



Canadian Cardiovascular Congress

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Guide to Maximizing Antiplatelet Efficacy in High-risk Patients

Edmonton - A series of major studies with different antiplatelet strategies have proven that treatment can be effectively individualized to improve protection against thrombotic events. The clinical application of these findings will be the topic of an important symposium to be held during the CCC. The Monday morning symposium will assemble several key experts to translate the data into practical treatment strategies. Since high-risk patients continue to experience thrombotic events on the previous standards for antiplatelet drugs, the identification of more effective strategies has been a breakthrough in risk management. Although there is some correlation with greater antiplatelet effect and increased risk of bleeding, a net benefit from highly effective antiplatelet drug regimens can be identified in many well-defined patient groups.

Edmonton - Il est ressorti d'une série d'études d'envergure sur diverses stratégies antiplaquetaires que l'on peut individualiser le traitement efficacement pour mieux prévenir les événements thrombotiques. L'application clinique de ces résultats sera cette année le thème de l'un des symposiums les plus importants du CCSC. Ce symposium – qui aura lieu lundi matin – rassemblera plusieurs experts de renom qui discuteront de la portée clinique de ces données. Comme les schémas antiplaquetaires traditionnels ne réussissent pas à prévenir les événements thrombotiques chez les patients à risque élevé, la découverte de stratégies plus efficaces est une percée dans la prise en charge du risque. Certes, il y a une certaine corrélation entre un effet antiplaquetaire plus marqué et un risque hémorragique accru, mais les schémas antiplaquetaires très efficaces sont associés à un bénéfice net dans de nombreux groupes bien définis de patients.

By Ted Bosworth

The thienopyridine clopidogrel plus ASA has been a standard antiplatelet regimen for many high-risk groups including those who are being managed for an acute coronary syndrome (ACS). However, non-response to clopidogrel has been detected in up to 30% of patients. In addition, recent studies suggest that greater protection against thrombotic events can be achieved with greater antiplatelet effects. This premise underlies a variety of recent studies, including those with double-dose clopidogrel and prasugrel, another thienopyridine associated with greater antiplatelet effect in both ex vivo and clinical studies. In a symposium chaired by Dr. Shaun Goodman, Associate Head, Division of Cardiology, St. Michael's Hospital, Toronto, Ontario, progress in this area will be translated into current concepts of patient care.

Non-Responsiveness, Interaction with PPIs

The issue of clopidogrel non-responsiveness will be discussed by interventional cardiologist Dr. Robert Welsh, Associate Professor of Medicine, University of Alberta, Edmonton. He will review the risk of non-response or suboptimal response to clopidogrel and then explore the causes, which include genetic polymorphisms affecting hepatic metabolism of this agent. Hepatic metabolism is an essential step to translate clopidogrel, a prodrug, into its active metabolite. A problem with clopidogrel is that screening for poor metabolizers is not routine, so those individuals who respond poorly to clopidogrel go unrecognized.

Among other suspected causes of clopidogrel non-responsiveness, one potential cause that has been largely refuted by new clinical trial data is an interaction with proton pump inhibitors (PPIs). Widely prescribed for esophagitis, to control dyspepsia and to prevent peptic ulcers associated with NSAIDs,

PPIs have been implicated by case-control studies in a diminished antiplatelet activity and increased risk of thrombotic events in patients taking clopidogrel. This is consistent with competition in hepatic metabolism and with experimental studies suggesting an interaction.

However, Dr. Welsh is expected to review data from two recent studies, including a prospective randomized trial designed specifically to test for an interaction, that refute the case-control studies. In the multinational prospective study, called the COGENT trial, 3627 patients at 393 sites receiving clopidogrel were randomized to the PPI omeprazole or placebo. At the end of three years, the survival curves for cardiovascular (CV) events were superimposable. In another study, two datasets, including one generated by TRITON-TIMI 38 (Trial to assess improvement In Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel—Thrombolysis In Myocardial Infarction 38), investigators were unable to find any adverse effect from PPIs on the antiplatelet activity or risk of events in patients taking either clopidogrel or prasugrel.

Emerging Alternatives

Alternatives to clopidogrel are an important step towards broader protection from thrombotic events in high-risk patients, and these will be the focus of two presentations on Monday morning. In one, by interventional cardiologist Dr. Jean-François Tanguay, Montreal Heart Institute, Quebec, and Associate Professor of Medicine, Université de Montréal, the focus will be on early use of glycoprotein (GP) IIb/IIIa agents in patients presenting with either a non-ST-segment elevation MI (NSTEMI) or a STEMI as well as on ticagrelor, an investigational P2Y₁₂ inhibitor. Although some GP IIb/IIIa inhibitors have demonstrated activity in ACS, Dr. Tanguay is

expected to discuss the specific indications for which they have been tested. It is not clear whether these agents are interchangeable because of potential differences in both antiplatelet effects and bleeding risk, making evidence-based application essential.

