Leading with Innovation
Serving with Compassion
St. Michael's Hospital
A teaching hospital affiliated with the University of Toronto

Cardiology

University of Toronto

Special New Feature
Visit us at www.cardiologyupdate.ca for PowerPoint teaching slides on this topic

AN EDUCATIONAL PUBLICATION BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Acute Coronary Syndrome without ST-Elevation: What's new?

Originally presented by: J De Lemos, MD; FE Rademakers, MD; ML Simmoons, MD; DL Bhatt, MD; and SM Cobbe, MD

An Educational Publication based on Presentations at the European Society of Cardiology Congress 2005

September 4, 2005 Stockholm, Sweden

By DAVID FITCHETT, MD

Evidence-based management strategies have had a significant impact on the reduction of adverse outcomes in patients with acute coronary syndromes (ACS). Yet, recurrent ischemic events remain all too frequent despite advances in both diagnosis and medical, interventional, and surgical treatment.[1] Chest pain is a common complaint, and the evaluation of patients with a possible ACS in the hospital emergency department is a challenge. Optimizing outcomes depends upon improvements in patient management during all stages of the care process (Table 1). This issue of *Cardiology Scientific Update* reviews developments that have the potential to improve patient outcomes.

Novel techniques for diagnosis and risk stratification

Clinical judgment and the electrocardiogram (ECG) are important in the diagnosis and risk stratification of patients with chest pain. However, the majority of patients have atypical symptoms and ECGs are not always diagnostic of an ACS. In these patients, biomarkers and noninvasive imaging techniques may provide a rapid diagnosis and predict short- and long-term outcomes. Furthermore, additional information available from biomarkers may lead to an optimal management strategy.

Biomarkers

Cardiac troponin (cTn) I and cTn T are the most useful markers for both diagnosis and risk assessment. In the patient with symptoms compatible with an ACS, small increments in cTn not only confirm the diagnosis, but also indicate a higher risk of recurrent events. A meta-analysis of the prognostic value of cTn in patients with chest pain reveals that a positive cTn confers an almost 4-fold greater risk for both death and death/myocardial infarction (MI).[2] An increased cTn is more often associated with the presence of thrombus, stenosis severity, total coronary occlusion, and impaired microcirculatory flow.[3] Furthermore, patients with increased cTn levels have enhanced benefit from treatment with an early invasive strategy, the use of the low-molecular weight heparin (LMWH), enoxaparin, and the early use of glycoprotein (GP) IIb/IIIa inhibitors.[2] Consequently, patients with a suspected ACS and detectable levels of cTn constitute a high-risk group who benefit from an aggressive management strategy.

However, it is apparent that many patients with ACS are at a high risk of adverse events despite a lack of either high-risk clinical features or ECG findings, and cTn levels beneath the normal reference range. New biomarkers (eg, B-type natriuretic peptide [BNP][4] and myeloperoxidase[5,6]) hold promise for the detection of higher risk individuals without either elevated cTn or other high-risk features. It is likely that the use of multiple markers will provide the best application of biomarkers for risk stratification.[7] The development of multi-marker panels will provide a valuable clinical tool for diagnosis and risk stratification and act as a guide for optimal management strategy. As yet, the new markers, either alone or in combination, have not helped in determining specific management strategies and are still under investigation to establish their clinical application.[8]

Noninvasive imaging techniques

Noninvasive imaging technology has increasing promise in the diagnosis of ACS, the detection and quantification of

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: Management of the patient with chest pain	
Stage 1	Diagnosis – Is this an acute coronary syndrome?
Stage 2	Risk Stratification – What is the risk of an adverse outcome?
Stage 3	Immediate management – Prevention of recurrent thrombotic occlusion
Stage 4	Revascularization – How early should the patient have angiography?
Stage 5	Long-term vascular protection – Stabilize atherosclerosis

necrosed and at-risk myocardium, identification of myocardial ischemia and infarct-related coronary artery stenosis, and the establishment of both prognosis and risk/benefit of treatments.

