Canadian Cardiovascular Society
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1992 CANADIAN CONSENSUS CONFERENCE ON CORONARY THROMBOLYSIS

Table of Contents

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1992 CANADIAN CONSENSUS CONFERENCE ON CORONARY THROMBOLYSIS

Introduction: Why a consensus conference on coronary thrombolysis ?

Merril L Knudtson MD FRCPC, Hugh Scully MD FACS FACC FRCSC

In Canada in each year, 50,000 people are hospitalized with acute myocardial infarction, and up until 1985 about 17% of them did not survive their hospital stay. Large clinical trials of coronary thrombolytic agents in conjunction with acetylsalicylic acid, have demonstrated reductions of in-hospital mortality of up to 40%. Although there have been many excellent randomized controlled trials of coronary thrombolytic therapies, major uncertainties persist about which patients should receive such treatment, and about which adjuvant treatments and subsequent management strategies should be employed. Perhaps in part because of these uncertainties, coronary thrombolytic therapy is not as widely used as it might be, to the detriment of many patients. Hence, coronary thrombolysis was considered by the Canadian Cardiovascular Society to be ideal as the topic of a formal consensus conference.

The consensus conference Chair was selected by the executive of the Canadian Cardiovascular Society. To make up the primary consensus panel, a representative group of Canadian investigators was selected, with expertise in clinical and experimental thrombolysis, interventional cardiology, cardiac surgery, epidemiology, consensus conference methodology and health economics. At the first meeting in January 1992, it was agreed that our ultimate goal was to develop a set of recommendations for the use of thrombolytic therapy in acute myocardial infarction. We also planned that the formal literature reviews would eventually be published to provide appropriate background for the consensus recommendations. It was

agreed that the available literature would be critically reviewed, that studies would be graded for their scientific rigour, that recommendations would be based upon the scientific studies and that these recommendations would be graded according to the rigour of the supporting data. We agreed to follow formal but simple criteria previously developed by David Sackett.

The task was divided among the panel members as outlined in the table of contents. The literature reviews were conducted between February and May 1992. Each author or group was asked to prepare a written, referenced review, to draw conclusions and to make recommendations. These were circulated among the group and there was a face-to-face meeting of the entire group in Toronto on June 23, 1992. At this consensus meeting, each author or group presented their data and recommendations, and we attempted to reach a preliminary consensus on the recommendations for each component. Authors then revised their manuscript and recommendations in response to these discussions, and made further modifications in response to editorial input.

The entire draft manuscript was then assembled and sent to the members of the consensus panel for approval of their own contributions and overall input to the entire document. It was also sent out for review to a panel of 40 secondary reviewers, recommended to the Chair by the Canadian Council of Cardiovascular Nurses, the Canadian Critical Care Society, the Canadian Association of Emergency Physicians and, in each province, the Ministry of Health, the Provincial Medical Association and the Provincial Hospitals Association. We asked these individuals to review the manuscript and recommendations particularly from the perspective of their constituency. We are deeply indebted to these individuals who reviewed the lengthy manuscript and who provided us with valuable input on many issues.

In October 1992 the consensus panel recommendations were sent to all 800 members of the Canadian Cardiovascular Society for review. At the annual meeting of the Canadian Cardiovascular Society there was a one-hour presentation of the consensus recommendations by selected panel members. Subsequently, written comments were received from many members of the Canadian Cardiovascular Society.

The panel members were asked for further revisions to their manuscripts, and the comments of the secondary reviewers and the interested members of the Canadian Cardiovascular Society were reviewed in detail. Any dramatic divergence from the panel recommendations or the reviewer's text was studied and discussed, and in many instances changes were made to clarify text, correct errors and modify recommendations. The near final manuscript and recommendations were circulated yet again to the consensus panel membership to achieve agreement prior to submitting the document to *The Canadian Journal of Cardiology for peer review.*

The undertaking of the consensus panel has been to prepare literature reviews and to make recommendations according to formal rules of evidence based upon published literature. The panel has kept aware, throughout its deliberations, of major ongoing research in coronary thrombolysis. The Late Assessment of Thrombolysis Efficacy (LATE) Study was presented at the European Society of Cardiology meeting in September 1992 and is under review by Lancet. The GUSTO trial was completed in January 1993 and presented publicly at the annual meeting of the American Federation for Clinical Research (AFCR) in Washington on April 30, 1993. The final publication is not likely to be available for several months. Although the results of this trial provide important new information on the comparative efficacies of various regimens of thrombolytic therapy and adjuvant heparin, and further insights into the relationships among coronary patency, left ventricular function and clinical outcomes, they do not influence the major components of the consensus manuscript and recommendations. Nevertheless, the consensus panel felt it was important to take note of the GUSTO results in the manuscript, and as appropriate in the recommendations. Accordingly, the chapters contain brief references to the GUSTO presentation as appropriate, as do the recommendations. Once the GUSTO manuscript is published, the consensus panel will reconvene to subject this evidence (and any other major published evidence appearing in the interim including the LATE Study) to its formal process of review and will issue an updated set of recommendations with any modifications that appear appropriate as of 1994.

This has been an undertaking of considerable magnitude, requiring more than one year to

complete. I am grateful to the members of the primary consensus panel, all of them heavily committed clinician investigators, who found the time and energy to contribute to this undertaking. They are Paul Armstrong, Toronto; Israel Belenkie, Calgary; Jack Hirsh, Hamilton; David Johnstone, Halifax; Merril Knudtson, Calgary; Michel Lemieux, Quebec; David Massel, London; David Naylor, Toronto; Louis Roy, Quebec; David Sackett, Hamilton; Pierre Théroux, Montreal.

I wish also to thank the secondary review panel members, many of whom contributed extensive commentary to help us in our task. Those who provided input were: Ms T Fawcett, Ms N Tee, Canadian Council of Cardiovascular Nurses; Dr J Christianson, Dr D Schreiber, Dr BH Rowe, Canadian Association of Emergency Physicians; Dr T Noseworthy, Alberta Ministry of Health; Dr DL Roth, Dr Wayne Warnica, Alberta Cardiovascular Society; Dr W Black, Alberta Medical Association; Dr C Wright, Dr TF Ward, BC Health Association; Dr C Thompson, Dr J Morch, Continuing Advisory Subcommittee on Cardiac Care - BC; Dr RA Steeves, Dr DW Olmstead, Dr A Jones, Health and Community Services, New Brunswick; Dr G Winsor, Newfoundland Department of Health; Ms P McGee, Ms M C Lindberg, Ontario Ministry of Heath; Dr C Cudmore, PEI Hospital and Health Services Commission; Dr Y Morin, Quebec Ministry of Health; Mr T Quinn, Saskatchewan Health; Dr JF Lopez, Saskatchewan College of Physicians and Surgeons; Dr N Habib, Saskatchewan; Dr PJ Anderson, Yukon; Dr JWI Morse, Dr S Chouinard, North West Territories.

We deliberately sought no commercial funding for this venture. Our gratitude is extended to the organizations which generously provided us with the necessary funds to undertake the consensus conference. These organizations were: Canadian Cardiovascular Society, Heart and Stroke Foundation of Canada, Ministry of Health of Ontario, and National Health Research and Development Program.

We wish to acknowledge Ms Dolores Lorenço who coordinated efforts at the office of the Canadian Cardiovascular Society. A special vote of thanks goes to Ms Roberta Petitti who has handled this huge manuscript as countless diskettes, faxes, 'phone calls and couriers went back and forth across the country. She ultimately assembled the document in publication format.

We also express our gratitude to the staff of Pulsus Group Inc, publishers of *The Canadian Journal of Cardiology,* for their expert and speedy preparation and publication of the manuscript.

Finally, we acknowledge our many colleagues in the Canadian Cardiovascular Society for their constructive input and encouragement throughout. We trust they find this publication useful in their patient care.

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1992 CANADIAN CONSENSUS CONFERENCE ON CORONARY THROMBOLYSIS

Part 1: General Considerations

Merril L Knudtson MD FRCPC, Hugh Scully MD FACS FACC FRCSC

Coronary thrombolysis: History and rationale

JOHN A CAIRNS

The evolution of coronary thrombolytic therapy began with the work of Tillett and Garner (1), demonstrating that human isolates of Lancefield group A beta hemolytic streptococci excreted a potent fibrinolytic substance into their culture medium. Studies of this `streptococcal fibrinolysin' led to an understanding of the role of plasminogen activation in fibrinolysis and fibrinogenolysis (2). A sequence of laboratory and clinical studies culminated in the availability of a preparation of streptokinase (SK) for intravenous (iv) use, which was relatively safe and efficacious for thrombolysis (3).

The clinical description of acute myocardial infarction (AMI) by Herrick (4) in 1912 embodied the concept that acute coronary thrombosis was responsible, and this view was widely accepted. The possibility of lysing primary or secondary occlusive thrombi was the principal rationale for the first published trial of thrombolytic therapy for AMI in 1959 (5). Additional benefit was anticipated by the mechanisms of protection and preservation of flow in the microcirculation of the peri-infarction zone, diminished blood viscosity, and reduced platelet aggregation. By 1960, a small study of intracoronary SK in patients with suspected AMI had

been reported (6). Over the next 25 years, 24 randomized studies of iv thrombolytic therapy were conducted, primarily in Europe (7). Treatment protocols varied widely, and in many instances there were long delays from onset of AMI to treatment. Nevertheless, five trials showed statistically significant mortality reductions, and several more showed trends favouring therapy. Despite the encouraging results, in particular those from the European Cooperative Study (8), thrombolytic therapy was not commonly used to treat AMI in Europe and virtually never in North America. In addition to a natural conservatism towards new and potentially dangerous therapies, physicians were presented with a number of autopsy studies reporting a low incidence of coronary thrombosis in fatal MI (9), and the pathogenetic role of the coronary artery thrombus was seriously questioned (10). There was also a general decrease in the enthusiasm for the use of anticoagulant therapy in AMI.

In the late 1970s, there was a reawakening of interest in the potential for thrombolytic therapy for AMI for three principal reasons: demonstration that coronary thrombosis is a very early event in most AMIs (11); recognition of the prognostic importance of infarct size (12); and evidence that infarct size might be limited by interventions early in the course of AMI (13) and, therefore, the expectation that reperfusion might lead to marked limitation of infarct size.

The renewed interest in thrombolytic therapy was directed initially at intracoronary administration, first reported by Chazov in 1976 (14). The expectation that local delivery of the thrombolytic agent would result in less systemic thrombolysis, and the initial studies reporting reperfusion rates of 70 to 80% with intracoronary SK (15) encouraged the conduct of randomized trials. These confirmed the presence of occlusion in the infarct-related artery in about 85% of AMIs, and demonstrated reperfusion in 70% (16). The reality that most hospitals do not have cardiac catheterization laboratories, and the recognition of the economic and logistic impediments to emergency cardiac catheterization even in referral hospitals, stimulated a re-evaluation of iv thrombolytic therapy (17,18). Several studies showed that in many instances, reperfusion could be achieved with iv thrombolysis more quickly than with intracoronary administration by avoiding the delay arising from the requirement for coronary angiography with the intracoronary strategy. Subsequently, three large studies of SK (19-21), one of anisoylated plasminogen streptokinase activator complex (APSAC) (22), and one of

recombinant tissue-type plasminogen activator (rt-PA) (23) were undertaken to evaluate the effect of thrombolytic therapy on mortality in AMI.

The initial agent in clinical use was SK. Urokinase (UK), a direct endogenous plasminogen activator secreted by human kidney cells, was extracted and purified by 1957 (24), was compared with SK in trials of pulmonary embolism (25) and was studied in early trials of AMI (7). rt-PA was first used in humans in 1983 (26). Subsequently, randomized controlled studies were undertaken to assess the efficacy of iv rt-PA in achieving coronary artery reperfusion and patency (27-29) and in preserving left ventricular (LV) myocardium by the measurement of LV function (30-32). APSAC offered theoretical advantages over SK (33) and was evaluated in a number of clinical trials. Single-chain UK plasminogen activator (scuPA), a precursor of UK, also offered theoretical advantages and clinical evaluation has been undertaken (34).

Concern about the problem of severe residual stenosis persisting after successful thrombolysis led to studies of ancillary percutaneous transluminal coronary angioplasty (PTCA), acetylsalicylic acid (ASA) and heparin in patients receiving thrombolytic therapy. The comparative effects of the various thrombolytic agents on coronary reperfusion, LV function, and morbidity, as well as their side effects, have been assessed in numerous clinical trials. Two large trials have compared mortality reduction by SK, APSAC and rt-PA and have found no differences (35-37). The recently completed GUSTO trial compared regimens of accelerated dose rt-PA, rt-PA/SK in combination and SK, and has documented the lowest mortality, highest early patency and best LV function with accelerated dose rt-PA (38).

In Canada, coronary thrombolytic therapy currently is administered to about 40% of patients hospitalized with AMI. The majority of these patients receive SK. Basic and clinical research continues to be conducted in the pursuit of better thrombolytic agents and adjuvant therapies, optimal therapeutic regimens, and risk benefit and cost utility evaluations of this highly effective approach to the management of acute myocardial infarction.

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Mechanisms of action of thrombolytic drugs

JACK HIRSH

Fibrinolysis is produced when the proenzyme plasminogen is converted to the proteolytic enzyme plasmin by the action of plasminogen activators. Plasminogen is a 90,000-dalton protein synthesized primarily in the liver. It has five `kringle' domains that mediate binding to fibrin and to endothelial cells. Proteolytic cleavage of a single bond by plasminogen activators converts the inactive plasminogen into proteolytically active plasmin. Plasminogen has a plasma half-life of approximately 20 h; it has a plasma concentration of approximately 2.4 mM. Plasmin is inhibited by a2-antiplasmin, a serine protease inhibitor (serpin) that is also synthesized in the liver. a2-antiplasmin is a very rapid inhibitor of plasmin and is present in the circulation in a concentration sufficient to inhibit approximately one-half of all potential plasmin activity. a2-antiplasmin inhibits plasmin activity by binding to both the serine protease active site and the kringle domains. Since plasmin binds to fibrin through the kringle domains, it is protected to a large extent from inhibition by a2-antiplasmin when bound to fibrin. Other plasma serpins can also inhibit plasmin, but not as effectively as a2-antiplasmin.

The physiological function of plasmin is to lyse fibrin. When present in low concentrations in the plasma, plasmin is rapidly inactivated by a2-antiplasmin. However, during therapeutic thrombolysis, the rapid conversion of plasminogen can result in active plasmin in the circulation because plasma concentrations of plasmin exceed the neutralizing capacity of a2-antiplasmin. Plasmin is then free to produce a systemic lytic state characterized by digestion of fibrinogen, factor VIII and factor V. In the process of both fibrinolysis and fibrinogenolysis, proteolytic degradation products (FDPs) are formed which influence hemostasis and the fibrinolytic response. FDPs inhibit fibrin polymerization and platelet aggregation, thereby, acting as natural anticoagulants; they can also become incorporated into the fibrin clot rendering it more susceptible to lysis; and some FDPs can enhance plasminogen activation by rt-PA in the same manner as does fibrin (1). Plasmin can also act on the platelet to decrease the aggregation response (2-4).

PLASMINOGEN ACTIVATORS

The plasminogen activators convert plasminogen to plasmin. Plasminogen activators are classified as exogenous (if they are not synthesized in humans) or endogenous (if synthesized in humans); they can be classified further as fibrin-specific or nonfibrin-specific based on their binding characteristics to fibrin. Of the plasminogen activators that have been evaluated in man, SK is exogenous and nonfibrin-specific, UK is endogenous and nonfibrin-specific, APSAC is exogenous and weakly fibrin-specific, and both rt-PA and single-chain UK plasminogen activator (scuPA) are endogenous and fibrin-specific.