In the PLATO study, which Dr. Tanguay is also scheduled to discuss, ticagrelor was associated with a 16% reduction ($P<0.001$) in the combined primary end point of CV death, MI and stroke relative to clopidogrel among ACS patients followed for 12 months. The difference in major bleeding was only significant for reasons not related to coronary artery bypass grafting (CABG), suggesting that this agent may have advantages over clopidogrel if it receives regulatory approval as expected.

In the second presentation, the immediate role of prasugrel as a more effective alternative will be discussed by Dr. Stephen D. Wiviott, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, senior author of TRITON-TIMI 38, which associated prasugrel with a 19% reduction ($P<0.001$) in the primary end point of CV death, MI or non-fatal stroke relative to clopidogrel at a median of 15 months after randomization. As in PLATO, the increased efficacy was associated with increased bleeding, but the net benefit favoured prasugrel. Its relative advantage would also be expected to increase if those subgroups found to be most at risk from increased rates of bleeding in TRITON-TIMI 38 were excluded. These included patients with a body weight <60 kg, those older than 75 years and those with a previous history of stroke or transient ischemic attack (TIA).

Potency and Rapidity of Action in the Context of Treatment Individualization

Although prasugrel is structurally related to clopidogrel, it is associated with more consistent, more rapid and more effective antiplatelet activity. In the ACS setting, one potential advantage is that the level of platelet aggregation inhibition achieved in 30 minutes is comparable to the peak inhibition achieved with clopidogrel at 6 hours. A more rapid onset and a greater degree of antiplatelet effect with prasugrel has also been documented relative to a double-the-dose clopidogrel regimen, which has been increasingly adopted at many institutions because of the inadequate effects achieved with the conventional regimen of a 300-mg loading dose followed by a 75-mg maintenance dose. The PRINCIPLE TIMI 44

(PRasugrel IN comparison to Clopidogrel for Inhibition of PlateLet aggrEgation TIMI 44) trial compared the same 60-mg loading dose and 10 mg prasugrel maintenance dose employed in TRITON-TIMI 38 to a 600-mg clopidogrel loading dose followed by a 150-mg maintenance dose. Measures of platelet aggregation again showed a significant advantage for prasugrel.

The opportunity to reduce thrombotic events with acceptable rates of bleeding will be one of the most important aspects of Dr. Wiviott's presentation. In the ACS population randomized in TRITON-TIMI 38, all of whom were scheduled for a percutaneous intervention (PCI), the results predict 23 fewer MIs with only six more major non-CABG bleeds for every 1000 patients treated. Only 46 patients are needed to treat (NNT) for every major end point presented over a 15-month period vs. 167 NNT for every excess non-CABG major bleeding event. However, even better figures will be generated by appropriate patient selection. Indeed, the greater individualization of care is expected to be a major theme of the symposium overall with each of the speakers providing guidance about how to match the right antiplatelet therapy to the right patient.

Individualization of care is essential because inhibiting platelets naturally links anti-thrombotic effects and bleeding risks. Data from such trials as TRITON-TIMI 38 demonstrate that there is an opportunity to reduce life-threatening CV events with more effective antiplatelet agents. The modest increase in bleeding risk must be weighed within the context of net benefits. Understanding this balance will be a major focus of the Monday morning symposium.

Summary

Major multinational trials have provided important new details about the opportunity to employ antiplatelet agents to reduce the risk of thrombotic events in ACS patients and other high-risk groups. While these studies confirm a relationship between greater reduction in thrombotic events and an increased risk of bleeding, they also show that more effective therapies can improve outcomes, generating a favourable benefit:risk ratio. Due to the relationship between antithrombotic effects and bleeding risk, therapy must be individualized, but the Monday morning symposium will provide important guidance on treatment selection so that patients at high risk of thrombotic events are given the opportunity for maximum protection. □

Please plan to attend:

MONDAY, October 26

“Getting Personal in ACS: Matching Optimal Anti-Platelet Therapy to the Right Patient at the Right Time.” 7:00-9:00, Alberta AB Room, Lobby Level, Crowne Plaza Hotel.

These symposia are accredited and co-developed as an Accredited Group Learning Activity under Section 1 of the framework of Continuing Professional Development options as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada (RCPSC).

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