Available techniques include echocardiography (contrast and stress); nuclear (single proton emission computerized tomography [SPECT] perfusion and positron emission tomography [PET] perfusion and viability); magnetic resonance (perfusion, function, and infarct imaging); and multi-slice computed tomography (CT) (coronary angiography and cardiac function). Magnetic resonance imaging (MRI) has much potential for detecting recent ACS with a diagnostic accuracy beyond currently used techniques.[9] Furthermore, MRI imaging distinguishes acute from chronically infarcted myocardium.[10] Contrast echocardiography is valuable for the immediate assessment of patients presenting to the emergency department with chest pain before serum markers are known and when the ECG is not diagnostic.[11] Echocardiographic regional left ventricular function and contrast myocardial perfusion provide incremental prognostic value above the TIMI risk score in the prediction of short- and long-term clinical events. Noninvasive imaging techniques, perhaps in combination, have a definite role in assessing both short- and long-term risk and the indications and benefits of revascularization. However, before complex, expensive, and time-consuming techniques are more widely deployed, it is important to demonstrate that the greater diagnostic accuracy results in improved clinical outcomes.

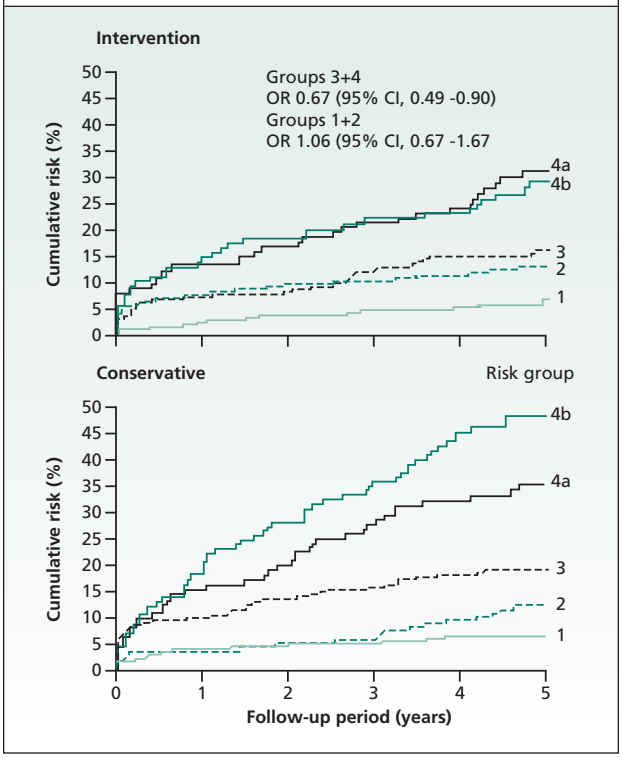
Early invasive versus conservative management of ACS

The American College of Cardiology (ACC)/American Heart Association (AHA)[2] and European Society of Cardiology[1] Guidelines recommend early coronary angiography and revasularization in patients with higher risk ACS. A recent meta-analysis[12] of all trials of early invasive vs conservative management indicates that an early invasive strategy reduces MI, severe angina, and rates of re-hospitalization over a mean follow-up of 18 months. High-risk patients with positive troponin and/or ST segment depression benefited most from an invasive strategy.

The 5-year outcome of the RITA-3 trial, which examined an early interventional strategy in moderate- and high-risk patients with non-ST-elevation (NSTE) ACS, was recently reported.[13] Although the 1-year RITA-3 results showed no difference in either death or nonfatal MI rates, the 5-year follow-up results showed that the group receiving early interventional treatment had a 32% reduction in cardiovascular (CV) death (odds ratio [OR] 0.68; 95% confidence interval [CI], 0.49-0.95, p = 0.026) and a 26% reduction in CV death or nonfatal MI (OR 0.74; 95% CI, 0.56-0.97, p = 0.030); (Figure 1). The study again confirmed that patients in the highest risk category were most likely to die or have a recurrent MI if managed by a conservative strategy that encompassed ischemia- or symptom-driven angiography.

Early coronary angiography and revascularization – preferably within 48 hours of presentation when feasible – is recommended in higher risk patients with NSTE ACS. The immediate administration of the most effective antiplatelet and antithrombotic combination reduces the risk of events prior to, and during, revascularization.

Figure 1: 5-year follow-up of the RITA-3 trial[13]
The early intervention and conservative groups are categorized into quartiles of risk, with the upper quartile further divided into equal-sized two-eighths of risk (4a and b). There is long-term reduction in death/MI. However, the benefit of an early interventional strategy is greatest in the higher risk patients.