Streptokinase: SK is a 47,000-dalton protein produced by the Lancefield group C strains of b-hemolytic streptococci. In contrast to all of the other plasminogen activators, SK is not an enzyme and, therefore, does not directly convert plasminogen to plasmin by proteolytic cleavage. Instead, SK binds noncovalently to plasminogen converting it to a plasminogen activator complex (5). The SK-plasminogen complex then acts on other plasminogen molecules to cleave a single bond to generate plasmin. SK has a plasma half-life of 30 mins. Because it is a bacterial product it stimulates antibody production and can produce allergic reactions. Antistreptococcal antibodies produced as a result of past streptococcal infections are present in variable titres in most patients before treatment and their presence may lead to an amnesic response which makes repeated treatment with SK ineffective for a period of months or years after an initial course of treatment.

Anisoylated plasminogen-SK activator complex: APSAC is a hybrid molecule of SK and plasminogen. The plasminogen is inactivated by acylation of its active centre so that the complex cannot convert plasminogen to plasmin until deacylation has occurred. Deacylation occurs spontaneously in plasma (6). The plasma half-life of APSAC is 70 mins. Unlike the other plasminogen activators, this complex is not inhibited by endogenous serpins. The lytic effect of APSAC may be blocked by neutralizing antibodies formed in response to previous treatment with SK or APSAC.

Urokinase: UK-type plasminogen activators (UPA) comprise a family of endogenous molecules synthesized by endothelial and mononuclear cells. The parent molecule is scuPA, also known as pro-urokinase (7). scuPA has a molecular weight of 54,000-daltons. It is uncertain whether it has any intrinsic enzymatic activity, but if it does, it is far less than its proteolytic derivative, two-chain UK. High molecular weight urokinase (HMW-UK) is produced as a result of proteolytic cleavage of a single bond of scuPA. HMW-UK is further cleaved to the 33,000-dalton product, low molecular weight two-chain urokinase (LMW-UK). UPAs also contain an aminoterminal kringle domain. HMW-UK and LMW-UK have plasma half-lives of 10 mins, while scuPA has a plasma half-life of 5 mins. Circulating plasma concentrations of scuPA are approximately 5 to 10 ng/mL.

Tissue-type plasminogen activator: rt-PA is synthesized by endothelial cells as a single-chain polypeptide of 72,000-dalton molecular weight (8). Proteolytic cleavage of the Arg 275-Ile 276 bond by plasmin, kallikrein, or factor Xa converts this single-chain form into a two-chain species. Both forms are enzymatically active but the two-chain species has a greater catalytic efficiency than the single chain rt-PA in the absence of fibrin (9,10). rt-PA has a plasma half-life of approximately 5 mins.

PLASMINOGEN

The native form of plasminogen secreted by the liver has a glutamic acid residue at its carboxyterminus (Glu-plasminogen). Limited proteolysis by plasmin converts this molecule into a modified, slightly smaller protein with a lysine, valine, or methionine at the aminoterminus (so-called Lys-plasminogen) (11). Lys-plasminogen has a greater affinity for fibrin than Glu-plasminogen, but Glu-plasminogen is a better substrate for scuPA and HMW-tc-UK than is Lys-plasminogen.

PLASMINOGEN ACTIVATOR INHIBITORS

Two classes of inhibitors of endogenous plasminogen activators have been identified. Plasminogen activator inhibitor type 1 (PAI-1) is synthesized by endothelial cells (12) and by

platelets and is responsible for most of the plasminogen activator inhibitor activity found in plasma. Plasminogen activator inhibitor type 2 (PAI-2) is synthesized in placenta (13) and mononuclear cells (14). Both serpins inhibit both rt-PA and UPAs, but PAI-1 is a more potent inhibitor of rt-PA than of UPAs. Other plasma serpins that inhibit or attenuate rt-PA's activity include a2-antitrypsin (15), and C1 esterase.

Fibrin/cell surface specificity: Neither SK nor LMW-UK contains fibrin-binding domains; as a result, these agents are equally effective at activating circulating plasminogen and fibrin-bound plasminogen. rt-PA and scuPA are fibrin-selective (compared with SK and LMW-UK) because in the presence of fibrin their catalytic efficiencies are markedly increased. rt-PA is fibrin selective because it binds to fibrin and undergoes a concomitant conformational change that increased its affinity for plasminogen (9). scuPA's fibrin selectivity is dependent more on the avidity of enzyme for fibrin-bound plasminogen than on a direct effect of fibrin binding of scuPA (16). These agents are only partly fibrin-selective since at therapeutic dosages both rt-PA (17) and scuPA (18,19) produce reductions in the plasma levels of plasminogen, a2-antiplasmin and fibrinogen, although considerably less than occurs with SK or UK. The incidence of bleeding complications is also no different between rt-PA and SK (17), indicating that bleeding is caused mainly by lysis of fibrin in hemostatic plugs rather than as a result of plasma proteolysis.

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Rules of evidence and clinical recommendations

DAVID L SACKETT

What rules of evidence ought to apply when expert committees meet to generate recommendations for the clinical management of patients? Should only the thoroughly validated results of randomized clinical trials be admissible to avoid or minimize the application of useless or harmful therapy? Or, to maximize the potential benefits to patients (including those possible from unproved remedies), ought a synthesis of the experiences of seasoned clinicians form the basis for such recommendations?

Ample precedent exists for the latter approach even when attempts are made to replace it (1). However, for the following reasons, the nonexperimental evidence that forms the recalled experiences of seasoned clinicians will tend to overestimate efficacy.

Favourable treatment responses are more likely to be recognized and remembered by clinicians when their patients comply with treatments and keep follow-up appointments. However, there are already five documented instances in which compliant patients in the placebo groups of randomized trials exhibited far more favourable outcomes (including survival) than their noncompliant companions (2-6). Because high compliance is therefore a marker for better outcomes, even when treatment is useless, our uncontrolled clinical experiences often will cause us to conclude that compliant patients must have been receiving efficacious therapy.

Unusual patterns of symptoms (e.g., transient ischemic attacks) or signs (e.g., high blood pressure levels) and extreme laboratory test results, when they are reassessed even a short time later, tend to return toward the more usual, normal result (7). Because of this universal tendency of `regression toward the mean', any therapy (regardless of its efficacy) that is initiated in the interim will appear efficacious.

Routine clinical practice is never `blind', and both patients and their clinicians know when active treatment is under way. As a result, both the placebo effect (which has shown, for example, that angina pectoris can be relieved by mock internal mammary ligation [8]) and the desire of patients and clinicians for success can cause both parties to overestimate efficacy.

For the preceding reasons, the `consensus' approach based upon uncontrolled clinical experience risks precipitating the widespread application of treatments that are useless or even harmful. These same treatments are much less likely to be judged efficacious in double-blind, randomized trials than in uncontrolled case series of unblinded, `open' comparisons with contemporaneous or historical series of patients; hence the maxim: `Therapeutic reports with controls tend to have no enthusiasm, and reports with enthusiasm tend to have no controls'.

The foregoing discussion should not be misinterpreted as constituting a mandate for discarding the large body of uncontrolled observations by clinicians who have used thrombolytic agents and adjuvant therapies in the treatment of AMI. In many instances, randomized control trials have never been (and, arguably, never could be) carried out, and the only information base for generating some of the recommendations comes from uncontrolled clinical observations.

What this does mean, however, is that it is important, whenever possible, to base firm recommendations (and especially those involving risk to patients) on the results of rigorously controlled investigations and to be much more circumspect when recommendations rest only on the results of uncontrolled clinical observations. This approach was adopted by the participants in the Canadian Consensus Conference on Coronary Thrombolysis and led to the definition and adoption of both Levels of Evidence and Grades of Recommendations.

LEVELS OF EVIDENCE

The participants in this undertaking, when summarizing what was known about the causes, clinical course, and management of a given clinical entity, specified the level of evidence that was being used in each case, according to the following classification.

Level I: Randomized trials with low false-positive (a) and/or low false-negative (b) errors (high power)

By `low false-positive (a) error' is meant a `positive' trial that demonstrated a statistically significant benefit from experimental treatment. For example, there have now been several randomized trials in which thrombolytic therapy has produced very large, statistically significant reductions in the risk of death among patients whose clinical presentation suggests they are having a myocardial infarction.

By `low false-negative (b) error (high power)' is meant a `negative' trial that demonstrated either no effect of therapy or no difference between therapies, yet was large enough to exclude the possibility of a clinically important benefit of active treatment over placebo, or of one active

treatment over another (ie, had very narrow 95% confidence limits that excluded any clinically important difference between treatment groups). For example, the recently completed comparison of SK, rt-PA and APSAC concluded no material difference in the efficacy of these agents, and the 95% confidence interval on their differences excluded any practical dissimilarity between them (9).

Table 1

Level of evidence	Grade of recommendation
Level I: Large randomized trials with clear-cut results (and low risk of error)	Grade A
Level II: Small randomized trials with uncertain results (and moderate to high risk of error)	Grade B
Level III: Nonrandomized contemporaneous controls;	
Level IV: Nonrandomized historical controls;	Grade C
Level V: No controls, case series only	

Level II: Randomized trials with high false-positive (a) and/or high false-negative (b) errors (low power)

By 'high false-positive (a) error' is meant a trial with an interesting positive trend that is not statistically significant. For example, the ISAM randomized trial identified only a trend in mortality favouring SK infusion among a relatively small number of patients with symptoms suggesting acute myocardial infarction. (10).

By 'high false-negative (b) error (low power'' is meant a 'negative' trial that concluded that therapy was not efficacious, or that two treatments had similar efficacy, yet because of small numbers of patients could not exclude the real possibility of a clinically important benefit or difference between agents (i.e., had very wide 95% confidence limits on the differences between treatment groups). For example, the GISSI study found very little effect of SK on mortality in inferior infarctions, but the 95% confidence interval for benefit extended to a relative risk reduction of 25% (11).

The advent of meta-analysis has a major impact here, for it can convert two or more high-quality, homogeneous but small (and therefore level II) trials into a single level I overview.

A special note about subgroup analyses in randomized trials

Both the writers and the readers of trial reports may be tempted to conclude that the efficacy of thrombolytic therapy differs in clinically important ways between subgroups of patients defined by the location or severity of their infarctions, the time between the onset of their symptoms an the administration of thrombolytic therapy, or other baseline features. Such `subgroup analysis', especially when it is carried out in an exploratory data `dredging', often leads to false-positive conclusions (that subgroups differ in their responsiveness to treatment when, in truth, they do not). For this reason, decisions on whether apparent differences in subgroup responses are real should require positive answers to questions, such as the following seven suggested by Oxman and Guyatt (12).

- Is the magnitude of the difference in subgroup responses clinically important (so that it would lead to different treatment recommendations for each subgroup)?
- Was the difference in subgroup responses statistically significant?
- Did a hypothesis that the subgroups ought to differ precede, rather than follow, the analysis?
- Was this subgroup analysis one of a small number of subgroup analyses performed in the study (one in 20 of which should be significant by chance alone)?

- Was the difference in subgroup responses suggested by comparisons within a study (as opposed to between two studies)?
- Was the difference in subgroup responses consistent across two or more studies?
- Is there indirect (e.g., biological) evidence to support the hypothesized difference in subgroup responsiveness?

Level III: Nonrandomized concurrent cohort comparisons between contemporaneous patients who did and did not receive thrombolytic therapy

In this case, the outcomes of patients who received (and complied with) thrombolytic agents would be compared with those of contemporaneous patients who did not (through refusal, noncompliance, contraindication, local practice, oversight, etc.) receive these same drugs. The biases described in the Introduction are usually in play here.

Level IV: Nonrandomized historical cohort comparisons between current patients who did receive thrombolytic agents and former patients (from the same institution or from the literature) who did not .

In this case, the outcomes of patients who received thrombolytic therapy (as a result of a local treatment policy) would be compared with those of patients treated in earlier era or at another institution (when and where different treatment policies prevailed). To the biases presented in the Introduction must be added those that result from inappropriate comparisons over time and space.

Level V: Case series without controls

In this case, the reader is simply informed about the fate of a group of patients. Such series may contain extremely useful information about clinical course and prognosis but can only hint at efficacy.

THE GRADING OF RECOMMENDATIONS

Finally, Consensus Conference participants classified their ultimate recommendations on the use of thrombolytic therapy into three grades, depending on the level of evidence used to generate them. These three grades of recommendations were as follows (Table 1).

Grade A: Supported by at least one, and preferably more, level I randomized trial(s)

For example, the grade A recommendation that every patient with an evolving acute myocardial infarction should be considered for intravenous thrombolytic therapy is based on three level I trials of SK, one level I trial of APSAC, one level I trial of rt-PA and several meta-analyses of all the randomized trials on this issue. Similarly, the grade A recommendation that a physician may choose any of SK, rt-PA or APSAC is based on a level I trial that demonstrated, with a very narrow confidence interval, that these three drugs are equivalent.

Grade B: Supported by at least one level II randomized trial

For example, the grade B recommendation that beta-blockade be added to thrombolytic therapy is based on a level II trial of this combination that yielded positive trends for several outcomes that were not statistically significant.

Grade C: Supported only by level III, IV or V evidence

For example, the grade C recommendation that 48 h of adjuvant anticoagulant therapy be considered following thrombolytic therapy is based on expert interpretation of trials from the prethrombotic era and the observation that the coronary patency rate is higher among patients who receive adjuvant heparin following thrombolysis.

It is hoped that advances in our understanding of both these thrombolytic agents and the mechanisms of the disorders in which they are employed will be matched by more level I evidence; such advances will be reflected in an ever-greater proportion of grade A recommendations in future reports.

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1992 CANADIAN CONSENSUS CONFERENCE ON CORONARY THROMBOLYSIS

Part II Clinical outcomes

John A Cairns

Coronary thrombolysis: History and rationale

The evolution of coronary thrombolytic therapy began with the work of Tillett and Garner (1), demonstrating that human isolates of Lancefield group A beta hemolytic streptococci excreted a potent fibrinolytic substance into their culture medium. Studies of this 'streptococcal fibrinolysin' led to an understanding of the role of plasminogen activation in fibrinolysis and fibrinogenolysis (2). A sequence of laboratory and clinical studies culminated in the availability of a preparation of streptokinase (SK) for intravenous (iv) use, which was relatively safe and efficacious for thrombolysis (3).

The clinical description of acute myocardial infarction (AMI) by Herrick (4) in 1912 embodied the concept that acute coronary thrombosis was responsible, and this view was widely accepted. The possibility of lysing primary or secondary occlusive thrombi was the principal rationale for the first published trial of thrombolytic therapy for AMI in 1959 (5). Additional benefit was anticipated by the mechanisms of protection and preservation of flow in the microcirculation of the peri-infarction zone, diminished blood viscosity, and reduced platelet aggregation. By 1960, a small study of intracoronary SK in patients with suspected AMI had been reported (6). Over the next 25 years, 24 randomized studies of iv thrombolytic therapy were conducted, primarily in Europe (7). Treatment protocols varied widely, and in many

instances there were long delays from onset of AMI to treatment. Nevertheless, five trials showed statistically significant mortality reductions, and several more showed trends favouring therapy. Despite the encouraging results, in particular those from the European Cooperative Study (8), thrombolytic therapy was not commonly used to treat AMI in Europe and virtually never in North America. In addition to a natural conservatism towards new and potentially dangerous therapies, physicians were presented with a number of autopsy studies reporting a low incidence of coronary thrombosis in fatal MI (9), and the pathogenetic role of the coronary artery thrombus was seriously questioned (10). There was also a general decrease in the enthusiasm for the use of anticoagulant therapy in AMI.

In the late 1970s, there was a reawakening of interest in the potential for thrombolytic therapy for AMI for three principal reasons: demonstration that coronary thrombosis is a very early event in most AMIs (11); recognition of the prognostic importance of infarct size (12); and evidence that infarct size might be limited by interventions early in the course of AMI (13) and, therefore, the expectation that reperfusion might lead to marked limitation of infarct size.

