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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

What is the Latest and Greatest Antithrombotic Regimen for Unstable Cardiac Ischemic Syndrome?

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The treatment of acute coronary syndrome is constantly evolving. At present, 4 established pharmacologic agents, including aspirin, unfractionated/low molecular weight heparin (UFH/LMWH), glycoprotein (GP) IIb/IIIa inhibitors, and clopidogrel, plus 7 combinations of these antithrombotic regimens, are being evaluated. However, several questions remain unanswered. First, is there a standard therapy in 2004? Second, should these antithrombotic therapies be stratified according to treatment approach, such as invasive versus conservative therapy? And, third, is there an appropriate long-term antithrombotic strategy for treatment beyond one year? This issue of *Cardiology Scientific Update* presents the latest developments regarding the practical use of antithrombotic regimens in acute coronary syndrome, with a focus on oral antiplatelet agents.

Pills (aspirin, adenosine diphosphate inhibitors)

New information on aspirin

Aspirin has been in use for over 100 years and yet, much remains to be learned regarding this drug. To determine the effects of antiplatelet therapy in patients at high risk of vascular events, a collaborative meta-analysis – the Antithrombotic Trialists' Collaboration – recently examined randomized trials of an antiplatelet regimen versus control or those comparing one antiplatelet regimen versus another in high-risk patients.[1] Overall, allocation to antiplatelet therapy reduced the combined outcome of any serious vascular event by one-quarter, nonfatal myocardial infarction (MI) by one-third, and nonfatal stroke by one-quarter. Aspirin was the most widely studied antiplatelet drug. One important observation from this systematic overview was the impact of aspirin dose. Trials that used aspirin at a dose of 75-150 mg daily were associated with a 32% reduction in composite vascular events, while a dose of 50-1500 mg daily was associated with a 19% reduction (recognizing that there were different study populations). This suggests that 75-150 mg daily is at least as effective as the higher dose. Results of trials with doses <75 mg daily are, however, less conclusive. In the recently-published Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial, a study of lotrafiban, an oral GP IIb/IIIa inhibitor, the use of a higher dose of aspirin >162 mg/day was associated with significantly higher risk of serious bleeding than a lower dose of 75-162 mg/day.[2] In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, the benefit from the addition of clopidogrel to aspirin on combined cardiovascular (CV) death, MI, and stroke was similar, regardless of the dose (100 mg, 101-109 mg, or 200 mg/day) of aspirin. However, the risk of major bleeding increased significantly with an increasing

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dose of aspirin, with or without clopidogrel, and with no increase in efficacy. The most commonly used dose of aspirin in clinical practice is 325 mg daily; however, based on the above observations, 81 mg/day appears to be the preferred dose for antithrombotic effect.

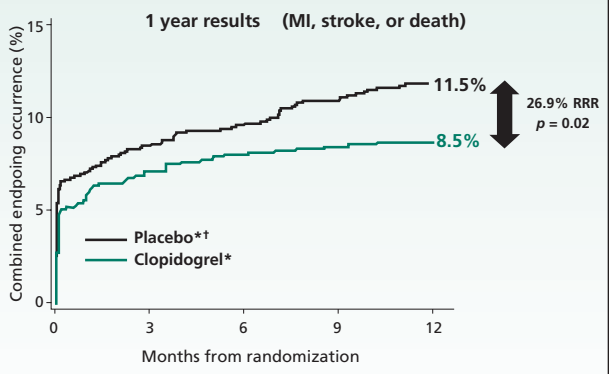
The mechanisms of the anti-inflammatory effect of aspirin are quite distinct from those of its antithrombotic effect and these mechanisms are just beginning to unfold. Atherogenesis and plaque destabilization involve immune-mediated mechanisms. Interleukin (IL)-7 is a regulator of T-cell homeostasis, but is also involved in inflammation. In patients with stable and unstable angina, plasma levels of IL-7 were significantly increased and, in these patients, increased release from activated platelets appeared to be a major contributor to raised IL-7 levels in patients with angina.[3] Importantly, aspirin reduced both the spontaneous and stimulated release of IL-7 from platelets. Another anti-inflammatory mechanism is through the initiation of resolvins, a novel family of bioactive products of omega-3 fatty acid transformation circuits that counter proinflammation signals.[4]