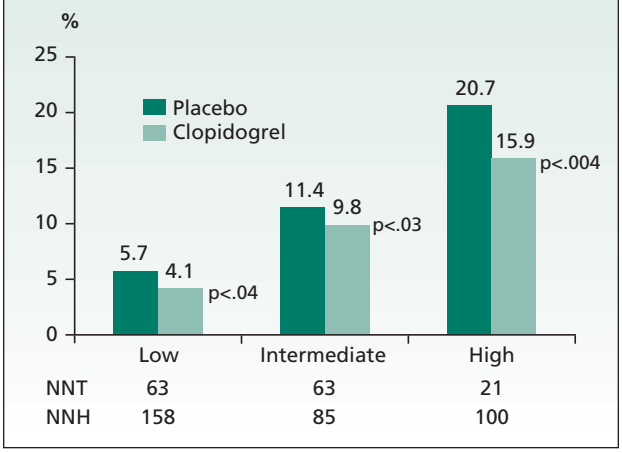
OR = odds ratio, CI = confidence interval

Combined antiplatelet therapy in the management of ACS

Inhibition of platelet function plays a vital role in the prevention of recurrent vascular events in a wide range of patients with acute and chronic coronary disease. Twenty years ago, aspirin (ASA) was shown to be beneficial in ACS management. In 4 trials that included >3000 patients, with or without MI, aspirin reduced recurrent cardiovascular events by 50%-60% in the first few days after presentation and over the next 2 years.[14-17] The thienopyridine adenosine diphosphate (ADP) antagonists, ticlopidine and clopidogrel, provide further inhibition of platelet activation and aggregation, with benefits additional to those provided by aspirin in both NSTE ACS and STEMI.

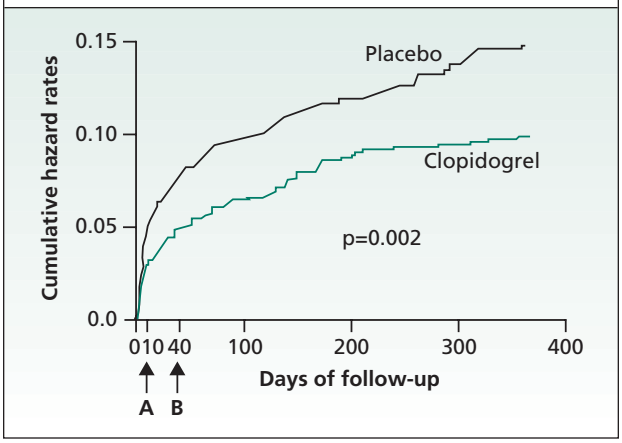
The CURE trial[18] demonstrated the early and long-term benefits of clopidogrel – in addition to treatment with aspirin – in patients with NSTE ACS. Patients entered into the CURE trial had been hospitalized within 24 hours after symptom onset and had ischemic changes on ECG (but not STE) or elevated cardiac markers to twice the upper limit of normal. Initially, patients >60 years old without ECG abnormalities, but with a history of coronary artery disease, were included. During the average 9-month period of the trial, cardiovascular mortality, nonfatal MI, and stroke were reduced by 20%. At 30 days, the absolute risk reduction was 1.2% and, at 9 months, 2.1%. The benefit of clopidogrel in the CURE trial was consistent across a wide risk range as stratified by the Thrombolysis in Myocardial Infarction (TIMI) risk score (Figure 2).[19] Patients undergoing percutaneous coronary intervention (PCI) benefited from pre-treatment with clopidogrel and had a reduction in events before and after the procedure (Figure 3).[20] Although major bleeding was increased by 1% in patients receiving aspirin and clopidogrel, there was no increase in life-threatening hemorrhage. Furthermore, in higher risk patients who have the same bleeding rates as lower risk individuals, the absolute benefit from clopidogrel greatly exceeds the bleeding risk.[19] A recent analysis[21] shows a modest increase in risk of hospitalization for bleeding from dual antiplatelet therapy in elderly patients after MI (ASA alone: 0.03/patient year; aspirin and a thienopyridine [clopidogrel or ticlopidine]: 0.07/patient year).