The renewed interest in thrombolytic therapy was directed initially at intracoronary administration, first reported by Chazov in 1976 (14). The expectation that local delivery of the thrombolytic agent would result in less systemic thrombolysis, and the initial studies reporting reperfusion rates of 70 to 80% with intracoronary SK (15) encouraged the conduct of randomized trials. These confirmed the presence of occlusion in the infarct-related artery in about 85% of AMIs, and demonstrated reperfusion in 70% (16). The reality that most hospitals do not have cardiac catheterization laboratories, and the recognition of the economic and logistic impediments to emergency cardiac catheterization even in referral hospitals, stimulated a re-evaluation of iv thrombolytic therapy (17,18). Several studies showed that in many instances, reperfusion could be achieved with iv thrombolysis more quickly than with intracoronary administration by avoiding the delay arising from the requirement for coronary angiography with the intracoronary strategy. Subsequently, three large studies of SK (19-21), one of anisoylated plasminogen streptokinase activator complex (APSAC) (22), and one of recombinant tissue-type plasminogen activator (rt-PA) (23) were undertaken to evaluate the effect of thrombolytic therapy on mortality in AMI.

The initial agent in clinical use was SK. Urokinase (UK), a direct endogenous plasminogen activator secreted by human kidney cells, was extracted and purified by 1957 (24), was compared with SK in trials of pulmonary embolism (25) and was studied in early trials of AMI (7). rt-PA was first used in humans in 1983 (26). Subsequently, randomized controlled studies were undertaken to assess the efficacy of iv rt-PA in achieving coronary artery reperfusion and patency (27-29) and in preserving left ventricular (LV) myocardium by the measurement of LV function (30-32). APSAC offered theoretical advantages over SK (33) and was evaluated in a number of clinical trials. Single-chain UK plasminogen activator (scuPA), a precursor of UK, also offered theoretical advantages and clinical evaluation has been undertaken (34).

Concern about the problem of severe residual stenosis persisting after successful thrombolysis led to studies of ancillary percutaneous transluminal coronary angioplasty (PTCA), acetylsalicylic acid (ASA) and heparin in patients receiving thrombolytic therapy. The comparative effects of the various thrombolytic agents on coronary reperfusion, LV function, and morbidity, as well as their side effects, have been assessed in numerous clinical trials. Two large trials have compared mortality reduction by SK, APSAC and rt-PA and have found no differences (35-37). The recently completed GUSTO trial compared regimens of accelerated dose rt-PA, rt-PA/SK in combination and SK, and has documented the lowest mortality, highest early patency and best LV function with accelerated dose rt-PA (38).

In Canada, coronary thrombolytic therapy currently is administered to about 40% of patients hospitalized with AMI. The majority of these patients receive SK. Basic and clinical research continues to be conducted in the pursuit of better thrombolytic agents and adjuvant therapies, optimal therapeutic regimens, and risk benefit and cost utility evaluations of this highly effective approach to the management of acute myocardial infarction.

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Important patient subgroups

PAUL W ARMSTRONG, C DAVID NAYLOR

Randomized placebo-controlled trials were considered where adequate samples of patients were available to perform meaningful comparisons between subsets. Of interest is the classification of AMI patients according to the TIMI investigators who are 'not at low risk' and include those more than 70 years old, prior MI, atrial fibrillation, systolic blood pressure less

than 100 mmHg and heart rate greater than 100 beats/min, Killip class 3 or 4 and anterior ST segment elevation on the qualifying electrocardiogram (ECG). Randomized trials of thrombolytic therapy have served a useful ancillary purpose in that they permit recognition of high risk subsets and highlight the broad spectrum of risk in differing groups of patients presenting with AMI. Moreover, although the risk of therapy may also depend on patient subgroups, i.e., greater risk of hemorrhage in patients with advanced age and females, these patient groups also experience higher mortality from AMI and thus may experience a greater absolute mortality reduction if an analogous treatment effect is shown to that seen in lower risk patients.

Table 1

Mortality: Effect of age in previous trials

Study (reference)	Age (years)	Number of Treatment	Deaths Control	Lives saved*	P
ISAM (1)	<70	37/728 (5.1)	48/726 (6.6)	1.5	0.21
	70-75	17/131 (13.0)	15/156 (9.6)	-3.4	0.37
GISSI (2)	<75	457/5268 (8.7)	552/5226 (10.6)	1.9	0.001
	>75	171/592 (28.9)	206/623 (33.1)	4.2	0.11
ISIS-II (3)	<70	482/6897 (7.0)	659/6879 (9.6)	2.6	0.0001
	>70	309/1695 (18.2)	370/1716 (21.6)	3.4	0.01
ASSET (4)	<66	92/1711 (5.4)	104/1641 (6.3)	0.9	0.24
	66-75	90/827 (10.8)	140/852 (16.4)	5.6	0.001
AIMS (5)	<65	21/405 (5.2)	35/411 (8.5)	3.3	0.06
	65-70	11/90 (12.2)	26/86 (30.2)	1.8	0.003
Pooled	Not elderly	1089/15,009 (7.3)	1398/14,883 (9.4)	2.1	0.0001
	Elderly	598/3335 (17.9)	757/3433 (22.1)	4.1	0.0001

*Number of lives saved per 100 patients (control group mortality minus treatment group mortality)

AGE

Table 1 represents a summary table on the effects of age on mortality in five large placebo controlled trials (1-5). Noteworthy is the consistent deleterious effects of advancing age on mortality in both treatment and control groups, i.e., approximately a 2.4 times increased mortality in older patients. Although the percentage relative reduction in mortality by treatment is similar, the increased risk in the elderly results in two additional lives saved per 100 patients treated, i.e., 4.1 versus 2.1 lives saved per 100.

SEX

In the GISSI-1 study, short term mortality appeared favourably influenced (approximate 20% reduction) in both males and females but overall placebo mortality was approximately double in females (22.6%) versus males (10.6%). Overall analysis of the GISSI-1 study and the other three level I studies (2-5) reveals a consistent 1.5 to 2 times increase in mortality in females (10.9 to 22.6%) versus males (9.4 to 12.0%). Hence, assuming an overall benefit of thrombolytic therapy of two lives saved per 1000, there would be expected to be an additional 1.5 to 2 female lives versus male lives saved.

PRIOR MYOCARDIAL INFARCTION

Placebo patients with prior infarction in GISSI-1 fared less well overall (16.5% mortality) compared with those without prior MI (12.3% mortality). Somewhat surprisingly, no treatment effect could be demonstrated in patients with prior myocardial infarction. This controversy has been resolved, however, in that both the ISIS-2 and AIMS study showed that patients with prior MI benefit from thrombolytic therapy. Although the relative benefit afforded patients with prior MI may on balance be less marked than those without previous infarction, the increased mortality associated with the former group can be expected to lead to the saving of at least two lives per 100 patients treated.

TIME FROM SYMPTOM ONSET

As recently reviewed by Grines and DeMaria (6), the clearest evidence for benefit from thrombolytic therapy exists in the 0 to 6 h window after symptom onset; their pooled analysis reveals 3.2 lives saved per 100 patients treated in this time interval. Although a post hoc analysis of the 0 to 1 h subset in GISSI-1 suggested striking incremental benefit during this very early time window, this finding was not confirmed in ISIS-2. AIMS and ASSET did not show a treatment effect gradient between 0 and 3 h opposed to 3 to 5 h (3,4). Treatment benefit between 6 and 12 h after symptom onset is less clear; in GISSI-1 no benefit was evident. In ISIS-2, there was benefit for treatment between 5 and 12 h (odds of vascular mortality reduced 16%, 2P=0.02) and between 13 and 24 h (odds of vascular mortality reduced 21%, 2P=0.08), although uncertainty exists about the exact patient selection criteria used in these categories (i.e., symptomatic patients perceived at high risk may have been treated and others not). A preliminary report from the EMERAS study, a 4000 patient SK study evaluating patients presenting 6 to 24 h after symptom onset, failed to show a benefit on mortality (American College of Cardiology Meeting, Atlanta, Georgia 1991). The LATE study (8) was a randomized, placebo controlled study of patients with AMI presenting 6 to 24 h after symptom onset. The treatment group received rt-PA and ASA and the placebo group ASA alone; 70% of patients received iv heparin. The overall results showed a 14.0% relative reduction in mortality from 10.3 to 8.8% (P=0.07, level II). Importantly, analysis of patients presenting 6 to 12 h after symptom onset revealed a mortality reduction of 27% from 11.9% to 8.7% (P=0.03, level I). Those patients presenting between 12 and 24 h after symptom onset experienced no benefit. The benefit among patients presenting between 6 and 12 h after symptom onset was confined to those with ST segment elevation.

Hence, the relative risk reduction and the statistical significance of the mortality reduction is most marked for the 0 to 6 h group, somewhat less for the 7 to 12 h group and uncertain for the 13 to 24 h group, although clearly some patients in this later time window can benefit from thrombolytic therapy.

HEMODYNAMIC STATUS ON ADMISSION

The most detailed hemodynamic information on admission is provided in the GISSI-1 study which showed a precipitous rise in mortality rate based on admission Killip class, i.e., 7.3, 19.9, 39.0 and 70.1% for placebo classes 1 to 4, respectively. Clear beneficial treatment effects of SK were seen in Killip class 1 and 2; there was a trend for such an improvement in Killip 3 and no benefit evident in patients in Killip class 4.

ECG CRITERIA

The four major randomized placebo controlled trials (2-5) identify unequivocally patients with anterior ST elevation as having the highest mortality untreated, i.e., 17.5 to 20.6%, whereas patients with inferior ST elevation have mortalities ranging from 7.2 to 10.2%. A recent pooled analysis by Grines and DeMaria indicates a clear benefit of approximately two per 100 lives saved in patients with inferior MI (6). The beneficial effect afforded patients with anterior MI appears proportionately to be at least as great (in ISIS-2 somewhat greater) such that it can be anticipated that four lives per 100 will be saved with treatment in this category. Mueller and Topol (7) have recently developed an analysis from the GISSI-1 investigators which demonstrates a clear gradient between number of leads with ST elevation and percentage mortality: SK exerted benefit in all subsets except the group with the smallest territory at risk. Patients with left bundle branch block in ISIS-2 - but not GISSI-1 - showed a striking benefit from treatment, i.e., 27.7% in control to 14.1% in the treated group. No benefit is evident in patients presenting with ST depression or normal ECGs.

The AIMS investigators undertook an interesting analysis of the effect of treatment on mortality according to a risk categorization developed on the basis of prior angina and MI, pretreatment heart rate, site of ST elevation and age (5). After assigning risk scores of 0 to 2 (low), 3 to 4 (medium) and 5 to 14 (high), they demonstrated a mortality gradient from 7.9% through 12.4% to 33.5% in these three groups. Moreover the absolute difference afforded by treatment was much greater in the high risk (15.1%) than in the other two risk categories (i.e., 3.1 and 3.9% for low and medium risk scores, respectively).

Although the recently presented GUSTO trial suggests a statistical and clinically important advantage of accelerated rt-PA with iv heparin over SK with iv or sc heparin, the margin of benefit appears to differ within certain prespecified subgroups. Further analysis of this issue will likely be useful to determine the most cost effective application of the benefit realized in the overall study population.

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Coronary thrombolysis: Nonmortality measures of efficacy

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The benefits of thrombolytic therapy in ami result from reperfusion of the infarct-related artery. In the animal model, myocardial salvage and recovery of function are inversely related to the duration of arterial occlusion before reperfusion; little salvage or recovery of function are apparent after approximately 3 h of occlusion (1,2). Because of myocardial stunning, recovery of function in viable, reperfused myocardium may take up to two weeks. Clinically, early patency is associated with recovery of function whereas it is unlikely if treatment is late, unsuccessful or followed by reinfarction (3-17). As in the animal model, recovery of function in humans occurs within approximately 10 days (18). The relationship between early patency and recovery of function also exists in patients who do not receive thrombolytic therapy (13,19-21) and in all infarct locations (22). Outcome can be modulated by the presence or absence of collateral flow (19,23,24), the degree of coronary artery patency and myocardial reperfusion (3,5,18,25,26) as well as by other factors. While it is possible that the relation between time to reperfusion and benefit may vary quantitatively from the animal model, it is clear that early treatment (and reperfusion) is most effective and that late reperfusion does not result in substantial recovery of contractile function. The inverse relationship of time and the reduction in mortality observed in GISSI-1 (27) is analogous to that relating time to myocardial salvage in the animal model (1). Those results were generally mirrored by other clinical trials (28-36).

Assessment of infarct-artery patency: Angiographic demonstration of infarct-artery patency is, of necessity, limited to single or shortly-spaced snapshots in time. Thus, precise time to reperfusion, dynamic reperfusion and reclosure, and late reocclusion (often asymptomatic)

cannot be easily determined. Importantly, late angiographic assessment may not accurately reflect the early patency which is generally accepted to be critical to achieve myocardial salvage. Moreover, effectiveness of reperfusion may also determine recovery of function while not necessarily having a similar impact on myocardial salvage and may therefore affect other outcomes (3,18,26,37-39).

Assessment of ventricular function: Ejection fraction is the measurement which is most commonly used to assess left ventricular (LV) performance. However, there are substantial problems associated with the use of this measurement in patients with acute infarction. Ejection fraction may vary considerably during the early hours of infarction so that a single measurement may not be a precise reflection of the underlying pathophysiology (40). Ischemic dysfunction is often partially compensated for by hyperkinesis in nonischemic regions; therefore, when only global function is measured, the amount of ischemic or infarcted myocardium may be substantially underestimated. Hyperkinesis in the remote region often diminishes after recovery of function in the ischemic region (41-43) so that the global measurement may mask recovery of function in the infarct-region. Measurement of regional (infarct-area) function has been shown to be a sensitive way to detect benefit (44) but this technique has not been widely applied. End-systolic volume may also prove to be a useful measure of benefit (45) but unfortunately, despite the ease of obtaining this measurement in angiographic studies, it has only rarely been related to outcomes.

The open artery hypothesis: No mechanism of benefit from thrombolytic therapy has been demonstrated other than reperfusion of the infarct-artery. Preservation of myocardium resulting in improved LV function post-reperfusion has been clearly demonstrated (Table 1) and is generally believed to be the major mechanism by which mortality is improved, function being the best independent predictor of survival (9,37,45-48). However, this relationship has not frequently been apparent in clinical trials. Although it is possible that there is no important relation between myocardial salvage and mortality, there are considerable data suggesting that such a relationship does exist (9,13,14,30,31,35-37,49,50-54) (Table 1). Despite the frequent lack of statistical significance in both improved LV function and reduction in mortality in

individual studies, a significant reduction in deaths was achieved in some, and there was an almost consistent trend for improved survival in the others. Improvement in mortality, salvage of myocardium and recovery of function were all demonstrated in the Dutch study; benefit was observed only in those patients who were enrolled within 2 h of symptom onset (57). Long term survival is also related to LV function at discharge (37). Another study demonstrated that recovery of infarct-region function at three days correlated well with survival (56), and another showed that early patency was associated with smaller infarct size, better LV function and lower morbidity and mortality (57). Thus, there are data to support the relationship between myocardial salvage and reduction in mortality, although it is clear that other factors may also be important. As discussed below, trial design may explain why the relationship has not been more clearly demonstrated. However, there are also data which suggest that late therapy, beyond a time when substantial myocardial salvage is probable, may improve survival (27-29,38), although the benefit is small by comparison to that with early therapy. Suggested mechanisms of benefit from late reperfusion include: greater electrical stability ñ fewer patients with patent infarct-arteries have ventricular late potentials (58-62) and inducible ventricular tachycardia (63,64); improved healing and reduced LV remodelling (65-70); possible preservation of collateral flow; and improved LV function, perhaps due to less hibernating myocardium (67).