In summary, recently reported data suggest that the optimal dose of aspirin is 81 mg per day (and certainly not more than 162 mg per day) in the treatment of patients at high-risk of vascular events. Aspirin appears to have unique anti-inflammatory mechanisms. In spite of the well-documented benefit of aspirin in the reduction of adverse events in coronary artery disease, in the recent RAND report of the quality of care delivered to adults in the United States,[5] only 61% of participating patients with MI who were considered candidates for aspirin therapy received the therapy, indicating a significant treatment gap.

Platelet adenosine diphosphate $P2Y_{12}$ receptor antagonists

Platelet activation occurs in response to vessel injury and is important to arrest bleeding. However, platelet activation in disease states leads to vascular occlusion and ischemic damage. The $P2Y_{12}$ receptor, activated by adenosine diphosphate (ADP), plays a central role in platelet activation. These receptors are the targets of $P2Y_{12}$ receptor antagonists (eg, clopidogrel) that are proven to have therapeutic value.[6] However, these drugs are currently used at doses that block only 40% to 50% of the $P2Y_{12}$ on platelets. Recent studies on $P2Y_{12}$ knockout mice have demonstrated that $P2Y_{12}$ is involved in many key thrombotic steps, including platelet adhesion/activation, thrombus growth, and stability.[7,8] These findings imply that more aggressive strategies of $P2Y_{12}$ blockade may be antithrombotic without the requirement of concomitant ASA therapy; be synergistic with thrombin inhibition; and provide benefits even in aspirin nonresponders.

Figure 1: Long-term benefits of clopidogrel in PCI patients[13]



* On top of standard therapy including ASA
† All patients received clopidogrel post PCI up to day 28

The effect of $P2Y_{12}$ receptor blockade may be broader than just an ADP-mediated event. Platelets express CD40 ligand (CD40L), a transmembrane protein structurally related to the cytokine tumour necrosis factor-α and, upon activation, triggers an inflammatory response in the endothelial cells of the vessel wall.[9] There is currently, therefore, a paradigm shift in the role of platelets in ischemia suggesting that platelets are not only involved in homeostasis, but are also a rich source of inflammatory mediators. The important point is that while commonly used antiplatelet agents such as aspirin have not been shown to influence CD40L, $P2Y_{12}$ inhibition has been shown to reduce soluble CD40L. In patients undergoing elective percutaneous coronary intervention (PCI), pretreatment with the platelet ADP receptor antagonist, clopidogrel, significantly reduced platelet CD40L (TRAP) and soluble CD40L.[10] Therefore, these data suggest an anti-inflammatory effect that may constitute an important mechanism underlying the early and sustained beneficial effect of clopidogrel observed in patients with acute coronary syndrome (ACS) and those undergoing PCI (Figure 1).[11-13]

Short-term ADP receptor antagonist therapy, in addition to aspirin, has been known to lead to greater protection from thrombotic complications than aspirin alone.[14,15] The Clopidogrel for the Reduction of Events During Observation (CREDO) trial was designed to establish the optimal duration of combination oral antiplatelet therapy and the benefit of loading therapy with clopidogrel in patients who were to undergo elective PCI or deemed to have a high likelihood of undergoing PCI.[13] Patients were randomly assigned to receive a 300-mg clopidogrel loading dose (n=1053) or placebo (n=1063) 3 to 24 hours before PCI. Thereafter, all patients received clopidogrel, 75 mg daily, through day 28.

From day 29 through 12 months, patients in the loading-dose group received clopidogrel, 75 mg daily, and those in the control group received placebo. After one year, long-term clopidogrel therapy in the loading group was associated with a 26.9% relative reduction in the combined risk of death, MI, or stroke. Although clopidogrel pretreatment did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularization at 28 days, in a pre-specified subgroup analysis, patients who received clopidogrel at least 6 hours before PCI experienced a relative risk reduction of 38.6% for this endpoint compared with no reduction with treatment <6 hours before PCI. These results, therefore, indicate that treatment with clopidogrel for 1 year following PCI significantly reduces the risk of ischemic events. Furthermore, a loading dose administered at longer intervals between the dose and PCI may reduce events at one month.

