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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

State of the art treatment of acute coronary syndromes

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The past decade has been marked by an incredible proliferation of therapeutic modalities for managing patients with acute coronary syndromes. An increasing number of choices with respect to thrombolytic therapy, percutaneous revascularization, and antiplatelet and antithrombotic therapy are constantly expanding our therapeutic armamentarium, so much so that the difficulty in making therapeutic choices now lies in identifying the right patient subgroup and the best therapeutic combination available to treat these patients. Some of these developments are reviewed here.

Evidence-based medicine

Cardiovascular disease will be the major cause of disability well into the next century.[1] Life expectancy will increase along with an increase in life expectancy that is free of disability. Physicians will be expected to deliver better than ever care against a background of increasing age of population and a pressure to decrease the cost of healthcare. The issues at hand range from a need for unifying nomenclature that reflects underlying pathophysiology and a continuing necessity for refinement in diagnosis and treatment. These issues will lead to the integration of healthcare management and its future evolution.

Nomenclature of acute coronary syndromes

The spectrum of acute coronary syndromes is schematically depicted in Figure 1. The common underlying pathophysiology is that of plaque formation and plaque rupture or erosion, with the increasing recognition of inflammation as an important modulator of the natural history. As the therapeutic implications of the inflammatory component continue to be uncertain, the therapeutic focus has been on fibrinolysis and prevention of recurrent thrombosis. The development of the latter has been driven by an increasing understanding of the coagulation system, its complexity, and the recognition that every component interacts with each other, (ie, a non-linear model). Among many available treatments for managing acute myocardial infarction (MI), the development of thrombolytic therapy and adjunctive antiplatelet and antithrombotic therapy has been of critical importance.

Thrombolytic therapy

Thrombolytic therapy in patients presenting with acute MI, especially when given early on, is associated with a significant reduction in mortality (Figure 2). While patients presenting with ST elevation or new bundle branch block are known to be the primary target for thrombolytic therapy, the picture is less clear for those presenting with ST depression. This group represents a high-risk subgroup in whom thrombolytic therapy has not been uniformly successful. This relates in part to the diagnosis of MI with respect to the benefit and potential risk of this therapy in patients without evidence of myocardial necrosis. Our post-hoc analysis of the LATE study suggests that patients with ST depression >2 mm on admission may benefit at least as much as, if not more than, patients with ST elevation when thrombolytic therapy is administered >6 hours of symptom onset.

The diagnosis of myocardial necrosis has been extended with the availability of troponin T or troponin I testing. These serum markers are able to identify high-risk sub-groups of patients beyond that available with conventional measure-

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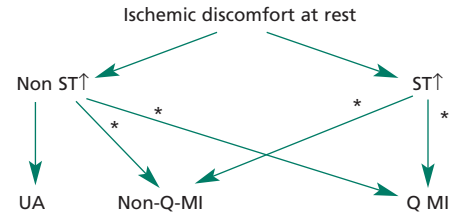
Figure 1: The spectrum of coronary syndromes



ment of CK or CK MB (see *Cardiology Rounds* on troponins, November, 1997).

Antithrombotic therapy in patients with non-ST elevation MI or unstable angina

Conventional treatment for patients with acute coronary syndromes has been the administration of unfractionated heparin, intravenous or subcutaneously, in addition to aspirin. While data showing the benefit of unfractionated heparin is limited (Figure 3), there are a number of practical and logistical limitations associated with its use, including the need for continuous monitoring because of unpredictable volume of distribution and nonspecific binding to endothelial surfaces, serum proteins, and platelet surfaces. Heparin binding to platelets and endothelial cells may lead to a greater risk of bleeding. Unfractionated heparin does not inhibit thrombin activity when thrombin is bound to fibrin — an important advantage of direct thrombin inhibitors. Because unfractionated heparin binds to thrombin with the same affinity as it binds to factor Xa, the inhibition of thrombin generation is not as profound as that achieved with some of the low molecular weight heparins.

Low molecular weight heparins (LMWH)

These compounds represent a heterogeneous class of drugs that have a predictable volume of distribution without

Figure 2: Fibrinolytic therapy trialists' collaborative group

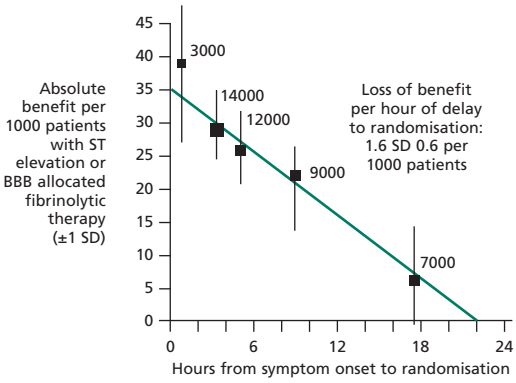
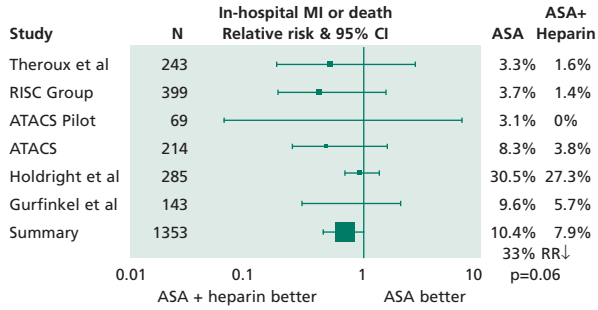


