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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Optimizing Therapy in Acute Coronary Syndromes and Percutaneous Coronary Intervention

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Reported and discussed by: Howard Leong-Poi, M.D.

The optimal anti-thrombotic therapy for patients presenting with acute coronary syndromes (ACS) and those undergoing routine percutaneous coronary intervention (PCI), including stenting, continues to evolve rapidly. This issue of *Cardiology Scientific Update* presents and discusses recent results from randomized clinical trials of anti-platelet therapy and anti-thrombin agents in ACS patients and those undergoing PCI, along with the latest "real-world" results from registry data.

Optimizing anti-platelet therapy: Insights from recent clinical trials

The current standard of practice for patients undergoing routine PCI and stenting includes dual anti-platelet therapy with aspirin and a thienopyridine. The main rationale for dual anti-platelet therapy remains the prevention of coronary stent thrombosis, a rare (~1%) occurrence, with potentially catastrophic consequences. Due to a higher incidence of unacceptable side-effects, ticlopidine has been supplanted by clopidogrel as the thienopyridine of choice. However, since the majority of the evidence for dual anti-platelet therapy in the setting of PCI or stenting involved studies with ticlopidine, there are several unanswered questions surrounding the use of clopidogrel in PCI, including:

- the best timing of administration of the loading dose of clopidogrel and need for pre-treatment
- the optimal loading dose to achieve effective anti-platelet effect
- the benefit of concomitant intravenous glycoprotein (GP) IIb/IIIa receptor blockers.

Studies have reported on the variability in platelet inhibitory response using the standard 300 mg loading dose of clopidogrel in patients undergoing elective PCI and stenting.[1,2] When poor platelet inhibitory response – termed "clopidogrel resistance" – presents in patients with the highest pretreatment platelet reactivity (eg, in the ACS setting), this can result in less cardioprotection because there is a higher risk for ischemic events and stent thrombosis.[3] Whether higher doses of clopidogrel or adjunctive pharmacological strategies with GP IIb/IIIa inhibitors would overcome these potential limitations and further prevent adverse ischemic events remains controversial.

ISAR-REACT

Recent evidence from the Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment (ISAR-REACT) study[4] suggests that in low risk patients undergoing elective PCI and stenting, pretreatment (at least 2 hours prior to the procedure) with the higher dose of clopidogrel (600 mg) alone negates the beneficial effects of additional GP IIb/IIIa receptor blockade. Monotherapy with high dose clopidogrel yielded clinical outcomes that were similar to a strategy of pretreatment with combination high-dose clopidogrel and abciximab. In addition, several studies have questioned the optimal timing of the loading dose, specifically the need for pre-treatment prior to PCI as opposed to loading during PCI and stenting.[5,6] The issue of pretreatment before coronary angiography/PCI remains relevant since the increased bleeding risk in patients who undergo subsequent coronary artery bypass graft (CABG) surgery within 5 days of receiving clopidogrel has to be balanced against the need for early surgical revascularization.[7,8]

CLEAR PLATELETS study

The recently published Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study[9] attempted to address some of these controversial issues, specifically the need for GP IIb/IIIa inhibitors when high dose clopidogrel

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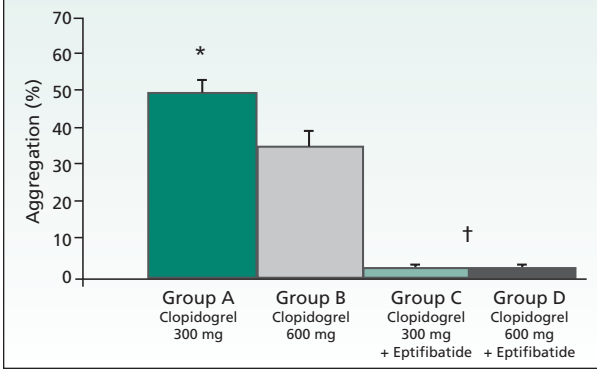
Figure 1: Mean platelet reactivity measured over 18-24 hours after stenting by 5 µmol/L ADP-induced aggregation



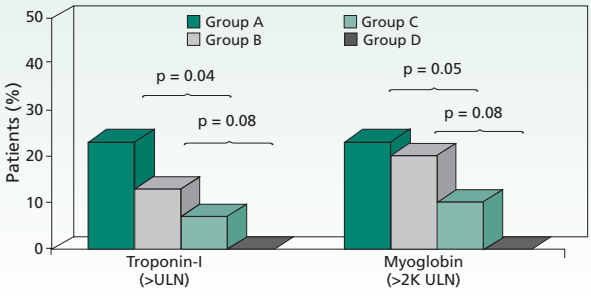
*p=0.002, group A vs B; †p<0.001, group C or D vs group A or B

is used without pre-treatment. In this study, a total of 120 low risk patients undergoing elective PCI and stenting were randomized to 1 of 4 treatment arms in a 2 × 2 factorial design:

- Group A – clopidogrel 300 mg
- Group B – clopidogrel 600 mg
- Group C – clopidogrel 300 mg + eptifibatide
- Group D – clopidogrel 600 mg + eptifibatide.