Table 1

Ejection fraction and mortality in placebo-controlled trials

Study (reference)	Agent	Agent	Placebo	Agent	Placebo	P	Agent	Placebo	P
OíRourke (31)	rt-PA	74	71	61 (64)	54 (62)	0.006	5.4	5.6	NS
Meinertz (96)	APSAC	162	151	Ant 53 (140)	Ant 54 (116)	NS	5.6	12.6	0.032
				Inf 60	Inf 61				
Van de Werf (36)	rt-PA	355	366	51 (289)	49 (283)	<0.05	2.8	5.7	0.053
White (30)	SK	107	112	59	53	<0.005	2.5	12.9	0.012
Armstrong (52)	rt-PA	59	56	54 (54)	48 (50)	<0.02	5.1	8.9	NS
Maublant (53)	APSAC	112	119	53 (106)	47 (103)	0.002	5.6	12.6	NS
Guerci (54)	rt-PA	72	66	53 (60)	46 (57)	<0.02	5.6	7.6	NS
Simoons (35)	SK	269	264	45 (218)	43 (200)	<0.05	5.2	9.8	0.05
Natíl Heart Founda-	rt-PA	73	71	58 (51)	52 (52)	0.004	9.6	4.2	NS
tion of Australia (49)									

APSAC Anisoylated plasminogen streptokinase activator complex; rt-PA Recombinant tissue-type plasminogen activator; SK Streptokinase

LV function and mortality: As discussed above, available data indicate that a relationship between myocardial salvage and reduction in mortality exists and that the difficulty in showing it may relate to trial designs. The relationship has been assessed mostly in trials which were too small to detect differences in mortality (31,49,71-73) (Table 1). Conversely, the large placebo controlled mortality trials did not include systematic measurement of LV function (particularly regional) as an end-point. Baseline ejection fraction is the best predictor of

recovery of function after thrombolytic therapy (57,74); improvement is greatest in patients treated early with the worst function. Thus, inclusion of a large proportion of patients with small infarcts or relatively late after symptom onset (and little potential for improvement) and a relatively small proportion of patients with large infarcts treated relatively early (and great potential for improvement), may result in modest overall benefit. The clear relationship between LV function at discharge and long term survival (37,75) and the data showing improvement in function following thrombolysis support the likelihood that thrombolysis improves survival by preserving LV function.

Additional potentially confounding factors exist when attempting to relate LV function to mortality. Recovery of function can only be expected to be substantial when treatment is begun early. The mean time to therapy was often quite late so that it would be important to assess results in patients treated within 2 to 3 h after symptom onset (as in the Dutch study), when the relation between function and mortality should be most apparent (9,50). The inability to study patients who die early (those with a high probability of a poor function) and the common reluctance to restudy those who are doing poorly (also likely to have poor function) may lead to an overestimate of average function in the placebo group. Greater survival of high risk patients may serve to lower the mean ejection fraction in the treated group. Thus, averaged function may not accurately represent that of the total population when a substantial proportion of patients does not undergo late evaluation, a common factor in clinical trials.

TABLE 2

Early patency and recanalization rates with SK and rt-PA

Study	n	Agent	Patency (%)	Recanalization (5)
PRIMI (80)	203	SK	64	-
ECSG-1(79)	62	SK	55	ñ
Stack (97)	216	SK	44	ñ
Fung (98)	34	SK	62	ñ
Schroder (6)	26	SK	52	-
Brochier (99)	53	SK	53	-
Hays (100)	27	SK	78	ñ
Spann (101)	43	SK	-	49
TIMI-1 (77)	119	SK	-	31
TAMI-1 (012)	386	rt-PA	75	-
TAMI-3 (89)	131	rt-PA	79	-
TAMI-4 (103)	25	rt-PA	60	-
TIMI-2A (104)	317	rt-PA	82	-
ECSG-1 (79)	61	rt-PA	70	-
ECSG-2 (105)	62	rt-PA	61	-
ECSG-1 (79)	61	rt-PA	70	-
ECSG-4 (107)	180	rt-PA	60	-
Topol (108)	38	rt-PA	71	-
Guerci (54)	72	rt-PA	66	-
GAUS (81)	121	rt-PA	69	ñ
TIMI-1 (77)	113	rt-PA	-	62
Williams (109)	37	rt-PA	-	68
TPA-COOP (110)	33	rt-PA	-	75
TAPS (76)	199	rt-PA*	84	-
Neuhaus (83)	74	rt-PA*	91	-
RAAMI (111)	128	rt-PA*	81	-

**Front-loaded recombinant tissue-type plasminogen activator (rt-PA);SK Streptokinase*

Clot-selective versus nonselective fibrinolytic agents: Fibrin-specific fibrinolytic agents (rt-PA and single-chain urokinase plasminogen activator [scu-PA]) are more effective in achieving early patency than nonselective agents (SK, urokinase, APSAC) (76-82). Table 2 lists studies which assessed early patency or recanalization; there is a clear advantage with rt-PA versus SK, which is likely to be even greater with front loaded rt-PA. Ultimately, there is a catch-up so that patency by 24 h and at discharge is similar with all the agents. Recently, front-loaded doses of rt-PA administered over 90 mins have been shown to result in early patency rates of 80 to 90% (60 min patency of 74%), thus enhancing the potential for myocardial salvage and survival (76,83) compared with the previously suggested 3 to 6 h regimens. There continues to be a catch-up phenomenon so that 24 h patency is similar with different agents (76,80). Reocclusion results in poor LV function and a mortality rate which is similar to that in patients who do not achieve patency in the first instance (3,11,84). Although there are data which suggest that a combination of a clot-selective agent with a nonselective one may reduce the rate of reocclusion (85,86), this was not confirmed in the combined rt-PA/SK arm of the GUSTO study. No difference in improvement of LV ejection fraction following therapy with the different agents has been demonstrated (10,82,87,88) (Table 3).

Adjunctive heparin therapy: The importance of administration of iv heparin with rt-PA to optimize infarct-artery patency has been clearly demonstrated. Although immediate administration of heparin may not be important (89), the studies of Hsai et al (80 mg ASA, catheterization at 18 h) (90) and Bleich et al (no ASA, catheterization at 40 h) (91) have shown that early patency is reduced substantially when heparin is not administered with rt-PA. In the study reported by the European Cooperative Study Group (250 to 300 mg ASA, catheterization at 81 h) (92), a higher late patency rate was observed in patients who were given heparin despite the expected catch-up. This difference was greater in patients in whom the activated partial thromboplastin time was in the therapeutic range compared with those in whom it was subtherapeutic. Other data suggest that the important benefit from iv heparin is in the first 24 h and that it is not required beyond that time as long as antiplatelet therapy is administered (93). There are data to suggest that heparin may be of marginal value in patients treated with SK (94,95), but the GUSTO trial has shown no difference in outcomes between the sc and the iv dose regimens.

In recent studies comparing mortality with different agents (SK, rt-PA and APSAC), heparin was administered subcutaneously after delays of either 4 or 12 h. As well, the subcutaneous heparin dose used has been shown to result in subtherapeutic levels in a substantial proportion of patients until more than 24 h after initiation. Thus, it may be that heparin was administered too late and at too low a dose to optimize infarct-artery patency in patients given rt-PA, ie, when most needed during the first 24 to 48 h. Indeed, early patency rates without heparin are similar to those achieved with SK. There is reason to hypothesize that optimal adjunctive heparin therapy might improve survival in patients treated with rt-PA, perhaps to a greater degree than in those treated with SK or APSAC. This hypothesis is supported by the results of the GUSTO trial.

TABLE 3

Ejection fraction in randomized comparison trials (streptokinase, urokinase or APSAC versus rt-PA

Study	n	Non-selective (%)	Selective (%)
TIMI (78)	290	50	49
White (112)	271	58	58
PAIMS (82)	171	55	53
Taylor (113)	200	52	52
GAUS (81)	246	55	55
TAMI-5 (85)	384	54	54
CRAFT (114)	408	53	53
TAPS (76)	433	57	57
Macheourt (115)	168	50	52

SUMMARY

- Early reperfusion during AMI results in myocardial salvage, recovery of function and reduced mortality (level I). This can be achieved with all of the currently available thrombolytic agents (level I).
- Benefits from late reperfusion are not proven but there are data which suggest that delayed reperfusion is better than persistent occlusion (level II).
- There is now clear evidence that accelerated dose rt-PA (plus heparin) is more effective in reducing mortality than is SK (plus heparin) or a combined regimen of rt-PA/SK (plus heparin) (level I). Soon-to-be published data will refine the extent to which different subgroups benefit and will provide a basis from which to select the most appropriate agent in individual patients. The overall benefit was the reduction of one death per 100 patients treated with rt-PA compared with SK, while the absolute benefit varied considerably among patient subgroups.

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Coronary thrombolysis: Hemorrhagic complications

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Bleeding is the major side effect of thrombolytic therapy. It usually occurs at the site of vascular invasion but can be spontaneous. Intracranial bleeding is the most feared bleeding complication occurring at a rate of 0.3% and 1% in patients treated with SK, anistreplase or APSAC or rt-PA. Bleeding is an inevitable consequence of the effects of plasmin-mediated proteolysis. The frequency and severity of bleeding is influenced by the use of invasive procedures, by other patient-related factors and by the concomitant use of anticoagulant therapy.

Plasmin produces dissolution of fibrin in the hemostatic plug, the main mechanism for bleeding. It also cleaves fibrinogen, factor V and factor VIII to produce a systemic hypocoagulable state. The proteolysis of fibrin and fibrinogen results in elevated plasma levels of plasmin-induced fibrin/fibrinogen degradation products which can act as thrombin inhibitors, interfere with fibrin polymerization and become incorporated into the fibrin component of hemostatic plugs to render them more susceptible to lysis. Platelet dysfunction may also play a role in the bleeding associated with thrombolytic therapy (1-3). Plasmin can cleave the platelet surface receptors glycoprotein Ib (GpIb) and glycoprotein IIb/IIIa (GpIIb/IIIa) which are important for platelet adhesion and aggregation.

The plasminogen activators, SK and urokinase, have minimal fibrin specificity and always induce plasma proteolysis when administered systemically in doses that induce thrombolysis. APSAC has only moderate fibrin specificity while rt-PA is fibrin specific and can induce fibrinolysis without inducing a plasma proteolytic state; although when administered in clinically recommended doses it usually induces some degree of plasma proteolysis. Despite these differences in fibrin specificity, clinical studies in patients with AMI have shown that bleeding complications occur with equal frequency with the nonspecific plasminogen activators and the fibrin specific plasminogen activators (see below); findings which suggest that lysis of fibrin in the hemostatic plug is the major mechanism for bleeding.

While there is no doubt that thrombolytic therapy increases the risk of bleeding, reliable estimates of the true incidence of bleeding in different clinical situations and in different subgroups of patients are difficult to obtain. This difficulty exists because the studies in which the incidence of bleeding was carefully documented using quantitative and explicit criteria are relatively small, because the definition of major bleeding differed between studies and because the large multicentre studies focused on mortality and reinfarction as the outcomes and might have under-reported bleeding complications. In addition, some of the studies included the use of iv heparin and/or invasive procedures. The very large trials do, however, provide unbiased estimates of the relative incidence of bleeding when different thrombolytic agents are compared with each other or an untreated control. In general, the definition of major bleeding includes cases of fatal bleeding, intracerebral bleeding, bleeding which produces permanent morbidity, retroperitoneal bleeding, bleeding requiring operative intervention and bleeding requiring blood transfusion. Intracerebral bleeding is the most important cause of major bleeding during and immediately after thrombolytic therapy and is listed separately in many of the studies.

In this section, the trials reporting on the incidence of bleeding during thrombolytic therapy will be discussed in the following categories: trials comparing thrombolysis with conservative care or placebo; small trials comparing different thrombolytic agents some of which used explicit criteria to assess bleeding and so provide reliable estimates of the absolute rates of bleeding

complications; large trials comparing different thrombolytic agents which provide reasonably reliable estimates of relative risks of bleeding, but which probably underestimate the absolute incidence of bleeding; and trials comparing an invasive to a less invasive strategy in the setting of coronary thrombolysis. In this context, an invasive procedure is defined as cardiac catheterization performed to assess infarct related artery patency.

TABLE 1

Thrombolysis in the treatment of myocardial infarction*

Study	Treatment	Number of patients	Major bleeds (%)	Intracranial bleeds (%)
GISSII (4)	SK	5860	19 (0.3)	-
	Control	5852	-	-
ISIS2 (5)	SK	8592	46 (0.6)	27 (0.31)
	Control	8595	18 (0.2)	13 (0.15)
European (9)	rtPA	366	5 (1.4)	5 (1.4)
Cooperative	Placebo	355	1 (0.3)	1 (0.3)
ASSET (10)	rt-PA	2512	35 (1.3)	7 (0.28)
	Placebo	2493	12 (0.4)	2 (0.08)
AIMS (16)	APSAC	502	25 (5)	5 (1)
	Placebo	502	9 (1.8)	2 (0.3)

**All studies noninvasive; Both groups received intravenous heporin; Both groups received intravenous heparin after 6 h*

TABLE 2

Thrombolysis in the treatment of myocardial infarction*

Study	Treatment	Number of patients	Major bleeds (%)	Intracranial bleeds (%)
European Co operative (6)	SK* Placebo	156 159	2 (1.3) 1 (0.6)	2 (1.3) 0
White (7)	SK Control	107 112	1 (1) -	0 0
ISAM (8)	SK* Control	859 882	51 (5.9) 13 (1.5)	4 (0.5) 0
Collen (12)	rt pA Placebo	31 14	0 0	0 0
Verstraete (13)	rtPA Placebo	62 62	0 1 (1.6)	0 0
Guerrci (11)	rtpA Placebo	72 66	7 (10) 5 (7)	0 0
Topol (14)	rtPA Placebo	75 25	5 (6) 1 (4)	1 (1.3) 0
TPAT(15)	APSAC* Control	59 56	1 (1) 3 (6)	0 0
Ikram (17)	APSAC* Control	76 73	0 0	0 0
Julian (18)	APSAC* Control	45 45	0 0	0 0
Bossaert (19)	APSAC* Control	48 39	5 (10) 0	0 0
Croyden (20)	APSAC*	35	0	0

	Control	30	0	0
Meinertz (21)	APSAC*	69	5 (7)	0
	Control	61	4 (6)	0

**Noninvasive studies, invasive studies. Intravenous heparin given*

Tables 1 and 2 present the results of trials in which patients were treated with either SK or control (4-8), rt-PA or control (9-15), and APSAC or control (16-21). The larger trials are summarized in Table 1 and the smaller trials in Table 2. The reported rates of major bleeding are highly variable but in four of the five large trials, the incidence of major bleeding (including intracranial bleeding) was higher in the patients receiving thrombolytic therapy (level I). The exception is the GISSI-1 study (4) in which the reported incidence of major bleeding with SK was very low (0.3%) with no reported intracerebral bleeds in 5860 treated patients. This very low incidence of major bleeding probably represents under-reporting of bleeding rates. The incidence of major bleeding in the ISIS-2 study (5) of 8592 patients randomized to the SK group was also low (0.6%) but three times higher than the placebo group ($P < 0.001$). The incidence of intracranial hemorrhage was also low (0.31%) but significantly higher than in the placebo group ($P<0.02$). In contrast in the ISAM study (8) of over 1700 patients, the reported incidence of major bleeding was almost 10-fold higher than the in ISIS-2 study (5) for both the SK (5.9%) and control (1.5%) groups ($P<0.001$), while the incidence of intracranial bleeding was reported to be 0.5% versus 0.0% respectively (not significant). Intravenous heparin was used in the ISAM study (8) and this could have contributed to bleeding. Two relatively large studies have compared rt-PA with placebo. The ASSET study (10) included 5011 patients and reported over a threefold increase in the incidence of major bleeding (1.3% versus 0.4%; $P<0.05$) and intracranial bleeding (0.28% versus 0.08%; $P<0.05$) in the rt-PA group. A similar relative increase in major bleeding (1.4% versus 0.3%) and intracranial hemorrhage (1.4% versus 0.3%) was reported in the rt-PA group of the European Cooperative study (9) which included 721 patients (level I). The only study using APSAC, the AIMS study (16) which included a relatively large sample (1004 patients) reported an approximately threefold higher

incidence of major bleeding (5% versus 1.8%) and of intracranial bleeding (1% versus 0.3%) in the APSAC group (level I).

Thus, there appears to be a greater than threefold increase in major bleeding (level I) and a two- to fourfold increase in intracranial bleeding with thrombolytic therapy (level I). The incidence of intracranial hemorrhage in the larger studies varied between 0.3 and 1.4% for an absolute increase of 0.2 to 1.0%; this appeared to be lower in patients treated with SK than with rt-PA or APSAC.

