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A Regional Perspective on the Evidence and Resulting Changes

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Introduction

Antiplatelet therapy in the management of acute coronary syndromes (ACS) has recently been revised at the William Osler Health System. The altered algorithm is designed to provide significant reductions in risk of major cardiovascular (CV) events by employing the newer antiplatelet agents compared to the previous standard of clopidogrel and ASA. The new algorithm specifies where prasugrel and ticagrelor should be employed to provide additional protection against major CV events. Guided by the large clinical trials that underlie the revised algorithm, the specific recommendations allow for the clinical gains from greater antiplatelet effect, including in some cases, a lower risk of death. They also balance benefit with an acceptably low risk of major or minor bleeding. Due to the fundamental importance of deactivating platelets to alter the natural history of evolving ACS events, optimal use of antiplatelet therapy should be considered an essential strategy for improving the prognosis of ACS. The new protocol is consistent with revisions in national guidelines.

Previous Standard: Need for Improvement

The dual antiplatelet strategy of clopidogrel and ASA in patients presenting with ACS has been a widely employed standard for more than 10 years. However, rates of CV events in ACS populations remain substantial. In the landmark CURE study, 10% of those receiving clopidogrel plus ASA went on to a recurrent myocardial infarction (MI), a persistent arterial occlusion or died of a CV cause despite the 20% reduction with the combination relative to ASA alone.[1] This study was performed in patients with unstable angina (UA) and non-ST elevation MI (NSTEMI). In the CLARITY-TIMI 28 trial, conducted in patients with ST elevation MI (STEMI), the residual risk of death, stroke or MI was 9% in the group receiving clopidogrel plus ASA despite a 31% reduction in risk of a major CV event relative to ASA alone.[2]

Since those studies established this dual antiplatelet combination as a standard in ACS, two large ACS trials have proven that more effective antiplatelet therapy will further reduce CV risk. One trial tested ticagrelor in an all-comer population of ACS patients.[3] The other study tested prasugrel in ACS patients scheduled for a percutaneous coronary intervention (PCI).[4] Data from these trials provide an opportunity to improve outcomes over the previous clopidogrel plus aspirin standard.

In the TRITON TIMI-38 study, 13,608 ACS patients scheduled for PCI were randomized. The UA/NSTEMI cohort had clopidogrel or prasugrel withheld until the anatomy was defined by angiography. The STEMI cohort was allowed clopidogrel or prasugrel prior to PCI, but 72% of these patients did not get the study drug until the coronary anatomy was known. In the experimental arm, patients received a loading dose of prasugrel (60 mg) followed by maintenance prasugrel (10 mg daily). The comparator arm received a loading dose of clopidogrel (300 mg) followed by maintenance clopidogrel (75 mg daily). Both groups received ASA. Approximately 25% of the ACS events were STEMI and the remaining UA/NSTEMI.

Relative to clopidogrel, prasugrel reduced the risk of the composite end point of death from CV cause, MI or stroke by 19% (HR 0.81; $P<0.001$). The risk of major bleeding on prasugrel was increased by 32% (HR 1.32; $P=0.03$) relative to clopidogrel. There was no difference in mortality. The authors concluded that the greater protection against ischemic events must be weighed against an increased risk of bleeding, but post-hoc analyses provided guidance for candidate selection.

In the PLATO trial, all individuals admitted to hospital with ACS were randomized regardless of planned procedure or pre-hospital antiplatelet treatment. The experimental arm received a loading dose of ticagrelor (180 mg) followed by maintenance ticagrelor (90 mg twice daily). The comparator arm received a loading dose of clopidogrel (300 or 600 mg) followed by maintenance clopidogrel (75 mg daily). Both groups received ASA. Approximately 37% of the 18,624 patients randomized had STEMI and the remaining had NSTEMI.

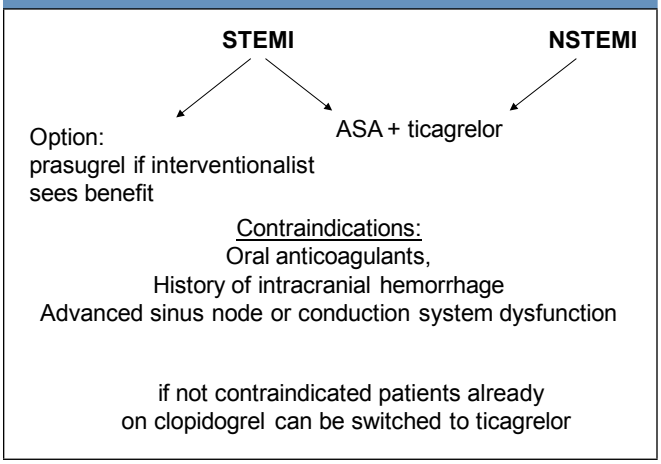
Relative to clopidogrel, ticagrelor reduced the risk of the composite end point of death from vascular causes, MI or stroke by 16% (HR 0.84; $P<0.001$). The difference in total major bleeding (11.6% vs. 11.2%; $P=0.43$) did not reach statistical significance. Unique to antiplatelet trials, ticagrelor was associated with a 16% reduction (HR 0.84; nominal $P<0.001$) in all-cause mortality.