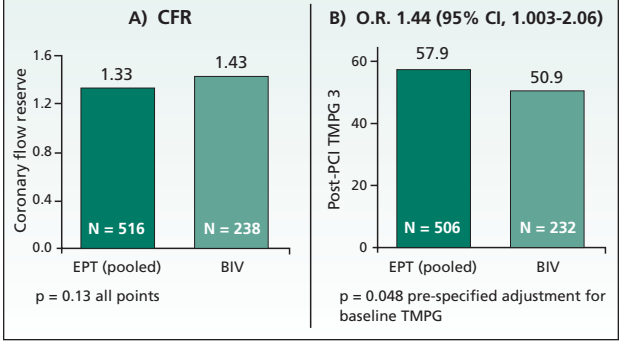
Clopidogrel was administered immediately after stenting, *without pretreatment*. Platelet activity was assessed *ex-vivo* by aggregometry and flow cytometry in all treatment groups. The results of this study demonstrated that the use of GP IIb/IIIa receptor blockade produced superior platelet inhibition (up to 24 hours post-stenting; Figure 1) and lower cardiac enzyme release (Figure 2) compared with either clopidogrel 300 mg or 600 mg alone. In addition, high-dose clopidogrel (600 mg) resulted in greater platelet inhibition than the conventional 300 mg dose, providing further evidence to studies supporting the use of higher dose clopidogrel. Patients with the highest measured platelet reactivity had the most peri-procedural myonecrosis, highlighting the importance of platelet inhibition. While these results suggest that additional GP IIb/IIIa receptor blockade yields improved platelet inhibition and less myonecrosis compared to higher dose clopidogrel alone, the beneficial effects on clinical endpoints need to be confirmed with an appropriately powered randomized clinical

Figure 2: Troponin-I and myoglobin release in the 4 treatment groups.



ULN = upper limit of normal

Figure 3: Comparison of A) coronary flow reserve (CFR), and B) TIMI myocardial perfusion grade (TMPG) in eptifibatide (EPT)-treated as compared to bivalirudin (BIV)-treated patients.



trial. In addition, this study did not address questions surrounding pretreatment and whether GP IIb/IIIa receptor inhibition had additional benefits in this setting.

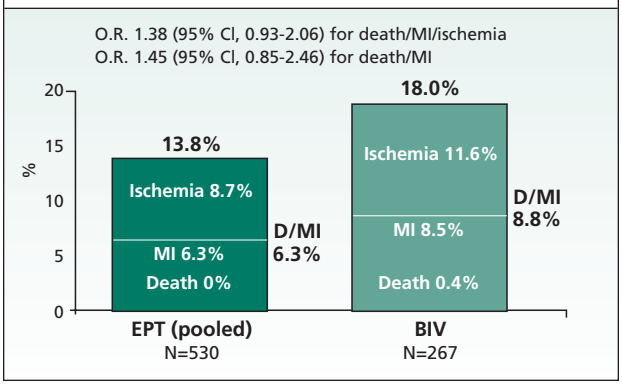
PROTECT

The PROTECT (Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents)-TIMI 30 trial compared the relative efficacy and safety of an anti-platelet strategy with GP IIb/IIIa receptor blockade, to a direct anti-thrombin agent-based strategy, in high risk ACS patients treated with early PCI. This study was presented at the recent American Heart Association 2004 Meeting.

PROTECT randomized 857 patients to receive either the GP IIb/IIIa inhibitor, eptifibatide, or the direct thrombin inhibitor, bivalirudin. Patients in the eptifibatide arm were further randomized to receive enoxaparin or unfractionated heparin (UFH). Randomization was stratified by clopidogrel pretreatment at >6 hours and ≤6 hours. In patients who did not receive pre-treatment, 300 mg of clopidogrel was given immediately prior to stenting. All patients received aspirin. After pre-specified adjustment for abrupt closure and thrombotic bailout, there was no significant difference in the primary efficacy endpoint of coronary flow reserve post-PCI, as determined by Thrombolysis in Myocardial Infarction (TIMI) frame count before and after adenosine, between eptifibatide and bivalirudin-treated groups (Figure 3A). The percentage of patients with TIMI myocardial perfusion grade 3 post-PCI was higher for those treated with eptifibatide, as compared to bivalirudin (Figure 3B), suggesting improved tissue microvascular perfusion with GP IIb/IIIa treatment. There were no differences in the secondary clinical endpoints of death/MI, and death/MI/ischemia on 48-hour Holter monitoring (Figure 4). Patients receiving eptifibatide did show a reduced duration of ischemia on Holter monitoring, as compared to those receiving bivalirudin (median duration 36 vs 169 minutes, respectively, p=0.013).