Figure 3: ASA vs ASA + heparin in unstable angina/ non-Q wave MI



the nonspecific binding seen with unfractionated heparin. Furthermore, LMWHs are not inactivated by platelet factor IV and some have a greater propensity for inhibition of factor Xa as opposed to thrombin. This is thought to be beneficial in the treatment of patients with acute coronary syndromes based on prevention of thrombin generation. These observations are supported by the results of comparative trials of enoxoparin that show a 3:1 ratio of Xa to IIa inhibition, indicating a significantly more favorable outcome when compared to unfractionated heparin[2] (Table 1).

Direct thrombin inhibitors

The importance of direct thrombin inhibition, including thrombin that is fibrin bound, has been tested in a number of prospective trials. Early experience was associated with a significant increase in hemorrhage presumably because of the utilization of a higher dose (GUSTO IIa, TIMI 9a). Modification of the dose regimen was associated with a modest but statistically insignificant result (GUSTO IIb). More recent results from the OASIS program suggest renewed optimism in this therapeutic approach and combined data from available trials (Table 2) suggest a favorable effect.

Antiplatelet therapy

Administration of aspirin has been the mainstay of treatment in patients with acute MI and unstable angina. Platelet adhesion, activation, and aggregation are key steps in intracoronary thrombus formation seen in patients with acute coronary syndromes. Treatment with aspirin, however, mod-

Table 1: ESSENCE

Triple endpoint rates: All randomized population

Death, MI recurrent angina (protocol definition)

	Heparin (n=1564)	Enoxaparin (n=1607)	Relative Risk Reduction	OR (95% CI)	p
48 hours	7.4%	6.2%	16.2%	0.83 (0.62,1.09)	0.178
14 days	19.8%	16.6%	16.2%	0.80 (0.67,0.96)	0.019
30 days	23.3%	19.8%	15.0%	0.81 (0.68,0.96)	0.016

Table 2: Hirudin; death and MI at 35 days

	Heparin	Hirudin	Odds ratio	p
OASIS-1	8.6%	6.1%	0.71	0.15
OASIS-2	7.7%	6.8%	0.88	0.07
GUSTO IIb	10.0%	9.1%	0.91	0.08
TIMI 9	9.5%	9.7%	1.02	0.85
Total	9%	8.1%	0.9	0.013

ifies only one pathway of platelet aggregation stimulation, the pathway related to thromboxane A_2. Recent results from the CAPRIE study[3] suggest that inhibition of a different pathway of platelet aggregation, that mediated by ADP, may be associated with improved outcome. A number of other specific antagonists to other stimuli of platelet aggregation are being developed, including serotonin, epinephrine, collagen, and shear-stress.

The most recent development in antiplatelet therapy has been in connection with the glycoprotein (GP) IIb/IIIa receptor, a member of the integrin family and the receptor that is most abundant on platelet surfaces. GP IIb/IIIa receptors represent a final common pathway for platelet aggregation with binding to the fibrinogen dimer.

A variety of receptor blockers have entered the therapeutic arena (Table 3). Initial development was undertaken in an angioplasty model and the greatest success was achieved with a nonspecific humanized antibody fragment — abciximab (ReoPro) — shown to be safe and effective in reducing unfavorable outcomes in stable and unstable patients undergoing percutaneous transluminal coronary revascularization (PTCR). One of these studies, CAPTURE (Figure 4) demonstrated the benefit of this type of antiplatelet therapy not only early on, in fact even prior to PTCR, but also with the risk associated with the revascularization procedure itself. Subsequent studies in patients with acute coronary syndromes

Table 3: IIb/IIIa integrin antagonists

Agent	Type	Route	t½	Notes
Abciximab	Antibody	IV	long (new platelet)	non-specific for integrin, binds vitronectin
Integrelin	Peptide	IV	10 min	marked specificity for integrin
Tirofiban	Small molecule	IV	short	non-specific

unrelated to PTCR have demonstrated a consistent and beneficial effect of GP IIb/IIIa receptor antagonism (Figure 5). The current stage of GP IIb/IIIa antiplatelet therapy has involved the use of oral compounds and results of studies are expected as early as March, 1999.

