels become an issue.

Q: In patients scheduled for a PCI, prasugrel was superior to clopidogrel in TRITON TIMI-38. You do not single out this group in your algorithm. Why?

Dr. Kim: In TRITON TIMI-38, the absolute reduction in risk of CV events exceeded the absolute increase in bleeding, but relative bleeding risk was higher in older patients, patients with a history of stroke or prior TIA, and in patients with low body weight. It is due to this bleeding risk that prasugrel is not featured on our ACS algorithm. In addition, prasugrel was compared to clopidogrel in the TRITON TIMI-38 trial only after the coronary anatomy had been defined and a PCI was scheduled. This decision point for initiating dual antiplatelet therapy is not consistent with practice at our center.

Q: Do you think that there may be room for even more aggressive antiplatelet regimens in those patients at highest risk for recurrent thrombotic events?

Dr. Kim: Bleeding risk will rise in proportion to the aggressiveness of antiplatelet/antithrombotic therapy. For instance, prolonged use of triple oral antithrombotic therapy has been shown to generally increase the bleeding risk to prohibitive levels. Overall, I think that in those patients at highest risk of MACE, the balance of risk and benefit weighs in favour of prolonged use of dual antiplatelet therapy (rather than the addition of another agent). □

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