Figure 2: The CURE Trial
Rates of primary outcome (cardiovascular death, nonfatal MI, or stroke) and major bleeding in low-, intermediate-, and high-risk patients.[19]



NNT = the number of patients to treat to avoid one of the primary outcomes.
NNH = the number of patients treated to encounter 1 major hemorrhage.
The greatest benefit /risk ratio is in the high-risk group.

Figure 3: PCI-CURE
Cumulative hazard rates for cardiovascular death or MI from randomization to end of follow-up. A benefit from early clopidogrel treatment is seen before and after PCI in patients with NSTE ACS.[19]



A: Median time from randomization to PCI
B: 30 days after median time to PCI

Recent studies demonstrate the value of clopidogrel in patients receiving thrombolysis for ST-segment elevated acute MI. In the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) TIMI 28 trial,[22] patients receiving thrombolysis were given either clopidogrel (loading dose 300 mg and then 75 mg daily) or placebo. Clopidogrel was continued until coronary angiography 2-8 days later. The trial revealed that clopidogrel improved the patency rate of the infarct-related artery and reduced ischemic complications without any increase in bleeding. Of the 3491 patients in the CLARITY study, 1863 went on to have PCI. In the patients undergoing PCI, there was a 46% reduction in CV death, MI, and stroke following PCI in the 30 days after randomization (clopidogrel 3.6%, no pretreatment 6.2%, OR 0.54, 95% CI, 0.35-0.85).[23] Clopidogrel pre-treatment reduced the risk of cardiovascular death or ischemic complications before and after PCI in patients who had received thrombolysis. Again, the benefit was observed without any increased hemorrhagic risk.

The platelet GP IIb/IIIa inhibitors have been widely evaluated in the management of patients with NSTE ACS. Although the GP IIb/IIIa inhibitors reduce cardiovascular death/MI during the administration of the agent, this benefit is reduced by 30 days

unless the patient undergoes early PCI.[24-26] The small molecule GP IIb/IIIa inhibitors, eptifibatide and tirofiban, are the only agents shown to result in any significant, albeit modest, overall benefit.[27-29] However, in high-risk patients with troponin elevation or other high-risk features undergoing early PCI, the early use of either eptifibatide or tirofiban reduces events prior to, and during, the procedure.[30]

Current guidelines support the use of aspirin and clopidogrel in the majority of patients with NSTE ACS. GP IIb/IIIa inhibitors (either eptifibatide or tirofiban) are recommended in high-risk patients (with troponin elevation and/or ST segment depression) who are likely to undergo early cardiac catheterization and revascularization.[2]

Resistance to antiplatelet agents and the need for multiple antiplatelet agents

A wide variability of inhibition of in vitro platelet aggregation has been described with aspirin and clopidogrel. Not only are the mechanisms of this variability unknown, but the clinical significance is also unclear. Furthermore, there is no standardized definition of resistance to antiplatelet agents. Aspirin "resistance" is reported in 8%-56% of individuals, depending on the test performed and the population studied.[31] A similar incidence of "clopidogrel resistance" has been described.[32] As yet, only one study has related clinical outcomes to the antiplatelet response of clopidogrel.[33] Patients with ACS have increased baseline platelet reactivity and a greater probability of a reduced antiaggregatory response. If the response to clopidogrel, as determined by laboratory tests, has any meaning, it is apparent that a reduced response to clopidogrel is minimized by the administration of a larger loading dose and a longer duration of treatment. A recent report[34] suggests that a larger loading dose of clopidogrel (600 mg administered 6 hours prior to PCI) reduces peri-procedural MI and appears to be safe when compared to the standard 300 mg loading dose. Furthermore, the ALBION study,[35] also reported at the European Society of Cardiology (ESC), indicates that an even larger loading dose of 900 mg prior to PCI, results in greater and faster platelet inhibition and a trend towards less major adverse events without any safety concerns. Although resistance to the small molecule GP IIb/IIIa inhibitors has not been described, there is considerable variability in the antiplatelet response to the antibody GP IIb/IIIa inhibitor, abciximab, and its effect appears to be reduced during infusions of >12-15 hours.[36]

Dual or triple antiplatelet therapy?

