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Scientific Update™

New Antithrombotic Therapies in Cardiac Ischemic Syndromes

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The acute coronary syndromes occur in the setting of coronary thrombosis as a consequence of activation of both the coagulation cascade and platelets. Antiplatelet and antithrombotic therapies therefore form the basis of medical therapy in patients presenting with a spectrum of diagnoses from unstable angina to myocardial infarction. In addition to ASA, newer antiplatelet strategies include the ADP- and glycoprotein IIb/IIIa-receptor antagonists; similarly, as alternatives to unfractionated heparin, low molecular weight heparins and direct thrombin inhibitors appear to offer additional antithrombotic benefit. Finally, in the setting of acute myocardial infarction and infarct-related artery occlusion, fibrinolytic therapy continues to be the mainstay of treatment. Beyond the refinement of currently available agents (eg, single bolus tenecteplase offers similar efficacy but enhanced safety as compared to the current fibrinolytic gold standard, alteplase), future management strategies will likely include new combinations of these therapies in an effort to maximize the benefit-to-risk ratio of the approaches applied presently.

Mechanisms of action of antiplatelet agents

The acute coronary syndromes (unstable angina, non-Q wave myocardial infarction [MI], acute [ST-segment elevation] MI, and abrupt closure after percutaneous coronary intervention [PCI]) share a common pathophysiology of atherosclerotic plaque rupture, activation of the coagulation cascade, and adhesion, activation, and aggregation of platelets.[1] While ASA (aspirin) continues to be an important treatment in the acute coronary syndromes,[2] it only partially inhibits platelet aggregation by inhibiting the thromboxane A_2 pathway. The thienopyridines – ticlopidine and clopidogrel – irreversibly block one of the three adenosine diphosphate (ADP) receptor subtypes on platelets; because ADP receptor blockade is incomplete, the thienopyridines alone provide only a modest benefit when compared with ASA alone (for example, as demonstrated in the CAPRIE study[3]). Regardless of the stimulus for activation, platelet-platelet interaction and thrombus formation is ultimately regulated through the platelet glycoprotein (GP) IIb/IIIa receptor–the the final common pathway of platelet aggregation.[4]

Glycoprotein IIb/IIIa antagonists

Intravenous monoclonal antibody (abciximab) and peptide (eptifibatide) and non-peptide (tirofiban, lamifiban) antagonists of the GP IIb/IIIa receptor have been tested in randomized, placebo-controlled trials of PCI and the acute coronary syndromes. A systematic overview (meta-analysis) of 16 trials (n=32,135) demonstrated a significant mortality reduction by GP IIb/IIIa inhibitors at 48-96 hours (odds ratios [OR] 0.70; 95% confidence intervals [CI], 0.51 - 0.96;

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Figure 1: The four "P" trials

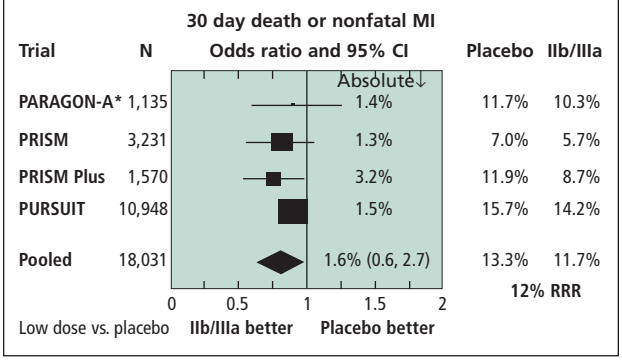
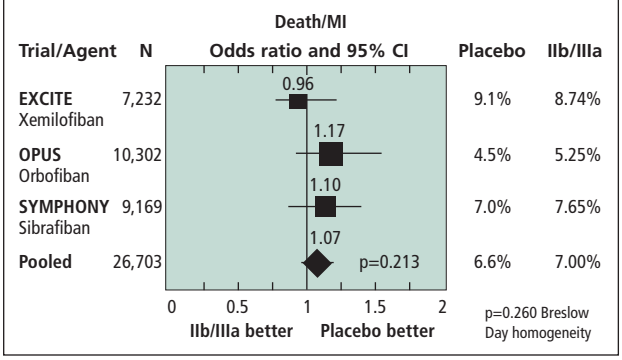


