



## Canadian Cardiovascular Congress

Toronto, Ontario / October 25-29, 2008

### Improving Outcomes with Antiplatelet Therapy: Practical Applications from New Research

**Toronto** - Most patients with ST-segment elevation myocardial infarction (STEMI) or high-risk non-STEMI (NSTEMI) should receive dual antiplatelet therapy on presentation, although a sizeable proportion of them still do not. Even if optimally used, there are limitations to currently available antiplatelet agents and efforts continue to be made to improve on existing therapies. In the meantime, the optimal approach to STEMI patients today is to proceed directly to percutaneous coronary intervention (PCI) as soon as possible following presentation. If direct PCI is not available, and there are no contraindications to thrombolysis, thrombolysis followed by immediate transfer to a PCI facility should be considered standard of care for virtually all STEMI patients.

**Toronto** - La plupart des patients en proie à un infarctus du myocarde (IM) avec sus-décalage du segment ST (ST+) ou à un IM sans sus-décalage du segment ST (ST-) à risque élevé devraient recevoir deux antiplaquettaires dès qu'ils se présentent, mais ce n'est pas encore le cas chez un pourcentage substantiel de patients. Les antiplaquettaires actuellement commercialisés étant lacunaires à certains égards même lorsqu'ils sont utilisés de façon optimale, on poursuit la recherche pour améliorer les traitements existants. Pour l'instant, la conduite thérapeutique optimale à tenir en présence d'un IM ST+ consiste à réaliser une intervention coronarienne percutanée (ICP) le plus tôt possible après l'arrivée du patient. Si l'ICP directe est impossible et que le patient ne présente aucune contre-indication à la thrombolyse, la démarche standard dans la quasi-totalité des cas d'IM ST+ est de procéder à la thrombolyse, puis de transférer le patient sans délai à un établissement habilité à pratiquer des ICP.

By Pam Harrison

Consensus indicates that in addition to ASA, a thienopyridine should be considered for all patients presenting with an ST-segment elevation myocardial infarction (STEMI) or most high-risk non-STEMI (NSTEMI) patients. Although these guidelines are supported by substantial evidence, not all facilities have adopted a dual antiplatelet strategy for candidate patients, and the use of clopidogrel may be as low as 50% to 60% in certain centres, especially when patients are medically managed. In contrast, ASA is given to as many as 95% of candidates in many institutions. Even if dual antiplatelet therapy were optimally applied, there are several limitations to current options.

Dr. John Eikelboom, Associate Professor of Medicine, McMaster University, Hamilton, Ontario, refers to the relatively slow onset of action of clopidogrel, its peak activity occurring about six hours after a standard loading dose. Perhaps more importantly, it inhibits platelet function both variably and incompletely. Many studies have shown that incomplete platelet inhibition in acute coronary syndromes (ACS) is associated with a higher event rate, underscoring the importance of achieving optimal platelet inhibition. "Offset of action is also slow," Dr. Eikelboom notes.

Several strategies are being explored to overcome these limitations, one of which is to use higher loading and maintenance doses of clopidogrel. "We might also try altering the timing of administration by giving a double bolus of clopidogrel separated by six hours," he adds. It has been suggested that the variability in platelet inhibition seen with clopidogrel may arise because of poor gastrointestinal absorption. By separating the two loading doses, platelet inhibition may increase.

"We have to remember that both ASA and clopidogrel have become entrenched in clinical practice because they are so valuable," Dr. Eikelboom observes. "So while we can talk about disadvantages of a drug, clopidogrel is widely used [and] it has served us very well."

### TRITON-TIMI-38

In discussing results with another thienopyridine, prasugrel, Dr. Shawn Goodman, Associate Professor of Medicine, University of Toronto, Ontario, will present a "real-world" approach to ACS patients in Canada which is different from the one used in most patients enrolled in the TRITON-TIMI-38 trial, an important factor to keep in mind when interpreting results of the trial. TRITON-TIMI-38 included both STEMI and NSTEMI/unstable angina patients who underwent coronary angiography first. Only when the coronary anatomy was known did they receive either clopidogrel 300 mg followed by a 75-mg maintenance dose, or a 60-mg loading dose of prasugrel followed by a 10-mg maintenance dose. All were scheduled for percutaneous coronary intervention (PCI).

As reported originally by Wiviott et al. (*N Engl J Med* 2007;357:2001-15), fewer ischemic events at 9.9% were observed at a median follow-up of 15.2 months in the prasugrel cohort compared with 12.1% for their clopidogrel counterparts ( $P<0.001$ ). On the other hand, rates of major non-CAD bleeds at 2.4% in the prasugrel arm were higher than the 1.8% seen in the clopidogrel arm ( $P=0.03$ ).

As reported by Montalescot et al. this year at the ESC, the STEMI subgroup in TRITON-TIMI-38 did not require an initial angiogram before proceeding to antiplatelet randomization and percutaneous coronary intervention (PCI). In this STEMI cohort, 12.4% of those randomized to clopidogrel followed by immediate PCI reached the primary end point at 15.2 months vs. 10% for those assigned to prasugrel for a relative risk reduction (RRR) of 21% ( $P=0.02$ ).