Bleeding complications in small trials comparing thrombolytic agents are summarized in Table 3 (23-28,30). There was no apparent difference in the incidence of major bleeding between the different agents and there was a tendency for major bleeding to be more common in the trials which used invasive procedures (level IV).

TABLE 3

Small comparative studies of thrombolytic agents in myocardial infarction

Study	Treatment	Number of patients	Major bleeds (%)	Intracranial bleeds (%)
Invasive				
Baussaud (23)	rt-PA	84	2 (2)	0
	APSAC	85	1 (1)	0
TIMI-1 (24)	rt-PA	143	41 (29)	0
	SK	147	39 927)	0
Verstraete (25)	rt-PA	64	2 (3)	0
	SK	65	4 (6)	0
TAMI-5 (30)	rt-PA	191	17 (8.7)	4 (2.1)
	UK	190	19 (10)	3 (1.5)
	Combination	194	23 (12)	0
TAPS (26)	rt-PA	217	6 (2.8)	2 (1)
	APSAC	216	17 (8.1)	2 (1)
Noninvasive				
Anderson (27)	APSAC	188	8 (4)	1 (0.5)
	SK	182	7 (4)	0
White (22)	rt-PA	135	3 (2.1)	2 (1.4)
	SK	135	1 (1)	0
PAIMS (28)	rt-PA	86	8 (9)	0
	SK	85	6 (7)	1 (1)

rtPA Recombinant tissueplasminogen activator; SK Streptokinase; UK Urokinase

TABLE 4

Large comparative trials of thrombolytic therapy in myocardial infarction

Study	Treatment	Number of patients	Major bleeds (%)	Number of patients	Intracranial bleeds (%)
GISSI - 2 (29)	SK rt-PA	10028 10067	64 (0.6) 96 (0.9)	10028 10067	44 (0.4) 30 (0.30
ISIS - 3 (30)	SK APSAC	13569 13607 13599 138 (1.0)	13569 13607 13599	89 (0.7) 32 (0.2) 75 (0.6)	
GUSTO (31)	rt-PA/IV heparin SK/sc heparin SK/IV	109 (0.8) 118 (0.9) heparin rt-PA/SK/IV heparin	9222 8663 9249 9184	32 (0.4) 29 (0.3) 48 (0.5) 52 (0.6)	10268 9709 10314 10248

iv Intravenous; rtPA Recombinant tissueplasminogen activator; sc Subcutaneous; SK Streptokinase

The three large trials comparing different thrombolytic agents are summarized in Table 4. In the GISSI-2 International Trial (29), 20,891 patients were randomized in a factorial design to receive either rt-PA or SK in combination with subcutaneous heparin or no heparin. Heparin was given in dose of 12,500 units starting 12 h after the initiation of the thrombolytic agent infusion and continuing on a twice daily schedule until hospital discharge. All patients were also treated with ASA 325 mg/day. The rate of major bleeding was higher with SK (0.9%

versus 0.6%, P<0.05). The total stroke rate was higher with rt-PA (1.3% versus 0.9%, P<0.05), and the incidence of definite hemorrhagic strokes was slightly more frequent in patients assigned to rt-PA (0.4% versus 0.3%) (level II). The use of subcutaneous heparin increased the incidence of major noncerebral bleeds from 0.55% to 0.99% (P<0.001), but did not appear to influence the incidence of intracranial bleeds (0.35% versus 0.37%) (Table 5).

The ISIS-3 trial (30) which also employed a factorial design included 41,299 patients. Patients were randomly allocated to receive SK, rt-PA, or APSAC and within each thrombolytic group were randomized to receive subcutaneous heparin 12,500 units every 12 h versus no heparin, beginning 4 h after the initiation of the thrombolytic agent and continued until hospital discharge. All patients received ASA 162 mg/day. The total stroke rate was 1.4% with rt-PA, 1.3% with APSAC, and 1.0% with SK; this difference was accounted for mainly by the `probable' cerebral hemorrhage rate which was 0.66% with rt-PA, 0.55% with APSAC, and 0.23% with SK; P<0.05 for SK compared with the other two groups. No differences were detected in `major' bleeding rates, which were 0.8% with rt-PA, 1.0% with APSAC and 0.9% with SK (Table 4). The use of heparin was associated with an increase of noncerebral major bleeds of 0.26% (1.2% versus 0.75%; P<0.01); and an increase of intracranial bleeds of 0.16% (0.56% versus 0.40%; P<0.05) (Table 5).

The recently completed GUSTO study (31) randomly allocated patients with evolving MI to four different strategies consisting of accelerated rt-PA plus heparin 5000 U iv bolus followed by a 1000 to 1200 U/h continuous infusion for at least 40 h with activated partial thromboplastin time (APTT) monitoring, or a combination of rt-PA and SK with iv heparin, or SK with iv heparin, or SK with subcutaneous heparin 12,500 U q12h for seven days (or until prior discharge). The rates of hemorrhagic stroke were 0.72% (rt-PA), 0.94% (rt-PA/SK), 0.54% (SK/iv heparin), and 0.49% (SK/sc heparin); this represents a significant excess of events in the rt-PA group compared with SK (P=0.03). The combined end-point of death or nonfatal hemorrhagic stroke was significantly reduced for the rt-PA group compared with the SK strategies (6.6% versus 7.5%, P=0.04). There was no difference in extracranial bleeding between the SK and rt-PA groups. The incidence of severe or life-threatening bleeding was 0.4% (rt-PA iv heparin), 0.5%

(SK/iv heparin) and 0.3% (SK/sc heparin). The incidence of moderate or severe bleeding was 5.4%, 6.3% and 5.8%, respectively. Thus, the improved survival seen in the rt-PA/high dose iv heparin group was associated with a small increase in the risk of hemorrhagic stroke and no increase in major extracranial bleeding.

The GUSTO study (31) showed no significant difference in hemorrhagic strokes or major extracranial bleeding between the iv and sc arms of the SK group.

The trials in which patients were randomized to an early invasive (cardiac catheterization) strategy or no early invasive strategy are summarized in Table 6. The incidence of major bleeding (but not of intracranial bleeding) in four of these studies was 10-fold higher in the noninvasive groups than in the very large trials (GISSI-I, GISSI-2, ISIS-2 and ISIS-3). However, iv heparin was used in both arms of the TAMI and TIMI studies and could have contributed to bleeding. The TAMI-I (Thrombolysis and Angioplasty in Myocardial Infarction) trial compared immediate angioplasty with deferred angioplasty in patients with successful thrombolysis with rt-PA (32). Both groups had a diagnostic cardiac catheterization immediately after thrombolytic therapy and the reported incidence of major bleeding was approximately 30%. The SWIFT study, in which all patients received APSAC, compared a strategy of early angiography and angioplasty in selected patients with a strategy of coronary angiography only in patients with clinical complications (33). There was a greater than 10-fold increase in the incidence of major bleeding in the group randomized to early angiography (level I). The TIMI-II (2,24) investigators carefully evaluated the effect of invasive procedures on rt-PA-induced bleeding. Patients in the TIMI-IIA study were randomized to immediate angiography after initiation of thrombolysis or to predischarge angiography (34). Those assigned to early intervention had a 20% transfusion rate compared with 7.2% of patients assigned to predischarge angiography (level 1). Patients in the TIMI-IIB study were randomized to early angiography (18 to 48 h after thrombolysis) or to angiography only if clinically indicated (35). In this relatively large study of 3339 patients, those assigned to early angiography had an moderate increase in hemorrhagic complications which occurred predominately at sites of vascular invasion (level II). The overall incidence of major bleeding was high in both groups. The incidence of intracranial bleeds in the 3648 rt-PA-treated patients in TIMI-II studies was 0.77%.

The TAMI-5 trial used a 3x factorial design to compare three thrombolytic agents with two catheterization strategies. The catheterization strategies were immediate angiography with angioplasty only in patients with failed thrombolysis and deferred (predischarge) angiography (36). There was a relatively high incidence of major bleeding in both groups.

RISK FACTORS FOR INTRACRANIAL BLEEDING

Intracranial bleeding is the most feared complication of thrombolytic therapy. A number of risk factor have been identified through subgroup analysis of the larger studies (levels III and IV).

Central nervous system bleeding appears to be more common in elderly patients (37,38). In the GISSI-2 International Study (29), increasing age was associated with an increase in stroke rates whether patients were treated with SK or rt-PA. Thus, the incidence of stroke was 2.7% with rt-PA and 1.6% with SK in patients over 70 years and 0.9% for rt-PA and 0.8% for SK in patients under the age of 70. In the TIMI-II study (35), there was a significantly increased frequency of intracerebral hemorrhagic with age, when age was treated as a continuous variable.

Uncontrolled hypertension is generally considered to be a risk factor for intracranial hemorrhage after thrombolytic therapy, but data supporting this contention is rather sparse. In ISIS-2 (5), the mortality in the SK group of patients with systolic hypertension (more than 175 mmHg) was lower (7.2%) than in those treated with placebo (8.7%). In TIMI-II (35), there was a strong (nonsignificant) trend for an increased incidence of intracranial hemorrhage among patients with a history of chronic hypertension compared to patients without a history of hypertension (0.9% versus 0.4%) (level IV).

A dose effect on bleeding was suggested by the results of the TIMI-II study (35). Thus, the incidence of intracerebral hemorrhage was significantly reduced when the dose of rt-PA was lowered from 150 to 100 mg (level IV). The validity of the observed dose response relation is confounded because the entry criteria were made more restrictive when the dose was lowered. Indirect evidence for a dose effect is provided by the observation that patients who weigh less

seem to have a greater risk of bleeding complications (39); these patients have higher rt-PA plasma concentrations and have a greater plasma lytic state and more fibrinogenolysis.

In TIMI-II (35), the use of calcium channel blockers was associated with increased frequency of intracerebral hemorrhage (level III). The mechanism for this observed association is not clear, although these agents inhibit platelet aggregation (40,41). Beta-blocker therapy has been reported to be associated with a lower incidence of intracranial hemorrhage (42) (level IV).

The association between an increased incidence of intracranial hemorrhage and a prior history of stroke is unclear. In the TIMI-II study, patients with a prior history of cerebrovascular disease within six months were excluded. In the early stage of the study, three of 30 patients who had a history of stroke, intermittent cerebral ischemia attack, or other neurological disease, developed an intracerebral hemorrhage. As a consequence, the protocol was changed so that patients with a past history of stroke or intermittent cerebral ischemic attacks were ineligible (43).

Thus there is evidence from subgroup analysis of prospective studies (level IV) that there is a higher risk of intracranial hemorrhage in the elderly, in hypertensive patients and in those of low body weight. Patients with a history of recent head trauma or prior cerebrovascular disease are likely also to be at increased risk (39).

TABLE 5

Influence of heparin on incidence of bleeding

Study	Regimen	Heparin	Control	Difference	Heparin>	No heparin	Difference
GISSI - 2 (29)	12,500 U sc q12h start- ing 12h after TT	0.99	0.55 P<0.001	0.44	0.35	0.37 NS	-0.02
ISIS - 3 (30)	12,500 U sc q12h start- ing 4h after TT	1.02	0.75 P<0.01	0.27	0.56	0.40 P<0.05	0.16

Patients in the GISSI2 trial were randomly allocated to receive either streptokinase (SK) or recombinant tissuetype plasminogen activator (rt-PA) treatment and those in the ISIS3 trial to receive either SK, rtPA or APSAC treatment independently of the allocation to heparin treatment (fact design). sc Subcutaneously. TT Thrombolytic therapy

TABLE 6

Trials comparing invasive and noninvasive approaches in myocardial infarction*

Study	Drug therapy	Catheterization strategy	Number of patients	Major bleeds (%)	Intracranial bleeds (%)
TAMI1 (32)	rt-PA	Acute PTCA	99	33 (33)	1 (1)
		Deferred PTCA	98	30 (31)	0
TIMI-IIa (34)	rt-PA	Acute angiography	195	39 (20)	1 (0.5)
		Deferred angio- graphy	195	14 (7)	1 (0.5)

TIMI-IIb (35)	rt-PA	18-48h angiography No angiography	1636 1626	254 (15.5) 206 (12.7)	14 (0.9) 12 (0.7)
SWIFT	APSAC	18-48h angiography No angiography	397 403	79 (20) 5 (1.6)	0 2 (0.5)
TAMI-5 (36)	rt-PA, UK Combina-tion	Acute catheteriza-tion; Deferred catheterization	287 288	32 (11) 28 (9.6)	3 (1.0) 4 (1.4)

**All patients received Intravenous heparin. Heparin therapy delayed for 4 to 6 h and bolus dose omitted. rtPA Recombinant tissuetype plasminogen activator, SK Streptokinase; UK Urokinase*

MAJOR NONCEREBRAL BLEEDING

The degree of vascular invasion was the strongest risk factor for bleeding complications (level I) (44). Bleeding was increased substantially with insertion of an intra-aortic balloon pump following thrombolytic therapy (45).

Combined ASA and rt-PA administration has been shown to prolong template bleeding times and increase bleeding (10). In ISIS-2, ASA use increased the incidence of minor hemorrhagic events but did not affect the risk of major events, even when combined with SK.

In the GISSI-2 (29) and ISIS-3 (30) studies, the addition of moderate doses of heparin to thrombolytic therapy produced a small but significant increase in major bleeding (level I). In the GUSTO study, comparison between the iv and sc heparin groups of the patients treated with SK revealed no significant differences in the roles of hemorrhagic stroke (0.54% versus 0.49%, respectively) of severe, life-threatening bleeding (0.5% versus 0.3%, respectively).

RELATIONSHIP BETWEEN BLEEDING AND LABORATORY TESTS OF FIBRINOGENOLYSIS AND IMPAIRED PLATELET FUNCTION

Subgroup analysis of cohort studies has demonstrated a relationship between the incidence of bleeding during thrombolytic therapy and the following abnormalities of hemostasis: low plasma fibrinogen, elevated fibrinogen degradation products (2,39,46), increase in the bleeding time, and a reduction in the platelet count (1,2,39,46). Although statistically significant, none of these laboratory findings is useful clinically in predicting the risk of bleeding in individual patients.

MANAGEMENT OF BLEEDING

The management of bleeding is influenced by the site of bleeding, its severity, its temporal relationship to infusion of thrombolytic agent, and by the concomitant use of heparin. The systemic (and potentially reversible) factors which contribute to bleeding are: coagulopathy produced by hyperplasminemia caused by the combination of hypofibrinogenemia and increased fibrinogen degradation products, and the reduction of factors V and VIII; and the increase in fibrinolytic activity produced by circulating plasminogen activator. The coagulopathy can be reversed by cryoprecipitate which contains fibrinogen and factor VIII, and by fresh frozen plasma which also contains factor V. The plasma fibrinolytic activity can be reversed by infusion of a plasmin inhibitor, either epsilon amino caproic acid or aprotonin. In practice, management of bleeding is not influenced by the results of laboratory tests because treatment decisions cannot be delayed until the results are obtained. A coagulation screen consisting of a prothrombin time, activated partial thromboplastin time, thrombin time and platelet count should be sent to the laboratory to obtain baseline values, but there is little point in performing tests of fibrinolytic activity because they cannot be obtained in a time-frame to influence management.

If bleeding is mild to moderate and from an accessible site of vascular invasion, local measures, such as direct compression of the bleeding site, should be applied. If bleeding is more severe but not life threatening, the infusion of a thrombolytic agent and/or heparin should

be stopped and blood replaced as necessary and replacement of coagulation factors by blood products should be considered as described below.

If bleeding is life threatening, the thrombolytic agent and/or heparin should be stopped and the potential hypocoagulable state reversed by replacement with blood, cryoprecipitate and fresh frozen plasma. Cryoprecipitate contains 250 mg fibrinogen per 5 mL; therefore, 20 units should supply enough fibrinogen to obtain adequate hemostasis. An equivalent amount of fibrinogen is contained in 10 units of fresh frozen plasma (500 mg fibrinogen per 200 mL), but in a much larger volume. If rapid reversal of coagulopathy is required, cryoprecipitate should be infused quickly and followed by a slower infusion of fresh plasma.