Patient selection

Given the number of therapeutic options available, patient selection, in particular the identification of high-risk patients, will be of critical importance since it will most likely be associ-

Figure 5: IIb/IIIa inhibitors. Acute coronary syndromes without persistent ST↑ trials

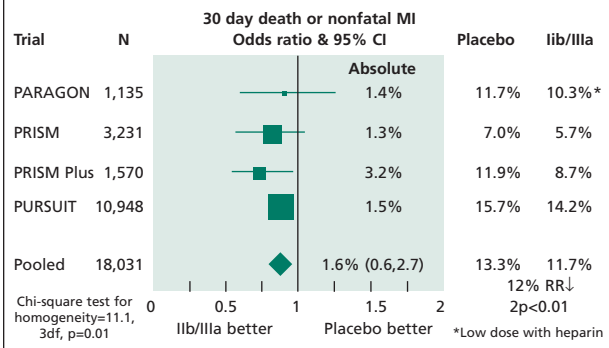
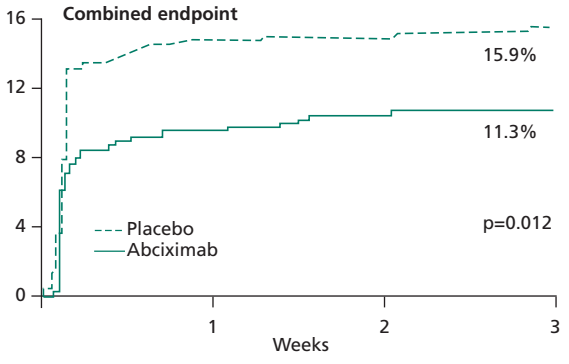
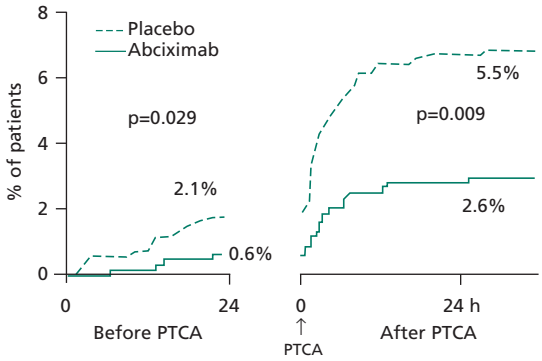


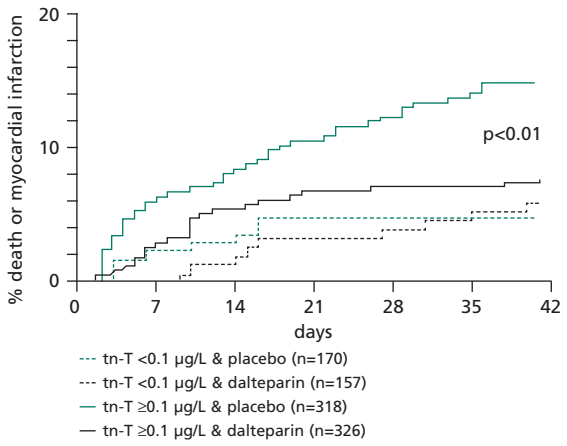
Figure 4: CAPTURE: Abciximab in PTCA for refractory ischemia





Major bleeding: 3.8% vs 1.9% p=0.043
Thrombocytopenia (<100,000): 5.6% vs 1.3%
At 6 mo.: no difference any end-point

Figure 6: Risk guided treatment in FRISC



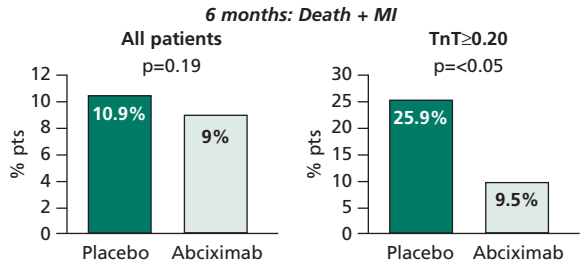
ated with a cost-effective approach. Examples of such risk stratification and related benefit are already available. In the FRISC study,[4] the benefit of LMWH administration was not seen in all patients, but was clearly demonstrated in those with troponin I positivity (Figure 6). Similarly, in the CAPTURE study, the greatest and only statistically significant benefit at six months was seen in patients with troponin T elevation (Figure 7).

An invasive vs a conservative approach

Formal comparisons of an invasive *vs* a conservative approach have clearly shown the benefits of watchful waiting associated with the conservative approach.[5,6] However, in these studies, patients in the conservative arm were still able to undergo frequent revascularization within short periods of time (ie, crossover). This realization underscores comparative studies of patients managed in the U.S. and Canada where the differences in interventional rates can be even more dramatic. The outcome in Canadian patients appears to be less favorable.[7-9]

Thus, intervention in high-risk patients, appropriately supported by on-going antiplatelet and antithrombotic treatment, is likely to be associated with the greatest benefit in patients with acute coronary syndromes.

Figure 7: Treatment benefit based on risk: CAPTURE



Summary

The 1990s can be truly characterized as the "golden era" of therapeutic efficacy. The immense expansion in our therapeutic armamentarium may lead to the next decade being characterized as an era of therapeutic "cacophony" with many beneficial therapies available, but a lack of true insight regarding how to use them most beneficially. The answer lies in public/private partnership for clinical development, appropriate utilization of clinical trials to identify treatments that work, outcomes research to help us with the understanding of how to deliver this therapy, and more focused risk stratification, including a genetically-based approach to identify those patients who should be treated for maximal benefit.

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