Preliminary data from a new analysis on the incidence of major adverse clinical events (MACE) at one year in patients in CREDO who survived to 29 days also suggest that long-term therapy with clopidogrel following PCI is safe.[16] From day 29 through 1 year following randomization, there were 138 bleeding events, 68 in the clopidogrel and 70 in the placebo arm ($p=0.84$). Of these, 112 (81%) were procedure-related, and most (82; 59%) occurred in the setting of coronary artery bypass graft (CABG) surgery. In a multivariable model that included demographics, comorbidities and concomitant medical therapies, independent predictors of bleeding were age, diabetes, and CABG. Clopidogrel therapy beyond 28 days was not a significant predictor of major or minor bleeding. During that same interval, 80 MACE occurred. A first MACE was significantly less frequent among those randomized to clopidogrel than placebo (3.0% vs. 4.7%, $p=0.043$).

The dose of clopidogrel may also be relevant. It should be noted that a 300 mg loading dose may block only 45% to 50% of the $P2Y_{12}$ receptors. In a recent study on patients undergoing stent placement, a 600 mg loading dose suppressed ADP-induced platelet aggregation (to about 25%) to a greater extent than 300 mg (to about 40%, which is similar to that achieved in the heterozygous $P2Y_{12}$ receptor knockout discussed above).[17]

This observation is particularly interesting in view of the findings of the just-published Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) study that explored whether the GP IIb/IIIa inhibitor, abciximab, was beneficial in patients undergoing elective PCI after pretreatment with clopidogrel.[18] Some 2159 patients were randomized to receive abciximab and placebo and all were pretreated with a 600-mg dose of clopidogrel at least 2 hours before the procedure. The primary composite of the outcome of death, MI, and urgent target-vessel revascularization at 30 days was not different between the 2 groups. Although these findings need to be confirmed in larger studies, they do raise the possibility that pretreatment with high-dose (600 mg) clopidogrel in low- to intermediate-risk patients undergoing elective PCI may obviate the need for GP IIb/IIIa inhibition.

If a $P2Y_{12}$ receptor inhibitor like clopidogrel is anti-inflammatory, given the known pathobiology of atherosclerosis, clopidogrel should be expected to stabilize or prevent atherosclerosis over the long-term in high-risk patients. This question is currently being addressed by the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial that is exploring the benefits of continuing clopidogrel and aspirin treatment out to an anticipated follow-up of 42 months in over 15,000 high-risk, but stable patients.

A likely strategy for prescribing antiplatelet agents in the near future would be to tailor agents and the dose of therapy to individuals based on platelet functional response or perhaps genomic testing. It was recently shown that in stable patients and in those undergoing PCI, the estimated 25% of patients with systematically documented aspirin resistance will have a significant increase in the risk of adverse events.[19-21] There are also increasing reports of clopidogrel resistance which, in some series, were estimated to comprise up to one-quarter of the patients evaluated.[22-25]

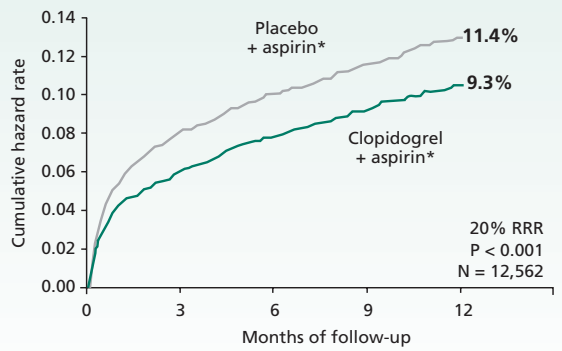
Furthermore, clopidogrel resistance may be associated with an increased risk of subacute stent thrombosis.[25,26] Indeed, a recent study in healthy subjects demonstrated an association between $P2Y_{12}$ gene sequence variations and ADP-induced platelet aggregation responses.[27] Carriers of the H2 haplotype appear to have an increased risk of atherothrombosis or a lesser clinical response to drugs inhibiting platelet function.