Figure 2: Meta-analysis of oral IIb/IIIa trials



p<0.03), equivalent to a reduction of 1 death per 1,000 patients treated.[5]

In the four 'P' trials (Figure 1), involving at least 1,000 patients with unstable angina or non-Q wave MI (n=18,276), 30-day death or MI was reduced with GP IIb/IIIa antagonists as compared to (PRISM[6], PARAGON-A[7]), or in addition to (PRISM-PLUS,[6] PURSUIT,[8] PARAGON-A[7]), unfractionated heparin (UFH) (11.7% vs. 13.3%; relative risk reduction [RRR] 13%). The preliminary results of the PARAGON-B trial (comparing intravenous lamifiban and placebo in >4,000 unstable angina/non-Q wave MI patients receiving ASA and UFH) will be presented at the American College of Cardiology (ACC) meeting in March, 2000.

Oral GP IIb/IIIa antagonists are being investigated for secondary prevention of cardiovascular morbidity and mortality. Early experience with these drugs raised concerns regarding the potential for bleeding with long-term therapy. However, the incidence of serious bleeding or thrombocytopenia appears to be very low in the initial reports of three large trials: OPUS (orbofiban), EXCITE (xemilofiban), and SYMPHONY (sibrafiban). Unfortunately, the benefit of the intravenous compounds has not translated to the oral GP IIb/IIIa antagonists (Figure 2):

- The EXCITE study showed no advantage of xemilofiban over ASA in patients undergoing PCI; however, a substantial number of patients in the control (ASA) group underwent coronary stenting and also received 2-4 weeks of ticlopidine.
- Patient enrollment in OPUS was discontinued prematurely because of excess mortality in one of the orbofiban arms; whether this was due to chance, diminished renal function (no dose adjustment was made in this trial), or a putative prothrombotic effect of this class of drugs (paradoxical activation of the receptor at certain doses) remains to be elucidated.
- The SYMPHONY study also failed to demonstrate an advantage of oral GP IIb/IIIa inhibition over ASA; the results of 2nd SYMPHONY where combination sibrafiban and ASA is being compared to ASA alone (total n=6,677) will also be available at the ACC meeting.

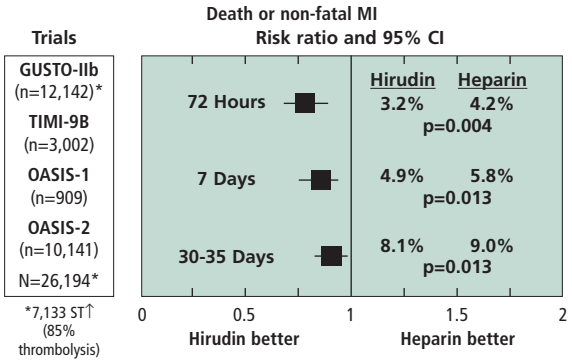
Antithrombin therapy

Since both platelet activation and thrombin generation are involved in the thrombotic process, there is a rationale for the use of both platelet and coagulation inhibitors in the treatment of acute coronary syndromes. A meta-analysis has shown that a combination of an intravenous infusion of UFH and ASA is more effective than ASA alone.[9] However, heparin is far from an ideal anticoagulant for the treatment of acute coronary syndromes since it is impractical to maintain a constant intravenous infusion and it is often difficult to obtain a predictable anticoagulant effect without repeated laboratory monitoring.