There was no significant difference between treatment groups in the primary safety endpoint of TIMI major bleeding; however the incidence of TIMI minor bleeding and transfusion requirements were significantly less with bivalirudin as compared to

Figure 4: Comparison of rates of death (D), myocardial infarction (MI) and ischemia on Holter monitoring in eptifibatide (EPT)-treated as compared to bivalirudin (BIV)-treated patients



eptifibatide. Overall, in this high risk ACS population undergoing PCI/stenting, there were no major differences between treatment with eptifibatide and bivalirudin, with any minor clinical benefits of eptifibatide balanced by a greater risk of bleeding.

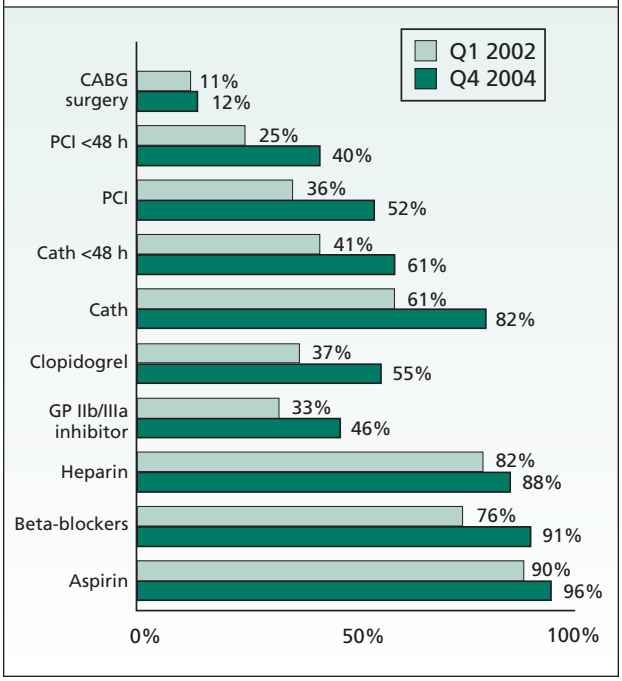
EARLY ACS

The EARLY ACS (EARLY glycoprotein IIb/IIIa inhibition in patients with non-ST-segment elevation Acute Coronary Syndrome) is an ongoing study randomizing 10,500 high risk (age >60 years, positive biomarkers, ST-segment shift on ECG) ACS patients to early front-loaded eptifibatide or placebo, with all patients receiving aspirin, clopidogrel, and heparin and under-going catheterization. The primary endpoint is the composite of death, MI, recurrent ischemia requiring urgent revascularization and GP IIb/IIIa inhibitor use for thrombotic bailout at 96 hours, with a secondary endpoint of death or MI. All patients will receive aspirin, heparin (either unfractionated heparin [UFH] or enoxaparin) and clopidogrel (300 mg load, then 75 mg daily). GP IIb/IIIa receptor blockade will continue for 96 hours, with PCI performed as needed after a minimum 72 hours. Safety endpoints will include hemorrhage, transfusion requirements, and stroke. Enrolment into the study is well underway, with results expected by 2006. This study will help to further define the role of GP IIb/IIIa inhibitors in the current acute management of ACS patients, particularly regarding the benefits of initiating treatment prior to PCI.

Current practice: latest insights from clinical registries

Current clinical practice guidelines are based in large part on the results of randomized, placebo-controlled, clinical trials. While extremely important, due to the careful patient selection and close clinical follow-up involved, the results of these clinical trials tend to overestimate the benefits, and perhaps underestimate the risks, otherwise derived in a more general population. In addition, the implementation of clinical trials results and practice guidelines into everyday practice remains less than adequate. Thus, data derived from clinical registries provide important information, both about the implementation of practice guidelines into general clinical practice and as a true measure of the resultant

Figure 5: Comparison between rates of ACS therapies in the first quarter (Q1) of 2002 and the fourth quarter (Q4) of 2004 in the CRUSADE registry



clinical outcomes obtained in a "real-world" population. As reviewed in a recent issue of *Cardiology Scientific Update*, numerous quality improvement programs have been initiated in the U.S. and in several countries worldwide with the goal of reducing the "care gap" that exists between guideline recommendations and actual patient care. One important quality improvement program is the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) quality improvement initiative.[10,11] This program collects data from over 400 hospitals to analyze current treatment practices and determines the degree of guideline compliance. Results are then reported back to the hospitals, informing them of individual institutional performance, along with the national rates of adherence for comparison. These educational interventions have led to an improvement in adherence to published ACC/AHA guidelines.[11]

As of December 2004, a total of 130,735 patients have been enrolled in CRUSADE. Compared to data obtained in early 2002, there has been a significant increase in the use of evidence-based treatments in the acute management of ACS patients (Figure 5). Similarly, over the same period of time, the rates of early catheterization and revascularization, both for PCI/stenting and CABG surgery, have also improved (Figure 5). Finally, the rates of discharge on medications recommended for secondary prevention have improved substantially as well. Importantly, improvement in adherence to guidelines has been shown to lead to greater benefit, with a mortality rate of 1.3% in patients who were managed with aspirin, beta-blockers, heparin, GP IIb/IIIa inhibitors, and early coronary angiography (<48 hours).