Fewer patients in the prasugrel arm also reached secondary end points of CV death, MI or urgent target revascularization at 30 days at 6.7% vs. 8.8% in the clopidogrel arm (RRR 25%). There was also a 42% RRR in stent thrombosis in favour of the prasugrel arm. In contrast to the overall TRITON-TIMI-38

cohort, bleeding rates in the STEMI cohort at 2.1% for prasugrel recipients vs. 2.4% for clopidogrel were similar. Findings from this particular subgroup analysis therefore suggest that “there is a potential window to give prasugrel instead of clopidogrel in STEMI patients because that was the practice in TRITON-TIMI-38 and they did better,” indicates Dr. Goodman.

Patients with diabetes in TRITON-TIMI-38 had an even greater response to prasugrel than patients without diabetes, likely a reflection of their heightened state of platelet reactivity, and where the more rapid, more consistent and more complete inhibition of platelet aggregation achieved with prasugrel exerts its greatest effects.

Patients who were 75 years of age or older, those who weighed less than 60 kg or those with a prior stroke or TIA were at highest bleeding risk in TRITON-TIMI-38. It is suggested that physicians should therefore avoid prasugrel in these groups of patients, as the lower risk of ischemic events achieved with prasugrel was offset by the higher bleeding risk.

### STEMI Management in 2008

Dr. Mouhieddin Traboulsi, Clinical Professor of Medicine, University of Calgary, Alberta, notes that in 2008, primary PCI should be the procedure of choice when STEMI patients present. Thus, it is imperative that hospitals organize efficient referral programs so STEMI patients can receive PCI at a tertiary care centre with minimal possible delay. That said, in a country such as Canada, particularly if patients present relatively early and have no contraindication for fibrinolysis, fibrinolysis followed by transfer for later PCI is better than fibrinolysis alone.

This strategy was supported by the Canadian-based TRANSFER-AMI study, in which a strategy of transferring STEMI patients for PCI within six hours of receiving thrombolysis at a non-PCI centre (pharmacoinvasive strategy) was associated with a clear benefit at 30 days compared with the more standard watchful waiting strategy. At 30 days, 10.6% of the pharmacoinvasive group in TRANSFER-AMI had reached the primary end point of death, repeat MI, heart failure, severe recurrent ischemia or shock compared with 16.5% for the wait-and-see group. Importantly, bleeding rates

were not significantly higher in the pharmacoinvasive group. Thus, as TRANSFER-AMI investigators concluded, the best practice hospitals can offer STEMI patients is to make sure they transfer them to a centre following fibrinolysis where they may undergo PCI within six hours.

### Looking Ahead

Dr. Pierre Thérault, Professor of Medicine, Université de Montréal, Quebec, will review emerging antiplatelet therapies that are showing promise in early trials. The furthest along would appear to be AZD6140, a direct reversible inhibitor of the P2Y<sub>12</sub> receptor. Onset of action occurs within two hours of administration and functional platelet recovery occurs as soon as drug levels wear off around 36 to 48 hours later. This means that patients who require surgery following administration of AZD6140 would no longer be at increased bleeding risk once plasma levels fall. In an early study involving 990 NSTEMI-ACS patients, participants received ASA plus either AZD6140 90 mg b.i.d., AZD6140 180 mg b.i.d. or 300 mg clopidogrel, followed by standard maintenance doses for 12 weeks. Rates of major or minor bleeding at four weeks—the primary end point of the study—were not different between clopidogrel at 8.1% vs. 9.8% for the AZD6140 90-mg group and 8.0% in the AZD6140 180-mg group. Favourable trends were also seen in rates of MI in the AZD6140 group as well.

The ongoing PLATO study will involve some 18,000 STEMI and NSTEMI patients, all of whom will receive ASA, then clopidogrel or AZD6140 within 24 hours of the index event. Unlike the TRITON-TIMI-38 trial, patients in PLATO will be randomized to antiplatelet therapy as they are here in Canada, as early as possible, without undergoing angiography.

The investigational intravenous ADP receptor antagonist cangrelor appears to have an immediate onset of action (within minutes) with recovery of platelet function in less than 60 minutes. Evidence so far suggests it has effects similar to those of abciximab in the setting of PCI. And the PAR-1 receptor antagonist SCH530348 has shown substantial inhibition of platelet aggregation at 120 minutes. There may also be a role for terutroban, a TP receptor antagonist, currently under development as well. □

### Please plan to attend:

“Improving Outcomes with Antiplatelet Therapy: Practical Applications from New Research.” Monday, October 27, 2008, 7:00-9:00, Room 701 AB.

This symposium is 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) *do not represent the opinions of the Canadian Cardiovascular Society.*

*Note: At the time of printing, prasugrel, AZD6140, cangrelor, SCH530348 and terutroban are not available in Canada.*

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