Low molecular weight heparins

Low molecular weight heparins (LMWHs) have been shown to be at least as effective as UFH in the prevention and treatment of venous thrombosis, and more recently, have been shown to be effective in preventing arterial and coronary thrombosis. The FRISC study[10] was the first large scale randomized clinical trial to demonstrate the benefit of LMWH in addition to ASA in unstable angina/non-Q wave MI. Data from the ESSENCE[11,12] and TIMI-11B[13,14] trials[15] supports the use of LMWH rather than UFH (in addition to

Figure 3: Hirudin vs heparin meta-analysis



ASA). The FRISC II study[16,17] also supports the use of LMWH in the acute phase, and suggests that continued use during the first month may lower the risk of events in patients waiting for invasive procedures.

Direct thrombin inhibitors

Resistance of coronary artery thrombosis to heparin likely reflects the inability of the heparin/antithrombin complex to inactivate thrombin bound to fibrin. In contrast to heparin (including LMWH), fibrin-bound thrombin is susceptible to inactivation by direct thrombin inhibitors (eg, hirudin and bivalirudin). These agents, which interact with exosite 1 and the active site of thrombin, compete with fibrin for thrombin binding and inactivate both fibrin-bound and fluid-phase thrombin. This explains why hirudin confers a benefit over UFH in patients, particularly those without persistent ST-segment elevation acute coronary syndromes, based upon the results of several large scale trials, including GUSTO-IIb,[18] and OASIS-2[19] (Figure 3). Despite the modest benefit of hirudin over UFH, concerns regarding an increased risk of bleeding and cost suggest that use of this agent will likely be limited (eg, as compared to LMWHs) to select patient groups, including those with heparin-induced thrombocytopenia.[20; 21]

Warfarin

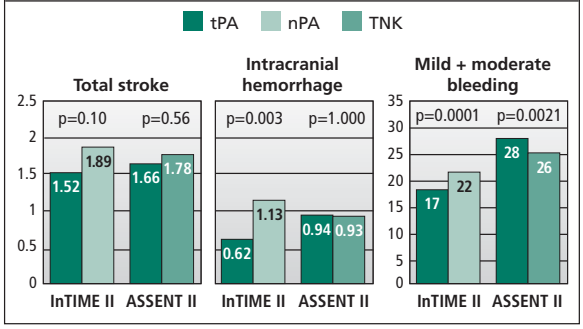
Many studies have shown overall antithrombotic efficacy of long-term anticoagulant monotherapy post-MI; however, the addition of warfarin (fixed, low-dose of 1 or 3 mg) to ASA in the Coumadin Aspirin Reinfarction Study (CARS)[22] did not provide any clinical benefit beyond that achieved with ASA (160 mg) monotherapy. While the fixed dose reduced the need for INR monitoring, even the 3 mg dose (with 80 mg of ASA) had a minimal effect on the mean INR (1.19, 95% CI, 1.08-1.44, n=2145) at 6 months. In contrast, the Combined Hemotherapy and Mortality Prevention (CHAMP) study used a dose-adjustment regimen aiming for an INR between 1.5-2.5. However, the preliminary results of this open-label VA Cooperative study in 5,059 post-MI patients comparing warfarin (mean INR achieved 1.9) and ASA (81 mg) with ASA alone (162 mg) over 2.75 years also indicate no significant difference in total or cardiovascular mortality, non-fatal stroke, or MI. Further, major bleeds were more common in the combination group. Thus, there is no evidence to support the use of combination ASA and warfarin as compared to ASA alone in post-MI patients for secondary prophylaxis.