As the variability of the antiplatelet response appears to be common and, as yet, unrecognizable in the individual patient, it makes sense to use dual antiplatelet therapy with ASA and clopidogrel in patients with an unambiguous diagnosis of an ACS. In higher risk patients who will undergo very early coronary angiography and revascularization, adding a small molecule GP IIb/IIIa inhibitor (eptifibatide or tirofiban) will prevent events before and during PCI. Recent data from the ELISA 2 trial support this approach.

The ELISA-2 trial, which was also presented at the 2005 ESC meeting, examined whether there are additional benefits from triple antiplatelet treatment with ASA, clopidogrel, and the GP IIb/IIIa inhibitor, tirofiban, compared to treatment with ASA and clopidogrel alone. The high-risk patients (84% Tn positive, 61% >0,1 mV ST depression) underwent angiography within 48 hours and 82% had PCI. The trial was underpowered to show a difference in the primary endpoint of infarct size. However, coronary flow in the infarct-related artery was improved and there was a strong trend toward enhanced event-free survival in patients receiving triple therapy, especially in those with both ST segment depression and troponin elevation. It is notable that there was no increase in non-coronary artery bypass graft (CABG) or CABG-related bleeding in the patients receiving the triple antiplatelet regimen for 24-48 hours.

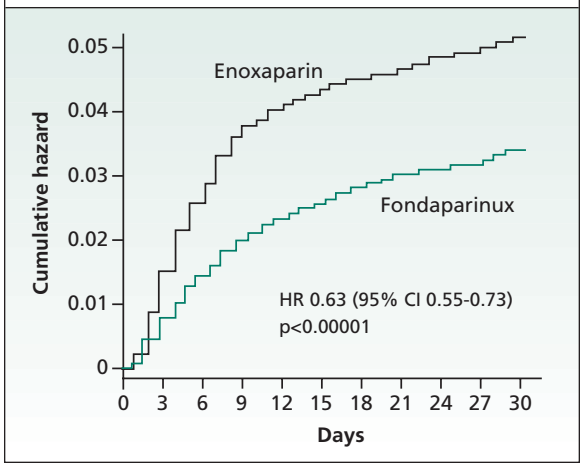
Although confirmation of the value of triple antiplatelet therapy will be provided in the on-going ISAR-REACT II study, current ACC/AHA[2] and ESC[1] guidelines recommend that high-risk NSTE ACS patients receive aspirin, clopidogrel, and a GP IIb/IIIa inhibitor. However, based on the Canadian ACS,[37] GRACE[38] and CRUSADE[39] registries, only 15%-33% of high-risk patients are currently receiving a GP IIb/IIIa inhibitor as early initial treatment.

Antithrombotic treatment and NSTE ACS

Addition of the antithrombin heparin to ASA in the early management of NSTE ACS results in an additional 62% risk reduction from early (1 week) death or non-fatal MI.[2] LMWHs, in general, appear to be as effective as unfractionated heparin (UFH).[2] However, only the LMWH, enoxaparin, has been shown to be superior to UFH in 2 trials.[40-41] Yet, when patients underwent early coronary angiography within the first 24-36 hours in the SYNERGY trial,[42] the benefits of enoxaparin observed in earlier trials were not seen and bleeding events were more frequent. However, SYNERGY (in >3,000 patients undergoing PCI), demonstrated that enoxaparin anticoagulation could be continued during the intervention without the need for additional anticoagulation. Similar periprocedural complication rates were observed in both treatment groups.

The STEEPLE trial, presented at the 2005 ESC meeting, demonstrated that enoxaparin can be used as the primary anticoagulant for elective PCI, yet with a 57% reduction in major bleeding rates compared to UFH. Again, enoxaparin was used as the sole anticoagulant during PCI and there was no difference in ischemic complications. It is possible that the increased bleeding observed in SYNERGY resulted from transitioning the patient from LMWH to UFH in the

Figure 4: OASIS-5
The cumulative incidence of major bleeding observed in the OASIS-5 trial over the first 30 days of the study. The duration of administration of enoxaparin was 5.2±2.3 days and fondaparinux 5.4±2.4 days.[43]



catheterization laboratory. Switching anticoagulants could have also been responsible for the increased major bleeding observed in patients randomized to enoxaparin compared to fondaparinux in OASIS-5.

