Medical *Education* Network

PRIORITY PRESS

Canadian Cardiovascular Congress 2011

Vancouver, British Columbia / October 22-26, 2011

Canadian Interventional Cardiology Guidelines: Recognizing Outcome Benefits of Newer Antiplatelet Strategies

Vancouver - New guidelines in Canada and Europe have been issued to identify where the new $P2Y_{12}$ inhibitors can be employed in the management of acute coronary syndromes (ACS) to improve outcomes. In the phase III trials that brought these agents forward, both were superior to clopidogrel, the previous standard, for the primary cardiovascular end points in the study populations. Here at the CCC, several presentations were devoted to defining where the newer agents are best applied. Both act more quickly, are more potent and more predictable than clopidogrel, but the trial evidence and the relationship between antiplatelet effect and bleeding define different roles. As these agents become available in community health centres, an understanding of how they are best applied is critical to incremental protection against mortality.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

Interventional cardiologists are reacting quickly to the availability of new oral antiplatelet therapies for the treatment of acute coronary syndrome (ACS) patients, judging from the series of symposia and presentations at the CCC designed to provide guidance about their indications and application. Antiplatelet therapy is one of the single most important steps in preventing a recurrence of cardiovascular (CV) events in the ACS patient, and the incremental gain from the newer agents has redefined optimal care.

"In the new European guidelines [www.escardio.org], clopidogrel is now recommended for those who are not eligible for ticagrelor or prasugrel," reported Dr. Lars Wallentin, Professor of Medicine and Head of Clinical Research, University Hospital, Uppsala, Sweden. Invited to the CCC to provide a European perspective, Dr. Wallentin indicated that the results of the large trials with ticagrelor and prasugrel confirmed that their more potent antiplatelet effects reduce events, moving clopidogrel to a second-line therapy. Prasugrel is recommended for $P2Y_{12}$-naive patients proceeding to percutaneous coronary intervention (PCI). Ticagrelor is considered appropriate for all ACS patients, regardless of initial treatment strategy, including a loading dose of clopidogrel (although clopidogrel should be stopped when initiating ticagrelor).

Corroborative Evidence

The differences in these recommendations are based on the evidence. There were few restrictions in the key phase III PLATO study with ticagrelor (Wallentin et al. *N Engl J Med* 2009;361:1045-57). Essentially, all ACS patients presenting at participating institutions within 24 hours of symptom onset were eligible for randomization, including those who had already received a loading dose of clopidogrel immediately prior to randomization (46% in the ticagrelor group and 46.1% in the clopidogrel group). In the key phase III TRITON-TIMI 38 study (Wiviott et al. *N Engl J Med* 2007; 357:2001-15), randomization to prasugrel or clopidogrel was limited to those with a planned PCI. The use of any $P2Y_{12}$ inhibitor within the previous 5 days before hospitalization was a contraindication for study entry.

In both trials, the newer $P2Y_{12}$ inhibitor, relative to clopidogrel (all arms also received ASA), was associated with an improvement in outcome, but differences in the relative benefit:risk ratio varied. In the all-comer PLATO design, ticagrelor was associated with a 16% ($P<0.001$) relative risk reduction in the composite end point of death from vascular causes, myocardial infarction (MI) or stroke; it was also associated with a 21% reduction ($P<0.001$) in CV mortality. There was no difference in PLATO-defined overall major bleeding ($P=0.42$), although further stratification of bleeding events did identify a modest increase in major bleeding not related to coronary artery bypass grafting (CABG) (4.5% vs. 3.8%; $P=0.03$).

In TRITON-TIMI 38, prasugrel was associated with a 19% reduction ($P<0.001$) in the same primary composite efficacy end point used in PLATO, but this was counterbalanced by a 32% increase ($P=0.03$) in total bleeding events. The agent was not associated with a significant reduction in mortality. In an effort to better identify where its greater antiplatelet effect might be employed, further stratification found that the increased risks for bleeding were concentrated in patients with low body weight (<60 kg), age over 75 years and prior history of a cerebrovascular event.