Fibrinolysis 2000

The last quarter of the 20th century has had a profound impact on the management of patients with acute MI, particularly those presenting with ST-segment elevation. The previous decade ushered in a new era of non-placebo-controlled trials of reperfusion strategies: eight large-scale trials comparing thrombolytic regimens and involving over 130,000 cases of acute MI presenting with ST-segment elevation were completed in the 1990s. In contrast to the results from GISSI-2[23] and ISIS-3,[24] in the GUSTO-I trial,[25] a statistically and clinically significant benefit was seen with accelerated/front-loaded t-PA (alteplase) and intravenous heparin as compared with two streptokinase strategies. The benefit of alteplase over streptokinase translated into 10 additional lives saved at 30 days per 1,000 patients treated; for the prevention of death and disabling stroke, this benefit was 9 per 1,000 patients treated, highlighting the precise quantitative trade-off between safety and efficacy.

The INJECT study[26] showed equivalence of double-bolus r-PA (reteplase) and streptokinase and the GUSTO-III trial[27] failed to demonstrate superiority of reteplase over alteplase. Despite the suggestion that this trial supports the "equivalency" of alteplase and reteplase, the GUSTO-III investigators themselves acknowledge that their study "was not designed to assess equivalence, nor did it have adequate power to do so."[28] Others also maintain that the GUSTO-III primary outcome event, 30-day mortality, provides "no convincing evidence that reteplase is equivalent to [alteplase]."[28]

Figure 4: Stroke and bleeding



More recently, the InTIME II study[29] demonstrated similar 30-day and 6-month mortality rates among n-PA (lanoteplase) and alteplase treated patients; however, despite apparent equivalence of these two agents with respect to mortality reduction, lanoteplase led to a significantly greater number of intracranial hemorrhages (ICH) and mild-moderate bleeding episodes (Figure 4). In contrast, the ASSENT-2 trial[30] confirmed the equivalence of TNK-tPA (tenecteplase) and alteplase, with similar rates of ICH, but significantly fewer mild-moderate bleeding episodes with TNK.

The emergence of new fibrinolytic agents (ie, tenecteplase) that are fibrin specific, resistant to plasminogen activator inhibitor, and engineered with a protracted half-life that facilitates single bolus administration, achieves a new standard of pharmacologic therapy. This is supported by the ASSENT-2 study, in which 16,949 patients with ST elevation MI of less than 6 hours duration were randomly assigned to alteplase or single bolus injection tenecteplase (30-50 mg according to bodyweight). All patients received ASA and UFH (target activated partial thromboplastin time 50-75 seconds). Co-variate adjusted 30-day mortality rates were almost identical for the two treatment groups (6.18% for tenecteplase and 6.15% for alteplase; p=0.0059 based on test for equivalence). Rates of ICH (Figure 4) were also similar (0.93% vs. 0.94%), but fewer non-cerebral bleeding complications (26.43% vs. 28.95%, p=0.0003) and less need for blood transfusion (4.25% vs. 5.49%, p=0.0002) were seen with tenecteplase. In view of its equivalence to the current gold standard alteplase, coupled with the safer profile and ease of administration, tenecteplase will likely become the new gold standard in fibrinolytic therapy once it becomes commercially available in Canada (estimated 2001).

Ongoing and future trials will focus on combination fibrinolytic and adjunctive therapies (eg, platelet glycoprotein IIb/IIIa inhibitors) in an attempt to further decrease time to treatment, adverse events (eg, ICH, reinfarction), and mortality.

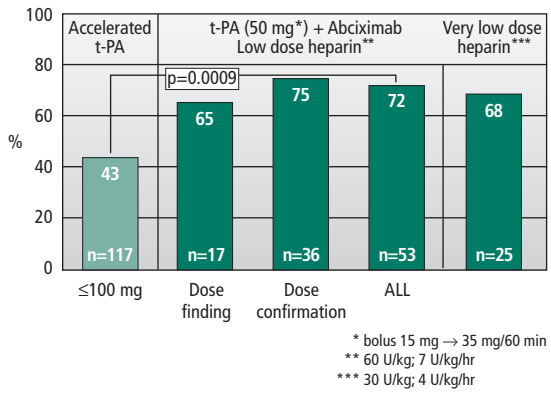
New frontiers in myocardial reperfusion therapy: thrombolysis and GP IIb/IIIa inhibitors

While intravenous thrombolytic therapy is the standard of care in patients with acute MI who present within 12 hours after symptom onset and have significant ST-segment elevation, there are still several limitations to this approach.