In summary, new data suggest that platelet $P2Y_{12}$ receptor inhibitors may exert an anti-inflammatory effect and a loading dose of 600 mg may be more effective than a lower dose in PCI. Data on the use of dual therapy with aspirin and clopidogrel in the setting of primary prevention are forthcoming.

What does the patient go home on?

Results of registries of patients with ACS have revealed that only a minority (<25%) of adverse events occur in hospital, with the majority (>40%) occurring 2 years after the index ACS event.[28] In spite of this fact, most of the therapies for ACS have been evaluated for benefit in the short-term.

Figure 2: Effect of clopidogrel on MI/stroke/CV death in non ST segment elevation acute coronary syndrome[12]



* In combination with standard therapy

Furthermore, an aggressive, early, invasive approach, while effective in relieving ischemic symptoms, is not necessarily associated with improved clinical outcomes.[28,29] Moreover, patients with acute MI may harbour multiple, small, complex coronary plaques, in addition to a single "culprit lesion." Simply because of the disease burden, these multiple smaller plaques are more likely to be associated with subsequent adverse clinical outcomes.[30-32] These observations, therefore, highlight the importance of a treatment strategy in patients with ACS that affects not only the acute thrombotic process, but also the atherosclerotic process of the smaller, but vulnerable plaques. Therefore, such a treatment strategy may benefit clinical outcome over the long-term.

The use of clopidogrel in conjunction with aspirin appears to fit into such a strategy. As shown in Figure 2, in the Clopidogrel in Unstable Angina to Prevent Recurrent Event (CURE) trial, the benefit of clopidogrel + aspirin over placebo + aspirin on the primary outcome of combined MI, stroke, and CV death was apparent within 24 hours after randomization.[12] Importantly, this benefit was sustained at 12 months as the event curves of the 2 study groups continued to diverge. Even if the data on the first 30 days are excluded from analysis, the difference between the 2 groups remained highly significant. The benefit of the combined regimen was maintained regardless of concomitant medications and was consistent across different doses of aspirin and various risk groups. As expected, the clopidogrel arm had a slight excess in major and minor bleeding, but no increase in life-threatening bleeding. However, when incorporated into the primary endpoint to provide a marker of net benefit, the trend still strongly favoured clopidogrel + aspirin therapy.

Table 1: Cost and cost difference between clopidogrel and placebo in PCI-CURE[33]

	Clopidogrel	Placebo	Δ	95% CI for Δ
Medicare	$14,855	$14,765	$90	-$724, $902
MEDSTAT	$20,195	$20,375	-$181	-$1267, $928
MEDSTAT/ Medicare	$17,831	$17.986	-$155	-$1178, $873

A cost-effectiveness analysis of the use of clopidogrel in the setting of PCI in ACS was recently conducted in 1730 patients who participated in the PCI-CURE trial.[11,33] Patients were pre-treated with clopidogrel or placebo in addition to aspirin. After PCI, >80% of patients received an open-label ADP-receptor antagonist for ~ 4 weeks, then the study drug for up to 1 year. The composite of CV death, stroke, or MI occurred in 76 (9.3%) clopidogrel patients vs 116 (12.8%) placebo patients (odds ratio, 0.73, $p = 0.021$).

Hospitalizations were assigned to a Diagnosis Related Group (DRG) and costs were estimated from:

- Medicare average reimbursement,
- MEDSTAT (private insurance)
- MEDSTAT age <65 years
- Medicare age ≥65. years