If the bleeding occurs during or within a few hours of the thrombolytic infusion, and is severe, reversal of the presumed coagulopathy might have to be combined with infusion of a plasmin inhibitor. Intracranial bleeding is the most serious complication. It should be treated with infusion of blood products (cryoprecipitate and fresh plasma) and, if it occurs during or within a short time of stopping thrombolytic therapy with epsilon amino caproic acid to inhibit the plasminemia. The starting dose is 5 g diluted in 250 mL D5W run in over an hour, and then 1 g/h, depending upon the effect on the coagulation profile. Aprotinin can also be used.

CONCLUSIONS

Bleeding is the most common and most important side effect of thrombolytic therapy.

- The risk of stroke and intracranial bleeding appears to be higher with rt-PA and APSAC than with SK (level I), although the magnitude of this difference is small.
- The risk of extracranial major bleeding is essentially the same for three thrombolytic agents (SK, rt-PA, APSAC) when used in the approved dose ranges (level I). Thus, the expectation that the increased fibrin specificity and reduced fibrinogenolytic effect of rt-PA would result in less bleeding has not been born out by the results of clinical trials.
- Invasive procedures are the most important predisposing factors to major extracranial bleeding (level I).

- The risk of major extracranial bleeding with thrombolytic therapy is increased by older age, smaller size, and female sex (level III). These three factors plus prior cerebrovascular disease and possibly a history of hypertension are risk factors for intracranial bleeding. These markers for bleeding are not contraindications to therapy (level III).

- The concomitant use of heparin or oral anticoagulants increases the risk of major bleeding but aspirin appears to have minimal or no effects on major bleeding (level I for heparin).

- There is a small, nonsignificant difference in the incidence of bleeding with iv heparin compared with sc heparin in patients treated with SK.

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Nonhemorrhagic complications

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The concern that successful reperfusion of the ischemic myocardium would result in the genesis of life threatening arrhythmia, thereby limiting the effectiveness of thrombolytic therapy has not been realized.

Although sudden reperfusion in the animal model frequently leads to ventricular tachycardia or

ventricular fibrillation (1,2), in man this has not proven to be a problem. Reperfusion following thrombolytic therapy has been associated with an increased frequency of salvos/couplets; however, the incidence of ventricular tachycardia and fibrillation has been the same or slightly less relative to control groups (3-6). The frequency of bradyarrhythmias (5-7) have either been the same or slightly decreased in patients receiving thrombolytic agents.

A reduced frequency of primary ventricular fibrillation (VF), late VF and VF secondary to cardiogenic shock has been described (8). This potential beneficial result has been further supported by the GISSI investigators (4), who demonstrated an overall reduction in the frequency of secondary VF by 20% in patients who received SK. In this study, secondary VF was defined as VF complicating AMI associated with any degree of clinical heart failure or shock. This protection appeared to be primarily in a reduced incidence of late VF occurring after the first day of hospitalization. In GISSI-2 (9), sustained ventricular tachycardia (VT), VF and asystole was similar in the rt-PA and SK groups.

The value of prophylactic administration of antiarrhythmic drugs before thrombolytic therapy has not been formally assessed; however, caution has been advised in the use of prophylactic lidocaine in patients with suspected or proved MI. A meta-analysis of the use of lidocaine in patients with AMI has demonstrated a trend to reduction of VF, but also a trend towards higher mortality among the lidocaine patients (10). It is difficult to comment on the impact of beta-blockers on arrhythmias following thrombolytic therapy. The reported reduced incidence of arrhythmia in the treated group may reflect a patient selection bias and the tendency not to give beta-blockers to patients with evidence of more impaired LV function and, hence, heightened risk of arrhythmia (11).

ALLERGIC REACTIONS

A wide range of possible allergic reactions has been reported in patients receiving thrombolytic therapy. These range from the more common, yet less serious, reactions (fever, chills, skin rash) to the more serious anaphylactic reactions (bronchospasm, shock). Both SK and the SK component of APSAC are produced by group C beta hemolytic-streptococci and, as foreign

proteins, potentially can interact with previously formed antibodies in man. Some evidence exists that anaphylaxis with SK is mediated by a SK-specific immunoglobulin (Ig) E (12). Late allergic manifestations following the administration of these agents are compatible with an immune complex disease caused by IgG-SK immune complexes.

Experience from large clinical trials indicates that allergic reactions are generally mild, and are not associated with any increased risk of death. Minor allergic reactions with SK range from 0.7 to 3.5% (3,9,13), with about a fivefold excess over placebo. With SK, the reported incidence of anaphylactic shock was 0.1% in GISSI-1 (3), and 0.2% in ISIS-2 (13). However, in the latter study, a posttrial review of cases cast some doubt as to whether individual cases were correctly diagnosed. In the AIMS trial (14), a pruritic rash was associated with APSAC in 0.7% of patients and anaphylaxis was seen in only 0.4% of patients.

Fewer suspected allergic reactions occur with rt-PA than with SK or APSAC. Minor allergic reactions occurred in 0.2% of patients receiving rt-PA versus 2% receiving SK. (9) Comparison of allergic reactions associated with rt-PA, SK and APSAC therapy in ISIS-3 confirmed this trend (15). Allergic reactions were reported more commonly with SK than rt-PA (3.6% SK versus 0.8% rt-PA, $P<0.0001$). About one in 10 were classified as causing persistent symptoms (0.3% versus 0.1%, $P<0.001$). Allergic reactions occurred in 5.1% of patients with APSAC therapy, which was significantly greater than with either SK or rt-PA ($P<0.0001$).

When allergic reactions are produced by SK, they generally resolve without any specific treatment other than slowing or discontinuing the infusion (15). Intravenous fluids may be required to restore blood pressure. Rarely, treatment for a severe anaphylactic reaction is required. The fact that APSAC is given as a bolus over several minutes may account for the increased incidence of allergic reactions reported. The prophylactic use of steroids is not recommended prior to therapy since allergic reactions were not significantly reduced in the subgroup of patients receiving prophylactic steroids in ISIS-2 (level III). Furthermore, severe anaphylaxis has been documented in a patient pretreated with hydrocortisone (12). Since severe allergic reactions are fortunately rare, the proposal to use SK skin tests (16) to detect patients at risk for immediate-type allergic reactions to SK therapy does not appear warranted.

In summary, the overall risk of allergic reactions from thrombolysis is small (less than 5% with SK and APSAC, much less with rt-PA). Serious allergic reactions are extremely rare, and this possibility should not deter the physician from administering a thrombolytic agent for AMI. Prophylactic steroids are of no demonstrated value.

HYPOTENSION

The various factors leading to hypotension in the patient with AMI must be quickly identified and treated. The leading causes of hypotension in this setting include severe LV dysfunction, right ventricular infarction and dysfunction, and volume depletion. Patients receiving thrombolytic therapy have the added risks of anaphylaxis, autonomic reflex activity (Bezold-Jarisch), bleeding and other direct/indirect effects of thrombolytic agents. One such factor is the increased production of bradykinin as a result of the increased plasmin in the systemic circulation. The hypotensive effects of iv SK have been carefully studied by Lew et al (17). Infusion of SK will result in a fall in systolic pressure of greater than 10% of baseline in the majority (more than 85%) of patients. In approximately 10% of patients, systolic pressure will fall to below 80 mmHg, and in another 10%, below 70 mmHg. These changes occurred despite pretreatment with steroids. The fall in blood pressure is associated with an increased heart rate, which is distinct from the bradycardia and hypotension seen following successful reperfusion of the inferior wall (18). The magnitude of the hypotension is related to the rate of infusion of SK and is similar in patients with either anterior or inferior infarction (17).

In clinical trials, hypotension is documented in approximately 10% of patients receiving SK (13) or APSAC (14). In the GISSI-2 study, severe hypotension was observed in 4.4% with SK, and only 2% with rt-PA. In ISIS-3, hypotension with SK (11.8%) and APSAC (12.5%) was more frequent than with rt-PA (7.1%, $P<0.0001$). Hypotension requiring treatment was identical among APSAC and SK-treated patients (7%) and was less with rt-PA (4.4%, $P<0.0001$). Given these findings, it has been suggested that rt-PA might be the agent of choice in patients with a low baseline blood pressure. However, clinical trial data do not support this suggestion. In GISSI-2 (9), the in-hospital mortality rate of Killip class IV patients was 78% in patients treated

with rt-PA and 65% with SK therapy. Because mortality in Killip class IV patients has remained high despite thrombolytic therapy (3,9), every effort must be made to differentiate treatable causes of hypotension from cardiogenic shock in patients being considered for thrombolytic therapy.

ANGINA

Although salvage of myocardium and patency of the infarct-related artery are two of the desired goals of thrombolytic therapy, the resulting viable myocardium in jeopardy could result in residual angina and a greater incidence of reinfarction in the post-MI period. Despite successful thrombolysis, the infarct vessel usually has a severe residual stenosis which has been shown to be associated with subsequent reocclusion (19).

The expected increased incidence of angina following thrombolysis has not been confirmed in clinical trials comparing either SK (3,5) or rt-PA (6) with placebo therapy. Following thrombolytic therapy, patients do not appear to require more revascularization procedures. In GISSI-1, the frequency of PTCA (0.3% versus 0.2%) and CABG (3% versus 2.8%) procedures were similar in the SK and control group during six months of follow-up. Studies involving the direct comparison of rt-PA and SK have failed to demonstrate any difference in the incidence of either post-MI angina (9) or need for angioplasty or surgical intervention (20) at follow-up.

REINFARCTION/REOCCLUSION

The incidence of reinfarction following thrombolytic therapy ranges from 2 to 5%. The clinical diagnosis is generally made on the basis of the presence of two or more of the following: prolonged chest pain, a second rise in cardiac enzymes and new ECG changes. In control trials, those allocated to SK have had an absolute excess of 1 to 2% in the rate of reinfarction (3,5,13) when ASA was not used. Although reinfarction was seen more frequently in the early follow-up, the total incidence of reinfarction after five years was equal in SK and control groups in the Netherlands Trial (21). Further, the risk of reinfarction was not increased in patients with exercise-induced ischemia. Reinfarction following rt-PA has been more variable, ranging from

no difference (6) to an excess of 4 to 5% (22,23). In trials where different thrombolytic agents have been compared, there has been little difference in the rates of reinfarction (9,15,20). In ISIS-3, there were significantly fewer reinfarctions with rt-PA (2.93%) than with either SK (3.47%) or APSAC (3.5%) (P<0.02). In GUSTO, the observed incidence of reinfarction was 4.0% with rt-PA and 3.7% with SK.

Reocclusion of the patent infarct-related artery following successful thrombolytic therapy can occur without significant associated symptoms (24). Reocclusion rates, therefore, can only be established in treatment groups which have undergone repeat angiography to assess the status of the infarct-related artery documented to be patent in the early infarct period. The clinical significance of reocclusion has been established by the TAMI investigators (24). Patients with reocclusion at follow-up angiography had more in-hospital complications and a higher in-hospital mortality rate (11%) compared with those without reocclusion (4.5%) (P=0.01). Further, patients with reocclusion at follow-up had worse infarct segment function and less recovery of both global and segmental function than patients with sustained patency.

Reocclusion rates may be influenced by the pharmacological properties of individual thrombolytic agents. By decreasing circulating fibrinogen and having longer half-lives, agents such as SK and APSAC should theoretically have a lower rate of late rethrombosis than rt-PA. In the TAPS study (25), early reocclusion (24 to 48 h) was documented in 10.3% of patients treated with rt-PA versus 2.5% with APSAC. However, at discharge, reinfarction rates were similar at 3.8 and 4.8%, respectively. Angiographic appearance of the infarct-related artery appears to influence the risk of subsequent reoclussion. Reocclusion following SK therapy occurred in approximately half of patients with a residual luminal cross sectional area less than 0.4 mm2 (19). With rt-PA, TIMI flow and infarct site appeared more important than the degree of residual stenosis. In the TAMI experience (24), reocclusion was greatest in the right coronary artery distribution, and a twofold increase in reocclusion occurred when TIMI flow grade 0 or 1 were demonstrated on the initial angiogram.

The efficacy of various adjunctive therapies, as well as treatment strategies following thrombolytic therapy, have been assessed in several large trials. In ISIS-2 (13), ASA significantly reduced nonfatal reinfarction by 50% (1% versus 2%). Further, the excess nonfatal reinfarction with SK, when used alone, was eliminated by the addition of ASA (ISIS-2). In GISSI-2 (9), the addition of subcutaneous heparin to ASA following either SK or rt-PA failed to significantly reduce the rate of reinfarction post-MI. The beneficial effect of beta-blockade was established in a large subgroup of patients in the TIMI-IIB trial. (26) Those receiving (in addition to rt-PA) immediate metoprolol (up to 15 mg) followed by oral metoprolol had significantly fewer nonfatal reinfarctions or ischemic episodes than did those among whom metoprolol was deferred until six days post-thrombolytic therapy. Finally, prophylactic PTCA offered no advantage from the perspective of reductions in the reinfarction rate over the conservative strategy of performing PTCA only in patients with spontaneous or exercise induced ischemia.

A recent meta-analysis of the effects of ASA on reocclusion rates concluded that treated patients had a reocclusion rate (11%) of less than half that of patients without ASA therapy (27). Although hampered somewhat by sample size, data from the Heparin-Aspirin Reperfusion Trial (HART) (28) suggest that ASA was as effective as heparin therapy in preventing reocclusion. Although early PTCA can be performed with a favourable angiographic result in the majority of patients, a high reocclusion rate appears to limit the usefulness of this approach. In the TAMI-1 trial (29), reocclusion rate after successful PTCA was 29%, despite heparin and ASA.

REPERFUSION FAILURE

Reperfusion failure is defined as a failure to recanalize an initially occluded infarct-related artery (IRA) following thrombolytic therapy. Accurate assessment of the true rate of reperfusion failure requires a pretreatment, baseline coronary arteriogram, as well as subsequent follow-up angiography, to document patency rates. The follow-up patency rate is influenced by the initial recanalization rate, the rate of reocclusion and the length of the follow-up period. To assess the success rate of the individual thrombolytic agents, the impact of spontaneous reperfusion and

reocclusion must be considered, as well as the number of patients dying or having revascularization procedures prior to the repeat angiogram. Spontaneous early recanalization occurs in 10 to 20% of patients with Q wave infarction (29,30), and generally increases throughout the hospitalization phase. The analysis of treatment failure is hampered further by the tendency to avoid the time delay involved in pre-treatment angiography in the majority of trials comparing thrombolytic agents.

Reperfusion success/failure usually is classified according to the TIMI angiographic scoring system, where grade 0 represents no perfusion (absence of contrast beyond the point of occlusion); grade 1, penetration of the thrombus with minimal perfusion; grade 2, partial perfusion; grade 3, complete perfusion (31). Reperfusion failure is generally considered present when perfusion of the IRA is grade 0 or grade 1 following thrombolytic therapy.

The recanalization rates achieved with the commonly used thrombolytic agents have been summarized in two recent reviews (32,33). Estimates of the frequency of early reperfusion failure range from 40 to 70% with iv SK, 40 to 50% with APSAC and 25 to 40% with rt-PA. In the TIMI-1 study (34) (angiography at 90 mins from starting therapy), reperfusion failure was observed in 38% of rt-PA patients and 69% SK patients ($P<0.001$). Although pretreatment angiograms were not performed in the TAPS study (25), patency rates with rt-PA were higher at 60 and 90 mins than with APSAC. However, APSAC therapy resulted in higher patency rates at 24 to 48 h, and the overall patency rates at 14 to 21 days were similar in the two treatment groups, implying that more reocclusion occurred with rt-PA. The findings in this study demonstrate the complexity of judging `success' or `failure' on the basis of an angiogram performed at any specific time following thrombolytic therapy and the potential for an agent with a higher rate of early reperfusion 'failure' to demonstrate a higher rate of coronary patency at a later time, as well as the possibility of greater reocclusion rates with agents associated with the highest rate of early reperfusion.