OASIS-5[43] randomized 20,078 patients with NSTE ACS within 24 hours of symptom onset to either enoxaparin (1 mg/kg twice daily) or the factor Xa inhibitor, fondaparinux 2.5 mg daily. Treatment in both arms was for an average of 5 days. There was no difference in the primary efficacy endpoint of death/MI/refractory ischemia at 9 days, with the confidence intervals of the point estimate meeting predefined non-inferiority criteria for fondaparinux. However, major bleeding by day 9 was 47% lower in the group receiving fondaparinux (Figure 4). By 30 days, there was a reduction in mortality in favour of fondaparinux compared to enoxaparin that was linked to a reduction in bleeding. In the 6207 patients undergoing PCI, there was a significant increase in thrombus formation on the PCI guide-wire in patients receiving fondaparinux. In the last 330 patients, routine UFH was given to the group receiving fondaparinux, and only one case of guide-wire thrombosis was observed.

In patients undergoing PCI randomized to enoxaparin, 53.8% also received UFH, compared to only 18.8% of the fondaparinux group. It is possible that combined and potentially excessive antithrombin activity in the enoxaparin group was responsible for some of the enhanced bleeding observed with enoxaparin. Additional analyses will be necessary before fondaparinux replaces enoxaparin as the most frequently used anticoagulant for the management of patients with NSTE ACS. However, the trial emphasizes the observation that early bleeding translates into later adverse cardiac outcomes. Consequently, it is important to be vigilant in our selection of antiplatelet and antithrombotic therapy and identify patients at higher risk of hemorrhage, such as the elderly and those with renal insufficiency.

Conclusions

Based on the above review, the following conclusions can be drawn:

- Diagnostic techniques that can recognize ACS earlier and predict the risk of an adverse outcome will optimize management for the individual patient. New biomarkers and noninvasive techniques show promise in achieving these goals.
- Recent studies, especially with longer-term follow-up, support the strategy of early cardiac catheterization and revascularization (when possible) in higher risk patients with NSTE ACS.
- Despite improvements in medical treatment, recurrent ischemic events remain common. Recent trials with dual and triple antiplatelet agents (aspirin, clopidogrel and an intravenous GP IIb/IIIa inhibitor such as tirofiban or eptifibatide) have been shown to reduce early and late ischemic events. Newer anti-thrombotic agents such as fondaparinux appear to achieve a comparable reduction in ischemic events, yet with a reduction in major hemorrhage.

Reference List

1. Bertrand ME, Simmoons ML, Fox KAA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000;21:1406-1432.
2. Braunwald E, Antman EM, Beasley JW, et al. ACC / AHA 2002 guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: a report of the ACC / AHA taskforce on practice guideline committee on the management of patients with unstable angina. http://www.acc.org/clininical/guidelines/update_index.htm. Accessed Sept. 20, 2005.
3. Wong GC, Morrow DA, Murphy S, et al. Elevations in troponin T and I are associated with abnormal tissue level perfusion: a TACTICS-TIMI 18 substudy. Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction. *Circulation* 2002;106:202-207.
4. de Lemos JA, Morrow DA, Bentley J, et al. The prognostic value of ß-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;345:1014-1021.
5. Baldus S, Heeschen C, Meinertz T, et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation* 2003;108:1440-1445.
6. Brennan ML, Penn MS, Van Lente F, et al. Prognostic value of myeloperoxidase in patients with chest pain. *N Engl J Med* 2003;349:1595-1604.
7. Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation* 2002;105:1760-1763.
8. de Lemos JA, Morrow DA. Brain natriuretic peptide measurement in acute coronary syndromes: ready for clinical application? *Circulation* 2002;106:2868-2870.
9. Kong RY, Scussheim AE, Rekhraj S, et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. *Circulation* 2003;107:531-537.
10. Abdel-Aty H, Zagrosek A, Schultz-Menger J, et al. Delayed enhancement and T-2 weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation* 2004;109:2411-2416.