The average wholesale price of clopidogrel was estimated to be US $3.22 per day. Lost life expectancy associated with CV death, non-fatal MI, and non-fatal stroke was estimated from published Framingham data, discounted 3%.[34] The preliminary results in terms of cost and cost-difference are shown in Table 1. The incremental cost-effectiveness ratio was: $918/life-year gained (LYG) with Medicare (38.4% dominant, 4.5% dominated, 89.9% <$50,000/LYG); dominant with MEDSTAT (57.2% dominant, 3.1% dominated, 90.97% <$50,000/LYG); dominant with MEDSTAT/Medicare (56.1% dominant, 2.8% dominated, 91.0% <$50,000/LYG). Results were similar when the Saskatchewan Health Database (patients with ACS requiring PCI) was used. The incremental cost effectiveness ratio compares favourably with that of GP IIb/IIIa inhibition in ACS ($16,491/LYG)[35] and that of statin therapy ($5400/LYG).[36] Notwithstanding that

the analysis is based on US practice models, these preliminary results suggest that clopidogrel is both effective and cost-effective in the setting of ACS in patients undergoing PCI.

In the management of these ACS patients, the role of strategies beyond those of antithrombotic agents is equally important. The benefit of lipid-lowering and angiotensin-converting enzyme (ACE) inhibition is well known. However, in none of the ACS treatment guidelines is the role of life-style modification – which is both effective and inexpensive – ever addressed. For example, unpublished data from the EPI-CURE study have demonstrated that there is a 20% excess risk of MI and death in the following year. Although exercise at least 3 times per week is associated with a 20% reduction in adverse clinical events, only 10% of ACS patients in CURE exercised at least 3 times per week one month after the ACS.

In summary, in patients with non-ST-segment elevation ACS, the combined use of aspirin and clopidogrel will reduce the risk of adverse clinical outcomes for at least 12 months (and likely beyond). Given the earlier discussion regarding the efficacy versus safety of low- versus high-dose aspirin and early versus deferred invasive approach, the benefit to risk ratio of combined antiplatelet therapy may be optimized with the use of low-dose aspirin and judicious timing of coronary revascularization procedures. Finally and importantly, the implementation of lipid-lowering therapy, ACE inhibition, and life-style modification will likely provide significant incremental long-term benefit.

Cardiac surgery in patients on antiplatelet therapy

Bleeding complications following cardiac surgery is associated with significant morbidity, including the need for re-exploration, prolonged ICU stay, and infections. Indeed, re-exploration for bleeding is a major risk factor for adverse clinical outcomes following cardiac surgery.[37] Given the potential for increased bleeding, there is always concern regarding the institution of oral antiplatelet therapy in patients who are about to undergo cardiac or other types of major surgery. In the case of aspirin, the bleeding risk is likely to be small since studies have demonstrated that preoperative aspirin use appears to be associated with a decreased risk of mortality in CABG patients without a significant increase in hemorrhage, blood product requirements, or related morbidities.[38] Therefore, unless there are special circumstances, aspirin does not need to be stopped for CABG in patients with ACS. The situation is quite different for clopidogrel where the bleeding effect may be significant. Patients with clopidogrel exposure within 7 days of CABG had significantly higher chest tube output, transfusion of blood products, and reoperation.[39] In the CURE study, no significant excess in bleeding was seen within 7 days after CABG when clopidogrel was stopped at least 5 days before CABG. However, in those who stopped taking clopidogrel within 5 days of CABG, there was a 53% (p=0.06) higher rate of major bleeding in the combination group.[12] Based on these data, clopidogrel should be withheld at least 5 days prior to CABG. Improved anesthetic, perfusion, and surgical techniques would also minimize the bleeding complications.

Whether combined antiplatelet therapy with clopidogrel and aspirin should be instituted in a patient with non-ST-segment elevation ACS immediately upon presentation depends on whether this patient is likely to go for early CABG. This would be determined by the perceived risk of the patient requiring urgent CABG (as opposed to medical therapy, PCI or deferred CABG) and very much by the mode of practice of the institution. In the CURE study, where almost all patients were recruited from centres where invasive procedures were not routinely performed, only 16.5% of patients went on to have CABG, representing 40% of patients who underwent angiography. It is therefore conceivable that, in Canada, where most centres do not follow the aggressive approach for early CABG even if anatomically suitable, the majority of patients presenting with non-ST-segment elevation ACS would be candidates for dual antiplatelet therapy with clopidogrel and ASA.

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