Several studies have confirmed the prognostic importance of reperfusion failure in patients receiving thrombolytic therapy. Death and other ischemic events are more common in the

treatment failure groups (28,29,34). Given the many problems of relying on emergency angiography to assess the early success or failure of thrombolytic therapy, noninvasive markers reflecting successful reperfusion have been sought. Relief of pain (35), resolution of ST segment elevation (36), sudden appearance of ventricular arrhythmias (37) and early peak in cardiac enzyme release (5) have been associated with successful reperfusion. Unfortunately, with each of these approaches there are limitations to the accurate prediction of perfusion status following thrombolytic therapy. The intensity of pain is difficult to quantitate, tends to decrease as the infarct evolves, and is influenced by both pain medications and sedatives. Detection of shifts in ST segments requires either continuous monitoring or frequent ECG recordings, and may be further affected by coexisting spasm of the IRA (36). Ventricular arrhythmias, including accelerated idioventricular rhythm, salvos and nonsustained VT, are common among AMI patients and are not confined to patients receiving thrombolytic therapy (3,5,6). Finally, creatine kinase release curves require frequent sampling, and this technique is limited by the delayed release of cardiac enzymes into the blood (39), as well considerable overlap of values between successful and failed reperfusion groups.

The value of commonly available clinical markers in predicting perfusion status following thrombolytic therapy has been reported (40). In 96% of patients with complete resolution of ST segment elevation and 84% of patients with complete resolution of chest pain successful reperfusion was demonstrated; however, these findings occurred in only 6 and 29% of patients having thrombolysis, respectively. Further analysis in a stepwise logistic model demonstrated that ST segment shifts contributed most of the predictive information. Unfortunately, no combination of clinical markers yielded diagnostic information with a high enough sensitivity and specificity to be useful at the bedside.

Finally, the question of whether patients with reperfusion failure should be managed more aggressively has been widely debated. In general, data from several studies (26,29,41,42) support a conservative approach, with no advantage of early revascularization. Similarly, delayed in-hospital prophylactic intervention with either PTCA or CABG failed to improve on the results achieved with conservative therapy alone (43).

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Part III: Clinical use of coronary thrombolytic therapy

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Contraindications

There are clear risks to the use of thrombolytic agents as a result of cerebral or other major hemorrhage, excessive hypotension, anaphylaxis, and possibly deleterious effects of early reperfusion (1-3). However, the overall mortality reduction is dramatic and it is clear that any risks of therapy are far outweighed by the benefits. The mortality risk arising from the myocardial infarction varies according to a variety of patient characteristics, while the mortality risk of thrombolytic therapy also varies according to a variety of patient characteristics. The absolute mortality reduction likely to be observed in any group of patients is the resultant of the potential mortality reduction and risk from the therapy. With any medication, certain contraindications are established. These contraindications should ideally define groups of patients among whom: (A) the therapy would be unlikely to confer any benefit; (B) the risk of therapy would be unacceptably high; or (C) the risk of therapy clearly outweighs the potential benefit.

The traditional contraindications to thrombolytic therapy have generally been established in an attempt to identify patients whose clinical symptoms may mimic an AMI (AMI), but who have another diagnosis and could not benefit from thrombolysis, or those who are at such high risk of major complications (usually hemorrhagic) that therapy is unwarranted. The published recommendations have generally been based upon uncontrolled trials and clinical experience (level III, IV, V), have been very conservative and may result in therapy being denied to

patients who could benefit. There are increasing amounts of data available, some of level I quality, allowing a better delineation of the risk of therapy in certain patients. A major effort is being made in the GUSTO trial to gather data on risks of bleeding and other major side effects in relation to the benefits of thrombolytic and antithrombotic therapy (1).

A patient who appears to be developing AMI may in fact have aortic dissection or pericarditis. Thrombolytic therapy could not help and might have disastrous consequences. Clearly these diagnoses must be considered in the patient with apparent AMI, and if there are features strongly suggestive of either diagnosis, thrombolysis is absolutely contraindicated. A patient with uncontrolled major bleeding would be at high risk from thrombolytic therapy and it should not be administered. Patients with known streptokinase (SK) resistance cannot benefit from SK or APSAC, which therefore would be absolutely contraindicated, and recombinant tissue-type plasminogen activator (rt-PA) should be used. A patient with a previous well-documented allergic reaction or anaphalaxis from SK or APSAC therapy has an absolute contraindication to repeat therapy with either agent and should receive rt-PA.

Most of the concerns about thrombolytic therapy and the resultant contraindications relate to the risk of bleeding (1,2, 4-9). The rate of major bleeding ranges from 0.5 to 1% in studies where invasive procedures are not routinely used (4), and is similar with SK, APSAC and rt-PA (10,11). The rate of cerebral hemorrhage ranges from 0.2 to 1% (4) and may be slightly more frequent with rt-PA than with SK (10,11). The major cause of bleeding appears to be lysis of pre-existing hemostatic plugs, rather than the creation of a systemic fibrinolytic state (6). Hence, the following 11 patient parameters define situations of relative contraindication to the use of thrombolytic therapy, and in each instance consideration must be given to potential benefits and risks of therapy.

Cerebrovascular accident: An analysis of the TIMI-II trial suggests that patients with any known history of cerebrovascular disease have a higher risk of cerebral hemorrhage (3.4% versus 0.5%) (8). However, the confidence limits are wide, such a history was not an independent predictor on multivariant regression analysis, some patients were receiving 150 mg of rt-PA and there was no control group. Accordingly the following considerations are appropriate (4,7,8):

- Primary cerebral hemorrhage - probably constitutes a permanent contraindication (level III, IV, V evidence).
- Thrombotic or embolic stroke - probably a contraindication for only two to six months (level III, IV, V).
- Transient ischemic attack - probably not a contraindication after about two months (level III, IV, V).

Intracranial vascular disease: Malignancy, atrioventricular (AV) malformation - probably an absolute contraindication (7).

Previous gastrointestinal (GI) or gastric ulcer (GU) hemorrhage: There are no firm data available, but clinical experience suggests that provided there is no cancer present and symptoms have abated, the risk of repeat hemorrhage is probably low by one to two months following GI or GU hemorrhage. H2 blocker therapy may be prudent in a patient with a history of upper GI hemorrhage. Active symptoms of peptic ulcer in the absence of previous hemorrhage might constitute a relative contraindication to thrombolytic therapy (level IV, V) (1).

Hemostatic plugs:

- Major surgery, organ biopsy, puncture of noncompressible vessel - clinical experience, and laboratory evaluation of clot formation and vascular repair suggest that with hemostasis, following a period of about 10 days, the risk of bleeding is minimal (level III, IV, V) (1,2).
- Major trauma, even minor head trauma - clinical experience indicates the importance of eliciting an appropriate history. A period longer than 10 days may be necessary to ensure safe use of thrombolytic therapy (1,7).

TABLE 1

Absolute risk reductions among certain patient subgroups receiving SK and ASA compared with placebo in the ISIS-2 trial

Patient group	Absolute risk reduction*
All	52
Age (years)	
Younger than 60	26
60 to 69	70
70 or older	80
Sex	
Female	52
Male	53
Diabetes mellitus	
Yes	55
No	51
Prior myocardial infarction	
Yes	42
No	54
Systolic blood pressure (BP) (mmHg)	
100 or less	85
100-124	59
125-149	54
150-174	43
175 or more	30
ECG findings	
Bundle branch block	136
Inferior ST elevation	34
Anterior ST elevation	106
Inferior and anterior ST elevation	54

ST depression	14
Other abnormality	24
Normal	-12

**Lives saved per 1000 patients treated*

Cardiopulmonary resuscitation (CPR): Tenagliu et al (12) found no difference in bleeding rates among 59 patients who underwent less than 10 mins of external massage for cardiac arrest. There were no bleeding complications directly attributable to CPR, and in particular there was no hemothorax and no tamponade. The decrease in hematocrit and requirement for transfusion was no greater than for patients not receiving CPR. Accordingly prior CPR should be a contraindication to thrombolytic therapy only when it has been prolonged, clearly traumatic, or the patient remains unconscious (level III, IV, V).

Diabetic proliferative retinopathy: The risk of ophthalmic hemorrhage is likely to be real but relatively low, and is far outweighed by the potential benefits of thrombolytic therapy in most diabetic patients with AMI (1).

Hypertension: A history of hypertension is found to be predictive of cerebral hemorrhage in some studies, although it is generally not an independent predictor (8). The presence of hypertension on admission is also found to be predictive in some studies (9). It is notable that in the ISIS-2 study (13), the absolute risk reduction among patients with systolic blood pressure greater than 175 mmHg was 3% versus 5.2% overall. However, this was not a high risk subgroup (placebo mortality 8% versus 13.2% overall). It is likely that only the most severe and uncontrolled hypertension should be a contraindication to therapy except in very low risk patients (level III, IV, V).

TABLE 2

Contraindications

Absolute contraindications
Aortic dissection
Acute pericarditis
Active bleeding
Problematic SK antibodies (substitute rt-PA)
Previous well-documented allergic reaction to SK or APSAC – rt-PA should be used
Repeat SK or APSAC therapy is unlikely to be effective when SK neutralizing antibody (NA) levels are markedly elevated. It is recommended that following an initial dose of SK or APSAC, once four days has passed, that neither therapy be repeated, unless measurement of SK NA titre has shown resolution of resistance. rt-PA should be substituted. Routine measurement of SK NA titre at six to 12 months following administration of SK or APSAC may provide further guidance as to the likely efficacy of repeat therapy with SK or APSAC

Relative contraindications
Potential hemorrhagic focus – thrombolytic agents are capable of lysing hemostatic plugs in many locations, and it appears that most hemorrhage occurs as a result of lysis of a hemostatic plug. The risk of bleeding diminishes as the time from formation of a hemostatic plug increases. The following suggestions for time limits following various clinical events are arbitrary and conservative:
at any time – cerebral hemorrhage, known intracerebral vascular disease (malignancy, AV malformation)
within past six months – GI or GU hemorrhage or stroke
within past two to four weeks – major surgery, organ biopsy puncture of noncompressible vessel, prolonged chest compression (CPR) in a patient who has evidence of resulting chest trauma or who remains unconscious, major trauma, even minor head trauma
diabetic proliferative retinopathy
severe, uncontrolled hypertension (systolic BP >200 mmHg and/or diastolic BP >120 mmHg)
Pregnancy
History of bleeding diathesis; hepatic dysfunction, cancer

Pregnancy: There is substantial risk of fetal mortality and premature labour when AMI occurs during pregnancy. However, except when a woman is already in labour, it is likely that any risk of maternal bleeding with thrombolytic therapy is outweighed by the potential benefits of lytic therapy except in very low risk infarction. Menstruation should not be a contraindication to lytic therapy (level IV, V).

Cancer: Metastatic cancer has an increased propensity to bleeding (level III, IV, V) (1,2).

History of bleeding diathesis, current oral anticoagulant therapy: These patients are at increased risk of bleeding in association with thrombolytic therapy and associated antiplatelet and anticoagulant therapy (7,9). However, this should be taken into account and probably with appropriate dose modification, and modification of acetylsalicylic acid (ASA) and anticoagulation therapy some benefit of thrombolytic therapy may still be achieved.

Age: The risk of cerebral and noncerebral bleeding increases with age, but absolute risk reduction increases with age, and therefore age alone is not a contraindication to thrombolytic therapy (7).

Table 1 presents absolute risk reductions in terms of lives saved per 1000 patients treated, among certain patient subgroups receiving SK and ASA compared with placebo in the ISIS-2 trial (13). In this study, the increased risk of major bleeding in the SK/ASA group was four per 1000 patients treated, and of intracerebral hemorrhage was 1.5 per 1000 patients treated. These risks of therapy compare extremely favourably with the overall salvage of 52 lives per 1000 patients treated. Within each patient subgroup, it is possible to determine the potential benefit of therapy and to balance that against the potential risk of life-threatening hemorrhage. A patient with a high risk of death from the MI should receive thrombolytic therapy even if there is a substantial risk of hemorrhage. A patient with a low risk from the MI should not receive thrombolytic therapy if there is a substantial risk of hemorrhage.

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Previous streptokinase therapy

DAVID MASSEL

During the first year following mi, up to 14% of patients will experience a recurrence and may be eligible for repeat thrombolytic therapy (1). However, SK is antigenic and antibodies develop in all patients treated with a conventional dose (2,3). Some of these antibodies have the potential to neutralize the lytic effect of SK. The development and persistence of antibody-mediated resistance to SK has the potential to limit the effectiveness of repeat therapy and would be a clear indication for the use of thrombolytic agents, such as rt-PA, that are not antigenic and not inhibited by these neutralizing antibodies (NA). A similar antibody response develops when SK is complexed with plasminogen as in APSAC. Concern has been expressed that the readministration of SK or APSAC may increase the risk of serious anaphylactic (immunoglobulin [Ig] E-mediated) reactions, although there is no support for this theoretical concern in the literature. However, in the presence of high NA titres, Ig-mediated reactions such as serum sickness and delayed hypersensitivity may occur as suggested by case reports in the literature. Such reactions might be even more likely if the dose of SK were increased in an attempt to overcome the neutralizing capacity of the antibodies. For the purposes of this discussion, SK resistance is defined as a titre of NA that will completely inhibit a conventional 1.5 million unit dose of SK.

SK RESISTANCE - CURRENT ASSAYS

Antibodies to SK can be demonstrated by: (A) measuring specific anti-SK immunoglobulins (IgG) using a variety of techniques including counterimmunoelectropheresis and radioimmunoassays; and (B) functional assays (SK resistance titres - SKRT) using clot lysis as the end-point (2). In the latter, plasma or whole blood is induced to clot. The potential for thrombolysis is then tested by incubating the clot with either increasing concentrations of SK in a fixed amount of plasma or serially diluting plasma while maintaining a fixed concentration of SK. The lowest dose of SK that is capable of inducing clot lysis is determined. In the presence of NA, it is expected that a higher concentration of SK or a higher dilution of plasma would be required before clot lysis occurred. As the end-point of this functional assay is clot lysis, it reflects the presence of all inhibitors including NA. Accordingly, it may provide a more clinically meaningful estimate of resistance to SK compared with the antibody assays which determine the presence of IgG antibodies but not their functional importance.

Several functional assays for NA have been developed, but in the absence of direct comparison studies it is uncertain whether the measures of SK resistance are equivalent. There is no criterion standard. In some studies the definition of resistance was not provided or lacked a sound theoretical basis. Moreover, in vitro tests may not reliably predict the results of the readministration of SK in vivo and, in particular, in the clinical setting. Correlation of in vitro SK resistance to in vivo reduced thrombolytic efficacy exists for only one of the functional assays (Behringwerke).

SK RESISTANCE AND ANTIBODY RESPONSES - PUBLISHED EVIDENCE

Initial recommendations for the readministeration of SK after six months were based on a study by Kostering et al (4) which demonstrated that following five to six days of SK infusion, mean SKRT was 2.6 million units at two months but was normalizing by six to seven months.

Jalihal and Morris (5) measured SK neutralization titres at two, four, six and 12 weeks in 25 patients treated for AMI. A final sample was obtained in 19 patients at 17 to 34 weeks after

treatment. At 12 weeks, neutralization titres were high and sufficient to neutralize a 1.5 million unit dose of SK in 96% of patients. In 90% of patients followed for 17 to 34 weeks, neutralization titres would have been sufficient to inhibit 50% of a conventional SK dose. In one patient, the neutralization titre at 34 weeks was 2 million units.

Buchalter and colleagues (6) measured antibody-mediated resistance to SK among two cohorts: (A) 40 patients on days 0, 4 and 10 following treatment for AMI; and (B) 12 patients given SK one year previously. Resistance to SK was determined on venous blood using a dilution neutralization assay. They estimated that a conventional dose would be ineffective in all patients at day 10 and in 66% of patients at one year.

Lee and colleagues (7) investigated anti-SK antibody levels and neutralization titres in two groups of patients following SK for AMI. The assay technique was not specified. In the first group, responses were measured in 36 patients prior to thrombolysis and daily for five days. In the second group, antibody responses were measured from 12 to 38 months following thrombolysis. Resistance to at least 1.5 million units of SK was observed as early as day 4. On follow-up, resistance to 1.5 million units was present for at least three years and two months although the number of patients was not described. Similar to other studies, the decline in the antibody response did not parallel the decline in the SKRT.