New Data Translated into Clinical Practice

The revised treatment algorithms for antiplatelet therapy in ACS patients are designed to capture the opportunity to improve outcome based on the PLATO and TRITON-TIMI 38 trials. The standard management of ACS patients has included early administration of dual antiplatelet therapy in the emergency room. This has made implementation of the TRITON-TIMI 38 protocol difficult as it called for most of these patients to first undergo coronary angiography which may not get done for 24-48 hours after hospital admission. Several large organizations have altered ACS antiplatelet guidelines on the basis of the PLATO and TRITON-TIMI 38 trials, but algorithms at the regional or hospital level have to be tailored to allow effective, safe and efficient implementation given local resources and practice standards.

At regional centres, including the William Osler Health System, the data generated by the PLATO and TRITON-TIMI 38 trials can be applied directly. In both NSTEMI and STEMI patients, ticagrelor is now the dominant partner in a dual antiplatelet strategy with ASA with important exceptions. These relative exceptions include patients on an anticoagulant or who have had a prior intracranial hemorrhage (Figure 1). Ticagrelor is also avoided in patients with advanced sinus node or conduction system dysfunction. In those not candidates for ticagrelor, clopidogrel remains the preferred partner with ASA. In those initiated on clopidogrel who are candidates for ticagrelor according to the algorithm, the therapy should be switched.

Figure 1. **William Osler Health System: ACS Simplified Algorithm**



Although the TRITON-TIMI 38 trial protocol allowed administration of prasugrel or clopidogrel prior to angiography, 72% of the STEMI patients did not receive the study antiplatelet agent until the time of PCI. Our past protocol includes immediate dual antiplatelet therapy in the emergency room or in STEMI patients who bypass the ER, on arrival to the angiography suite. In addition prasugrel was associated with high bleeding risk in certain patient groups (>75 years of age, those who weigh <60 kg and those with a prior transient ischemic attack or stroke) and is not indicated in such patients. One of the keys to successful implementation of any algorithm is simplicity and where possible to avoid multiple exceptions based on individual patient specifics. In order to make our protocol as generalizable as possible, without compromising patient care, we elected to also utilize ticagrelor as our preferred agent for STEMI patients. The interventional cardiologist has prasugrel available in the angiography suite for the select patients that he feels may benefit from this agent over ticagrelor or clopidogrel.

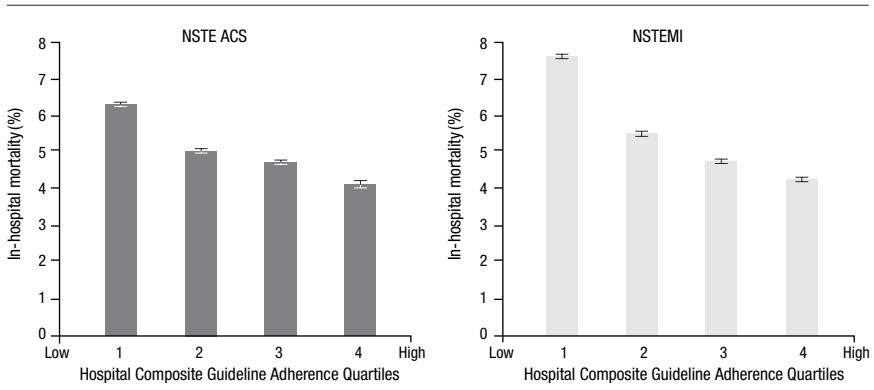
It is unlikely that there will ever be a direct comparison of prasugrel and ticagrelor. Furthermore, the difference in methodology of their respective pivotal trials makes it difficult to extrapolate any potential advantage of one agent over the other. Since our existing practice was most consistent with the PLATO protocol of administrating dual antiplatelet therapy in the emergency room early after ACS patient presentation it was elected to utilize ticagrelor as our preferred antiplatelet agent. This should provide our patients with the reductions in recurrent MI and stroke as well as the 1.4% absolute total mortality reduction seen in PLATO.