- First, even the best thrombolytic strategy (alteplase plus intravenous heparin) results in TIMI-3 flow in only 54% of patients at 90 minutes.[31]
- Second, the rate of ICH is relatively high (0.5-1%) and the event is usually catastrophic, resulting in disability or death.
- Third, while direct angioplasty of the infarct-related artery results in a higher rate of TIMI-3 flow than does thrombolytic therapy and has a much lower risk of ICH, this approach is logistically more difficult and tends to be associated with longer delays to therapy.
- Fourth, despite the use of ASA, platelet activation continues to occur, leading to aggregation and increased formation of thrombin. Acute plaque rupture leads to platelet-rich thrombi, which are often resistant to thrombolysis and have a greater tendency to produce reocclusion after initial reperfusion. Further, thrombolytics (or more accurately, fibrinolytics) are pro-thrombotic, and despite their ability to break down fibrin, the remaining thrombin leads to more thrombin generation and increased platelet activity.

Combination therapy with fibrinolysis and the glycoprotein IIb/IIIa inhibitors appears to hold great promise based upon the results of several phase II studies, including the TIMI 14, INTRO-AMI, and SPEED (GUSTO-IV Pilot) angiographic trials. For example, in the TIMI 14 study,[32] reduced-dose alteplase (15 mg

Figure 5: TIMI 14: TIMI 3 flow (core lab) at 60 minutes[32]



bolus plus 35 mg infusion over 60 minutes), in conjunction with abciximab and low-dose or very low-dose heparin led to better TIMI 3 grade flow rates at 60 and 90 minutes as compared to full-dose (100 mg) alteplase (Figure 5). Furthermore, the corrected TIMI frame count (a more refined measure of infarct-related artery reperfusion) was closer to normal and indicative of faster flow in the combination alteplase-abciximab group as compared to full-dose alteplase, streptokinase plus abciximab, or abciximab alone. Finally, patients receiving combination alteplase-abciximab had a greater rate of complete (≥70%) ST-segment elevation resolution (from baseline to 90- minute ECG: 59% vs. 37% in alteplase-alone patients, p<0.0001).[33] This latter finding suggests improved myocardial (microvascular) perfusion, in view of the fact that persistent ST-segment elevation (ie, limited or no resolution) is a marker of microvascular dysfunction and tissue injury and yields prognostic information which is distinct from that provided by the coronary angiogram.[34] Even when the TIMI 14 analysis was limited to patients with TIMI 3 flow, patients treated with combination therapy remained significantly more likely to achieve complete ST resolution than those receiving alteplase alone (69% vs. 44%, p=0.0002).[33]

The promise of reduced dose lysis and GP IIb/IIIa inhibition seen in the phase II studies will hopefully be borne out in the large scale phase III studies with clinical endpoints (eg, mortality) that are currently underway or soon to begin (eg, GUSTO-IV AMI, ASSENT 3) and will report in the next 12-18 months.

Conclusion

Current management of all acute coronary syndromes includes ASA; in patients without persistent ST-segment elevation, recent trial evidence supports the addition of either LMWH (eg, enoxaparin as an alternative to UFH) or GP IIb/IIIa inhibitors (eg, tirofiban or eptifibatide in addition to UFH). The recent CHAMP trial confirms that there is no role for warfarin in addition to ASA for secondary prophylaxis. Among ST elevation (or left bundle branch block) patients, single bolus lysis with tenecteplase will likely replace the current standard bolus + 90 minute infusion alteplase once the former becomes commercially available in Canada. The next frontier in reperfusion therapy may be a combination of fibrinolysis and GP IIb/IIIa inhibition; we await the results of large scale clinical outcome trials to confirm promising results from angiographic studies.