11. Tong KL, Kaul S, Wang XQ, et al. Myocardial contrast echocardiography versus Thrombolysis in Myocardial Infarction (TIMI) Score in patients presenting to the emergency department with chest pain and a non-diagnostic electrocardiogram. *J Am Coll Cardiol* 2005;45:920-927.
12. Mehta SR, Cannon CP, Fox KAA, Wallentin L, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes. *JAMA* 2005;293: 2908-2917.
13. Fox KAA, Poole-Wilson P, Clayton TC, et al. Five-year outcome of an interventional strategy in non-ST elevation acute coronary syndromes. The British Heart Foundation RITA-3 randomised trial. *Lancet* 2005;366:914-920.
14. Cairns J, Gent M, Singer J, et al. Aspirin, sulfinpyrazone or both in unstable angina: Results of a Canadian Multicentre Trial. *N Engl J Med* 1985;313:1369-1375.
15. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-1111.
16. Lewis H, Davis J, Archibald D, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. *N Engl J Med* 1983;309:396-403.
17. RISC Group. Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827-830.
18. The Clopidogrel in Unstable Angina to Prevent recurrent Events Trial Investigators. Effects of clopidogrel in addition to ASA in patients with acute coronay syndromes without ST segment elevation. *N Engl J Med* 2001;345: 494-502.
19. Budaj A, Yusuf S, Mehta SR, et al. Benefit of clopidogrel in patients with acute coronary syndromes without ST segment elevation in various risk groups. *Circulation* 2002;106:1622-1626.
20. Mehta SR, Yusuf S. Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention. *J Am Coll Cardiol*. 2003;41:79S-88S.
21. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med* 2005;165[784]:789.
22. Sabatine M, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-1189.
23. Sabatine M, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics. The PCI-CLARITY Study. *JAMA* 2005;294:1224-1232.
24. Boersma E, Akkerhuis KM, Theroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;100:2045-2048.
25. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *Lancet* 2002;360:342-343.
26. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189-198.
27. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998;338:1498-1505.
28. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators [published erratum appears in *N Engl J Med* 1998 Aug 6; 339(6):415]. *N Engl J Med* 1998;338: 1488-1497.
29. PURSUIT Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. *N Engl J Med* 1998;339:436-443.
30. Boersma E, Akkerhuis KM, Theroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;100:2045-2048.
31. Sanderson S, Emery J, Baglin T, et al. Narrative Review: Aspirin resistance and its clinical implications. *Ann Intern Med* 2005;142:370-380.
32. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005;45:1157-1164.
33. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109(25):3171-3175.
34. Patti G, Colonna G, Pasceri V et al. A randomized trial of high loading dose of clopidogrel for reduction of peri-procedural myocardial infarction in patients undergoing coronary intervention. *Eur Heart J* 2005;26 (Abstract Supplement):39.
35. Montelescot G, The ALBION Investigators. Assessment of the best loading dose of clopidogrel to blunt platelet activation, inflammation and ongoing necrosis. *Eur Heart J* 2005;26 (Abstract Supplement):484.
36. Steinhubl S, Talley JD, Braden GA, et al. Point-of-care measured platelet inhibiton correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention. Results of the GOLD (AU-assessing Ultegra) Study. *Circulation* 2001;103:2572-2578.
37. Yan R, et al. Greater use of evidence-based medical treatment in non-ST segment elevation acute coronary syndromes over time: Insights from the Canadian Acute Coronary Syndrome Registry. *Can J Cardiol* (In press).
38. Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes. Variation in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2002;23:1177-1189.
39. Peterson ED, Roe MT, Lytle BL. The association between care and outcomes in patients with acute coronary syndrome: National results from CRUSADE. *J Am Coll Cardiol* 2004;43(Suppl 2):406A.
40. Cohen M, Demers C, Gurfinkel EP, et al. Low-molecular-weight heparins in non-ST-segment elevation ischemia: the ESSENCE trial. Efficacy and Safety of Subcutaneous Enoxaparin versus intravenous unfractionated heparin, in non-Q-wave Coronary Events. *Am J Cardiol* 1998;82:19L-24L.
41. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;100:1602-1608.
42. The Synergy Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy. Primary results of the SYNERGY randomized trial. *JAMA* 2004;292:45-54.
43. Mehta SR, Yusuf S. Michalangelo: OASIS. *Eur Heart J* Presented at the Hotline Session, September 5, 2005, European Society of Cardiology, Stockholm, Sweden.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from sanofi-aventis/Bristol-Myers Squibb Canada to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.

Publications Post #40032303

202-066