Relevance of New Algorithm to Regional Centres

The objective evidence that newer antiplatelet therapies can improve the outcome in ACS patients informs but does not dictate adjustments in patient care. Due to substantial regional disparities in the care of ACS driven largely by variability in resources, such as the proximity of rapid response teams and differences in transfer intervals to catheterization laboratories, treatment guidelines must be adjusted for relevance to current practice. At regional centres, treatment algorithms must be adjusted for these variables. The same opportunities to improve outcome with more effective antiplatelet regimens should not be overlooked. Current practice at regional facilities is relevant to community hospitals whether or not the transfer of patients is common.

There are compelling data to conclude that implementation of more modern strategies for appropriate candidates will improve ACS outcomes including a reduction in mortality. The implementation and adherence to treatment guidelines in the management of ACS has been associated with statistically significant improvements in outcome. In an observational analysis that included 350 academic and non-academic centres, a stepwise 10% reduction in in-hospital mortality rates was associated with each 10% increase in adherence to evidence-based guidelines (Figure 2).[5]

Figure 2. **Association Between Hospital Composite Guideline Adherence Rate and In-hospital Mortality**



NSTE ACS indicates non–ST-segment elevation acute coronary syndrome; NSTEMI, non–ST-segment elevation myocardial infarction. The left plot shows risk-adjusted mortality rates for overall patients with NSTE ACS for that quartile, and the right plot shows risk-adjusted mortality rates for the NSTEMI subgroup. Standard error bars are also included for each group. All results were adjusted for age, sex, race, body mass index, patient insurance status, admission electrocardiograph (ST depression, transient ST elevation), admission cardiac marker status, presenting signs of heart failure, initial heart rate and systolic blood pressure, history of hypertension, diabetes mellitus, hypercholesterolemia, renal insufficiency, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, prior congestive heart failure, prior stroke, current/recent smoker, and family history of coronary disease.

Adapted from Peterson et al. *JAMA* 2006;295:1912-20.

Conclusion

The first-line antiplatelet strategies in ACS patients have been revised. The newer agents ticagrelor and prasugrel provide an important opportunity to improve outcome relative to clopidogrel when any of these agents is combined with ASA. In UA/NSTEMI and STEMI patients, the advantage of ticagrelor over clopidogrel in appropriately selected patients includes a mortality reduction. The guidelines developed by the William Osler Health System were designed specifically to identify these opportunities in a readily applied algorithm.

Question & Answers

Q: What is your perspective on the benefit-to-risk ratio that the newer antiplatelet agents offer within the revised algorithm for reducing the risk of thrombosis within an acceptable rate of bleeding?

A: In our approach to the benefit-to-cost ratio, the patient always comes first. Economics are secondary. In PLATO and TRITON-TIMI 38, ticagrelor and prasugrel clearly showed superiority to clopidogrel. The mortality advantage seen in PLATO is a most important parameter with a low risk of fatal bleeds. Despite cost, the patient should be administered the most effective and safe medication.

Q: The studies that led to changes in the guidelines compared therapies in different populations. What insights can you offer on why it was important to prove superiority of prasugrel or ticagrelor over clopidogrel in different ACS groups (STEMI, NSTEMI, unstable angina, etc)?

A: From our perspective, it is easier to apply PLATO results than TRITON-TIMI 38 because PLATO included UA, NSTEMI and STEMI patients treated in the ER. This is where the majority of patients are treated in our centres. In TRITON-TIMI 38 patients waited 1-2 days before angiography and the subsequent initiation of dual antiplatelet therapy.

Q: What is your point of view on the possible side effects associated with the newer agents vs. the opportunity to improve outcomes?

A: While increased bleeding risk is always a factor to consider, there was no difference in fatal bleeds in PLATO, and ticagrelor is a reversible platelet inhibitor. While the early reduction in mortality in PLATO was reassuring, the reduction in recurrent MIs will also protect the heart muscle, which also has implications for long-term outcome. In our experience, the feeling of breathlessness may persist for several weeks, but we reassure patients that it will subside. That effect appears to be caused by nitric oxyde (NO). It is thought that the ticagrelor breathlessness is caused by its promotion of adenosine which in turn increases vascular NO. The increase in NO may explain some of the mortality benefit of ticagrelor over clopidogrel beyond the critical ACS period.[6]

Q: The algorithm introduces some decision points not previously required when all patients were treated with clopidogrel plus ASA. What action needs to be taken to improve outcomes?

A: To reduce error, we minimized the decision points. For simplicity, efficacy and without compromising patient care, we chose ticagrelor + ASA as the standard of the treatment unless contraindicated. For example, if the patient has had an intracranial bleed then discussion with the interventionalist is certainly indicated. □

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