References

1. Madan M, Berkowitz SD, Tcheng JE. Glycoprotein IIb/IIIa integrin blockade. *Circulation* 1998;98:2629-2635.
2. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
3. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-1339.
4. Vorchheimer DA, Badimon JJ, Foster V. Platelet glycoprotein IIb/IIIa receptor antagonists in cardiovascular disease. JAMA 1999;281:1407-1414.
5. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation* 1998;98:2829-2835.
6. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;338:1498-1505.
7. The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. *Circulation* 1998;97:2386-2395.
8. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes without persistent ST-segment elevation. *N Engl J Med* 1998;339:436-443.

9. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996;276:811-815.
10. Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;347:561-568.
11. Cohen M, Demers C, Gurfinkel EP, et al for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447-452.
12. Goodman S, Langer A, Demers C, et al for the ESSENCE Group. One year follow-up of the ESSENCE trial (enoxaparin vs. heparin in unstable angina/non-Q wave myocardial infarction): sustained clinical benefit. *Can J Cardiol* 1998;14:122F. (Abstract)
13. Antman EM, McCabe CH, Gurfinkel EP, et al, for the TIMI 11B Investigators. Enoxaparin for the acute and chronic management of unstable angina/non-Q wave myocardial infarction: results of TIMI 11B. *Circulation* 1999;100:1593-1601.
14. Antman EM, McCabe CH, Gurfinkel EP, et al. Treatment benefit of enoxaparin in unstable angina/non-Q wave myocardial infarction is maintained at one year followup in TIMI 11B. *Circulation* 1999;100: I-497. (Abstract)
15. Antman EM, Cohen M, Radley D, et al for the TIMI 11B (Thrombolysis in Myocardial Infarction) and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) Investigators. 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.
16. FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Long-term low molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701-707.
17. FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:708-715.
18. The Global Use of Strategies to Open Occluded Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;335: 775-782.
19. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1998; 353:429-438.
20. Greinacher A, Völpel H, Janssens U, et al. Recombinant hirudin (Lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia - A prospective study. *Circulation* 1999;99:73-80.
21. Greinacher A, Janssens U, Berg G, et al, Investigators HAT. Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. *Circulation* 1999;100:587-593.
22. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet* 1997;350:389-396.
23. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990;336:65-71.
24. ISIS-3 (Third International Study of Infarct Survival Collaborative Group). ISIS-3: a randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:753-770.
25. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-682.
26. INJECT Investigators. A randomised double-blind comparison of reteplase double-bolus administration with streptokinase in patients with acute myocardial infarction (INJECT): a trial to investigate equivalence. *Lancet* 1995;346:329-336.
27. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997;337:1118-1123.
28. Massel D. Evidence-based medicine and reteplase: inductive arguments over deductive reasoning. *Can J Cardiol* 1999;15:999-1005.
29. Antman EM, Wilcox RG, Giugliano RP, et al. InTIME II Investigators. Long-term comparison of lanoteplase and alteplase in ST elevation myocardial infarction: 6 month followup in InTIME II trial. *Circulation* 1999;100:I-498. (Abstract)
30. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716-722.
31. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, left ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615-1622.
32. Antman EM, Giugliano RP, Gibson CM, et al. TIMI. Abciximab facilitates the rate and extent of thrombolysis - Results of the thrombolysis in myocardial infarction (TIMI) 14 trial. *Circulation* 1999;99:2720-2732.
33. de Lemos JA, Antman EM, Gibson CM, et al for the TIMI 14 Investigators. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction. Observations from the TIMI 14 Trial. *Circulation* 2000;101:239-243.
34. Schroder R, Wegscheider K, Schroder K, Dissmann R, Meyer-Sabellek W, for the INJECT Trial Group. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. *J Am Coll Cardiol.* 1995;26:1657-1664.