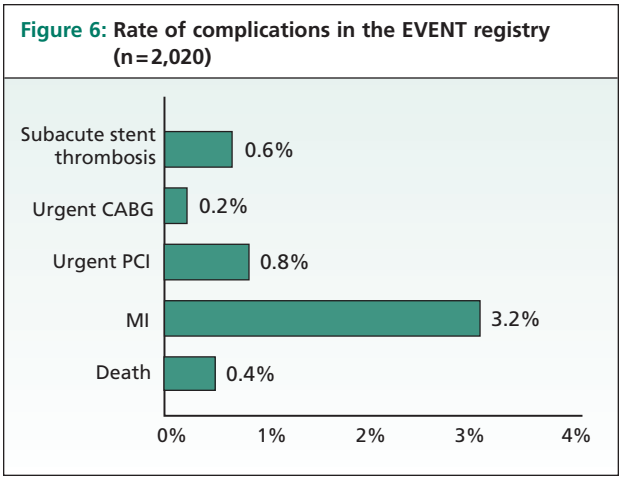
CRUSADE demonstrates that in a "real-world" setting, adherence to practice guidelines and, therefore, overall care of ACS patients, is improving over time and resulting in improved clinical outcomes. There remains, however, room for further improvement, with large gaps still existing in the use of GP IIb/IIIa inhibitors, angiotensin converting enzyme inhibitors, and clopidogrel.

Drug-eluting stents

In the current era of PCI and intra-coronary stenting, use of drug-eluting stents (DES) has increased exponentially due to several clinical trials showing drastically reduced rates of in-stent restenosis with these devices.

The EVENT (Evaluation of drug eluting stents and ischemic events) registry is a U.S.-based multicentre registry aimed at following and assessing "real-world" PCI practice patterns and clinical outcomes in the DES era. This registry will enroll consecutive patients undergoing PCI and stenting in discrete waves of 2,500, with a total expected enrolment of 7,500-10,000 patients at approximately 60 test sites. The collected data will include procedural and stent data, concomitant medication use, periprocedural complications, and cardiac enzyme levels. As of March 1st, 2005, 2,020 patients at 31 active sites have been enrolled. Preliminary data reveal that, overall, 87.5% of the patients received a DES, with 8.3% receiving a bare metal stent, and the remainder a combination of stents. Of the DES used, 53.7% were Cypher stents and 46.3% were Taxus stents. Approximately half of the patients enrolled received a direct thrombin inhibitor and half received a combination of heparin (UFH or enoxaparin) and a GP IIb/IIIa inhibitor. Of the GP IIb/IIIa inhibitors, the majority (88%) received eptifibatide, with the remainder receiving abciximab or tirofiban. Just over half (54.5%) received GP IIb/IIIa inhibitors electively in the catheterization laboratory, with 14.9% receiving upstream GP IIb/IIIa inhibitors and 30.6% starting during PCI, likely representing bailout use. Importantly, clopidogrel pre-treatment (>6 hours pre-PCI) occurred in only 38%, mostly in elective patients, likely due to concerns over bleeding risk in patients who qualify for CABG surgery. To date, only investigator reported complications are available, with a 4.6% rate of complications (Figure 6). The rate of subacute stent thrombosis was low at 0.6%. Overall, this first look at this important registry reveals a high utilization of DES. Several different anti-thrombin and anti-platelet regimens are being used, highlighting the ongoing debate as to the best anti-thrombotic regimen during PCI and stenting. Notably, the incidence of ischemic complications remains significant in this "real-world" population, establishing the need for further studies.

Figure 6: Rate of complications in the EVENT registry (n=2,020)



Conclusions

While ongoing quality improvement initiatives have resulted in improved adherence to clinical practice guidelines and subsequent patient outcomes, there remains room for improvement. Early anti-thrombotic therapy in patients with ACS and those undergoing routine PCI and stenting is continually evolving. Numerous questions surrounding clopidogrel, GP IIb/IIIa inhibitors, and direct anti-thrombin use in this patient population remain unanswered. The results of ongoing clinical trials designed to answer these specific questions are eagerly awaited.

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