Guideline Implications

In Canada, there is also a new set of antiplatelet guidelines, but these address outpatient use (Bell et al. *Can J Cardiol* 2011; 27:S1-S59). Although there is a substantial section on the use of newer $P2Y_{12}$ inhibitors after discharge for ACS, the focus at the CCC was on the upfront use in the acute setting. The

Continued

Canadian guidelines identify both clopidogrel and ticagrelor as acceptable agents for outpatient care after discharge for most forms of ACS (prasugrel is recommended for patients who received a coronary stent and have both a high risk of stent thrombosis and low risk of bleeding). Interestingly, the choice of agent during the acute treatment often dictates the treatment used in long-term maintenance.

Some of the tertiary care treatment centres in Canada now have formulary access to the newer $P2Y_{12}$ inhibitors, but participants at CCS-accredited symposia reported that smaller centres are still working to put these agents on formulary. Systematic approaches are needed for optimal use, but the introduction of newer $P2Y_{12}$ inhibitors may not substantially complicate treatment when appropriate decisions are needed rapidly.

"There is concern that you can get this wrong, but the recommendations are quite clear," confirmed Dr. Wallentin, referring to the evidence-based European guidelines. He emphasized that treatment with ticagrelor is not contraindicated in patients who reach the emergency room with a loading dose of clopidogrel, which is common practice for many emergency response teams working in Canada.

"In regard to NSTEMI patients, it really is a no-brainer at this point," observed Dr. Robert Welsh, Director of Cardiac Catheterization and Interventional Cardiology, University of Alberta, Edmonton. Referring to preferential use of ticagrelor over clopidogrel to prevent recurrent events and improve survival in the NSTEMI population, Dr. Welsh indicated that the trial data are clear.

Practical Considerations

The relative risks and benefits of the newer $P2Y_{12}$ agents in STEMI patients receiving fibrinolytic therapy is not clear due to a lack of safety and efficacy data; hence, both prasugrel and ticagrelor are contraindicated in this ACS patient population. For STEMI patients managed by primary PCI, emerging outcome data for ticagrelor and prasugrel in this subgroup were consistent with the primary composite end points for both the PLATO and TRITON-TIMI 38 studies, respectively. Over the past 18 months, prasugrel is being initiated in Canadian centres in some patients being managed by primary PCI, usually in patients who are clopidogrel-naïve. From a practical perspective, the indication for PCI is not always clear at the time of ACS admission and many current ACS protocols suggest that clopidogrel be initiated shortly after diagnosis. Although prasugrel can also be expected to improve outcomes when used appropriately, well-organized methodology of patient selection is called for.

Overall, a systems approach to emergency ACS management is fundamental to the effort to improve outcomes. For example, in Alberta, a province-wide response to ACS emergencies includes a tightly defined protocol designed to initiate appropriate therapies, including antiplatelet agents, at the earliest safe point. Dr. Welsh said that the effort to create an evidence-based, systematic approach has focused on practical issues. In a vast province such as Alberta, where the closest tertiary care centre can be a thousand kilometres away, "knowing your numbers is key." This means frequently reviewing the time to response and the time to treatments in an effort to constantly seek improvements in quality of care delivery.

Perhaps the most important opportunity for improving outcome comes "at the point of first contact," according to Dr. Welsh. The goal is to make the diagnosis as quickly as possible. He noted that while 45% of all STEMI patients in Alberta occur in a rural setting, the right decisions early in patient care, including initiation of effective therapies, can improve outcomes.

Summary

The introduction of ticagrelor and prasugrel has produced new opportunities to improve outcome in the emergency and long-term care of ACS patients. Evidence-based guidelines are being adjusted to accommodate these new therapies, both of which can significantly reduce the risk of recurrent CV events relative to clopidogrel. Ticagrelor, which is more broadly applicable on the basis of randomized studies, is associated with a reduction in CV mortality. It is expected that these agents, already being utilized in many tertiary care centres in Canada, will rapidly be incorporated into protocols in all centres that routinely manage patients with ACS. □

To view an electronic version of this publication along with related slides if available, please visit www.mednet.ca/2011/pp12-031e.

Medical Education Network Canada Inc. 132 chemin de l'Anse, Vaudreuil, Quebec J7V 8P3

PP12-031E ML