Elliott and colleagues (8) measured SK neutralizing titres and specific IgG (ELISA) titres in 145 patients treated with SK 11 to 45 months previously. Neutralization titres sufficient to neutralize 1.5 million units of SK were present in 50% (95% CI, 36 to 64) at two years, 52% (95% CI, 38 to 66) at three years and in 49% (95% CI, 31 to 66) at four years. Levels of IgG remained constant over the four years. There was a modest correlation between NA titres and IgG titres (r=0.45).

Unpublished work from Beecham Pharmaceuticals on SKRT obtained from patients participating in a trial comparing SK with APSAC showed that resistance titre responses to both drugs were similar. They were found to increase dramatically at day 5 and peaked between two and four weeks. Baseline level responses were demonstrated in 73 and 92% of

patients at six months and one year, respectively. Anti-SK IgG antibody concentrations declined more gradually than the SKRT response over the course of the study.

Massel et al (9,10) have performed similar studies on patients treated with SK. They have shown that NA increases to high levels as early as day 4 and complete resistance develops in all patients. They have identified a technical problem with their assay system which has been corrected. However, their previous suggestion that resistance persists in about 50% of patients at 18 months is an overestimate. It appears that resistance is present in about 15 to 20% of patients at one year and is present in isolated patients at 18 months. For the present, they have no data on patients beyond 18 months.

In summary, there is only a modest correlation between results of the functional assays and the measurement of anti-SK IgG, likely because not all IgG antibodies have the capacity to neutralize the lytic effects of SK (11). There is consistent evidence among the studies that resistance to SK may develop as early as day 4. The time course of persistence of resistance is more controversial. In the published studies there is a substantial variation that may reflect different patient demographics, study methodology and assay techniques. Until such time as more definitive evidence becomes available, rt-PA should be used in all patients previously treated with SK or APSAC (12).

NA titres can be estimated using: (A) functional assays with clot lysis as an end-point; or (B) by measuring specific anti-SK immunoglobulins. There is a modest correlation between the two methods likely because not all immunoglobulins formed against SK have neutralizing capacity. In vivo correlation of resistance to SK and reduced thrombolytic efficacy exists only for the functional assays. For the present, the functional assays are preferred over the direct measurement of antibodies for the estimation of SK resistance.

Antibodies develop in all patients who receive a conventional dose of 1.5 million units of SK or 30 units of APSAC. Antibody levels sufficient to neutralize a conventional dose of SK develop as early as day 4 and may persist in some patients as long as four years and perhaps beyond.

For the present, the urgent estimation of resistance (using a functional assay) in the clinical setting is impractical because of the imposition of substantial delays in the initiation of thrombolytic therapy.

Skin testing has not been shown to be of value in identifying patients at risk of allergic reactions.

Further research is required into: (A) the clinical importance of NA; (B) the time course of development and persistence of NA; and (C) the development of better and more clinically applicable assays.

Formal economic analyses may provide a means of establishing the costs and consequences of various management strategies for recurrent infarction following SK therapy including: routine NA measurement, the routine use of rt-PA or the selective use of SK.

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APPENDIX

Potential strategies for treating patients with suspected SK resistance

- When a patient who has previously received SK presents with a suspected AMI and is eligible for thrombolysis, measure NA titres using a functional assay and appropriately increase the dose of SK to overcome their inhibition. This is impractical as the available assay techniques are not suitable for the immediate determination of resistance and would entail an important delay in the initiation of thrombolytic therapy. In addition, it would expose the patient to the risk of Ig-mediated reactions. When a patient who has previously received SK presents with a suspected AMI and is eligible for thrombolysis, immediately measure NA titres using a functional assay. If the patient is resistant to a conventional dose of SK, administer rt-PA. This has the same practical limitations as described above. When a patient who has previously received SK presents with a suspected AMI and is eligible for thrombolysis, administer a conventional dose of SK. One hour later measure a coagulation profile (prothrombin time [PT] or international normalized ratio [INR], partial thromboplastin time [PTT]). If there is no evidence of a

systemic lytic state it may be assumed that resistance exists and rt-PA should be administered. This would delay the initiation of thrombolytic therapy for about 1 h but has the advantage of reserving rt-PA for those who are resistant. This strategy has not been tested in the clinical setting.

- Determine, using natural history studies, the time course of development and persistence of SK resistance. Administer rt-PA to all patients until such time as the possibility of resistance no longer exists. However, it has not been determined what minimal threshold (probability that a patient might remain resistant at any point in time) is acceptable to practising physicians. For example, if it were estimated that 5% of patients remained resistant at two years, should all patients be treated with rt-PA up to two years? This strategy would mean that statistical outliers would dictate therapy for all patients (rt-PA) despite the supposition that SK would be efficacious for the vast majority. This is particularly true if the accepted threshold is that no possibility of resistance exists. This strategy is perhaps the most costly but ensures that all patients have the potential to receive an effective thrombolytic agent.

- In patients previously treated with SK, determine the presence or absence of SK resistance using a functional assay at six months. If a recurrent infarction develops prior to the determination of the SKRT, administer rt-PA. After six months, the use of SK or rt-PA will be dictated by the presence of SK resistance. In those patients who have SK resistance at six months, serial SKRT assays would be required.

Coronary thrombolysis: prehospital use

PIERRE THEROUX

The evolution in myocardial damage following coronary artery occlusion is rapid and the first few hours are critical for the success of any salvage intervention. The earlier that reperfusion can be achieved, the greater is the expected benefit. Numerous small observational studies have suggested better preservation of left ventricular (LV) function when fibrinolysis was

initiated within 1 to 2 h after onset of pain (levels III and V) (1-3). Subset analyses of large level I randomized trials have also suggested that time to treatment was an important determinant of mortality. The overall reduction in mortality in the GISSI trial was 18%, but in the subset of patients who received SK within 1 h after onset of pain, mortality was reduced 47% (4). In ISIS-2, the reductions in the odds of vascular death among patients randomized 0 to 4, 5 to 12 and 13 to 24 h after onset of pain were, respectively, 35, 16 and 21%; in this study, however, the benefit was not substantially greater among patients randomized within 1 h than among those randomized within 2 to 4 h (5). Efforts made to begin treatment earlier are thus desirable, and pre-hospital thrombolysis could represent an attractive approach by saving a significant amount of time otherwise necessary for transport to hospital, hospital diagnosis and other steps preparatory to drug administration.

The feasibility of prehospital thrombolysis by a physician attending a mobile coronary care unit and the possible gains of this approach have been evaluated in many studies including the pilot studies of two more definitive randomized major trials, the Myocardial Infarction Triage and Intervention Project (MITI) and the European Myocardial Infarction Project (EMIP). Koren et al (3) initiated an infusion of SK in the prehospital phase in nine patients, Weiss et al (6) in 29 patients and Villemant et al (7) in 41 patients. APSAC was evaluated in 62 patients in a multicenter Belgian study (8) and tissue plasminogen activator in 74 patients by Roth et al (9). These level III studies reported no additional complications compared with contemporary patients treated in hospital while allowing initiation of thrombolysis 25 to 64 mins earlier than it would have been in hospital. Clinical benefits could not be demonstrated in these small trials (9) although one study suggested that infarct size was reduced using as indices the peak creatine kinase (CK) value, QRS score and ejection fraction (EF) (6). Castaigne et al (10), in a level II study, randomized 100 patients to APSAC or to placebo at home, documenting that prehospital fibrinolysis was safe and allowed treatment initiation 60 mins earlier.

The Seattle MITI trial, conducted in a large metropolitan area and suburban surroundings with extensive experience in prehospital care, used trained paramedics operating under remote physician direction by cellular phone. In a pilot study of 2472 patients screened for chest pain,

677 (27%) had a suitable clinical history and 107 (4%) had ST segment elevation on the transmitted 12-lead electrocardiogram (ECG) (11). The average time from onset of chest pain to prehospital diagnosis was 72 æ 52 mins. A further 73 æ 44 mins elapsed before the administration of thrombolytic treatment in hospital. The time required to check the inclusion criteria and to transmit the ECG was 18 mins.

The EMIP trial was conducted in Europe and North America, generally employing mobile coronary care units attended by physicians. The pilot study of 2443 patients for this trial confirmed the usefulness of the initial ECG, with an 88% incidence of confirmed myocardial infarction when ST segment elevation was present (mortality 11%) and of 29% when absent (mortality 4%). It was calculated that prehospital treatment would reduce the time to treatment by about 1 h (12).

The final results of the MITI and EMIP trials were presented at the April 1992 meeting of the American College of Cardiology. The MITI trial screened 6585 patients with suspected myocardial infarction; 27% had a myocardial infarction and 12% were eligible by entry criteria, and 360 patients were enrolled, representing 5.5% of the patients screened and 81% of the eligible patients. rt-PA was given before hospitalization in 175 patients and in hospital in 185. Time from onset of symptoms to phone call was 27 mins, to paramedics' arrival 8 mins, to randomization 20 mins, and to hospital arrival 37 mins for patients treated in ambulance and 23 mins for patients treated in hospital. The net gain in time to initiation of thrombolyte infusion was only 35 mins in the out-of-hospital group. No differences in clinical outcome were demonstrated. The most striking finding of this trial was a very short in-hospital delay for the administration of the thrombolytic agent compared with previous observations.

The larger and more universal EMIP trial enrolled 5469 patients in a double-blind randomized trial of prehospital versus in-hospital APSAC 30 U given intravenously. The study was terminated early because of funding constraints. The median time from onset of pain to treatment with APSAC was 130 mins in patients randomized to prehospital treatment and 190 mins for patients randomized to in-hospital treatment. Only 15 mins elapsed from hospital

admission to treatment. Thirty-day mortality was 9.8% in the prehospital group versus 11.1% in the in-hospital group (not significant). However, when the groups were analyzed jointly to consider only time to treatment, very early treatment Ð less than 90 mins after onset of pain Ð was associated with a mortality of 1% compared with 10% with later treatment. This could suggest a lack of statistical power of the EMIP trial, despite its large size, to detect an independent effect of prehospital treatment. However, as in the MITI trial, the most important determinant of prognosis was early treatment. Prehospital treatment was not an independent favourable factor. The indirect and important benefit of these trials was to show that in-hospital treatment of patients with myocardial infarction can be greatly accelerated by appropriate prehospital diagnosis and identification of patients to treat. A recent report from Scotland has shown that it was also possible to accelerate treatment using a fasttrack system with eligible patients seen by a cardiac team, bypassing routine evaluation by the emergency department and the duty medical system (13).

SUMMARY

Strong evidence supports the concept that earlier application of fibrinolytic treatment can maximize the benefits derived. The results of two level I trials have shown that prehospital thrombolysis is feasible and safe. Although the trials have not proven that prehospital thrombolysis improves prognosis, they have shown that early identification of eligible patients can greatly accelerate the process of drug administration.

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Coronary thrombolysis in community centres and emergency rooms

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Given that the benefits from thrombolytic therapy are greatest in patients receiving treatment with the shortest possible delay between symptom onset and treatment (1,2), it is evident that the use of thrombolytic drugs cannot be restricted to tertiary care medical centres, cardiological intensive care areas or patients who have had formal evaluation by a cardiologist. Results of several thrombolytic trials (3-7) supporting a conservative, rather than a more aggressive, approach support the use of thrombolytic therapy in community hospitals that are not equipped with cardiac catheterization facilities or have the capability of performing revascularization procedures.

Identification of the various factors leading to time delays in patients receiving thrombolytic therapy supports a policy of community hospital involvement and underscores the importance of an established protocol for thrombolytic therapy usage in the emergency room. A review of the experience of centres served by a 911 emergency medical system (8) found that 46.1 æ 8.2 mins elapsed from the activation of the 911 call until arrival of the patient at the hospital. Further, the average in-hospital time delay to thrombolytic therapy was 83.8 æ 55 mins, and was similar for both tertiary care facilities (catheterization labs/cardiac surgery) and community hospitals without these facilities. Hospital delays accounted for 59% of the total time from symptom onset to treatment in the TIMI-2 trial (9). Precious time is lost while awaiting the

results of diagnostic tests (ECGs, chest x-rays, enzymes) and routine blood work, and consultation with the patient's private physician or cardiologist.

Several groups (8,10) had succeeded in shortening the above time delays by implementing a protocol-driven prehospital diagnostic strategy, including a patient selection checklist and ECG transmission to the base hospital. With this approach, emergency room physicians, working in conjunction with paramedics (10,11), have been able to accurately identify candidates for both prehospital or emergency room thrombolytic therapy. The American College of Emergency Physicians has endorsed the concept that the decision to employ thrombolytic therapy should be made in the emergency department by the emergency physician (American College of Emergency Physician Accreditation Information). The importance of a pre-established role for nursing care has been emphasized to ensure a team approach to patient care. Generally, thrombolytic therapy entails a one-to-one nurse: patient ratio, yet other team members must assist with the insertion of the various intravenous (iv) lines and drawing blood for laboratory testing, as well as preparation and mixingof the thrombolytic agents (12).

In Canada, many medical centres will be required to treat patients with thrombolytic agents without paramedics, prehospital ECG transmission or on-site cardiology consultation. The minimum requirement, therefore, should be that these centres be staffed with individuals trained in the diagnosis and treatment of patients with AMI and be equipped with an ECG monitor. Staff should receive training in the use of individual thrombolytic agents and be knowledgeable of the adjunctive therapies and potential complications. A protocol for dealing with a patient who has received thrombolytic therapy in the acute infarct period should be available to guide treatment. Medical staff should be aware of the need to obtain several repeat ECGs in the first hours of presentation to establish the diagnosis of AMI and the need for thrombolytic therapy. Community centres should develop formal lines of referral/communication with regional centres or tertiary care facilities which could assist in the postthrombolytic management of complex patients.

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New dose regimens for coronary thrombolysis

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The aims in the exploration of new approaches are to develop regimens that enhance thrombolytic efficacy (rapidity, quality, overall success), maintain reperfusion by decreasing reocclusion, favourably alter the balance between efficacy and safety, and reduce cost without reducing benefit or compromising safety.

There are remarkably few data assessing dosing strategies with SK as they relate to thrombolytic efficacy or other outcome measures. The standard dose of 1.5 million units of SK has been widely adopted although some investigators - White in particular - have endeavoured to give this dose more rapidly over 30 mins than over the conventional 60 min administration time as defined by the GISSI investigators (1,2). As articulated by Marder and Sherry (3), "thrombolytic treatment regimens are intended to flood the circulation with a very high concentration of activator as quickly as possible and to maintain a high level long enough to affect dissolution of the thrombus but short enough to limit the likelihood of bleeding". Based on these principles, 1.5 million units of SK infused over 1 h and 30 U of APSAC over 2 to 5 mins have become standard modes of administration of these agents in AMI (3,4). Whereas there were initial progressive increments in the dose of rt-PA to 150 mg over 3 h (the majority of which is given within the first 60 mins), an untoward increase in incidence of intracranial hemorrhage resulted in a reduction of the standard dose to 100 mg (5). The 3 h duration for rt-PA treatment was arbitrarily chosen as a likely optimal time to minimize early rethrombosis given the very short half-life of this agent opposed to the nonfibrin selective agents.

Several subsequent initiatives are pertinent in consideration of dosing strategies for rt-PA:

- Weight adjusted doses designed to reduce fibrinogen breakdown and bleeding complications without compromise of thrombolytic efficacy (6).

- Longer maintenance infusions were studied with a view to minimizing thrombotic reocclusion because of the increased likelihood of rethrombosis after initial successful thrombolysis with rt-PA. Although there has been controversy from two small studies, a recent larger study shows that despite maintenance infusions ranging between 9 and 21 h, a 16.5% incidence of reocclusion persisted (7-9). Moreover, there was a strong association between total dose and duration of rt-PA and the incidence of serious bleeding. Low body weight and female sex were also found to be predictive of serious bleeding (9).

- The conventional thrombolytic ceiling of 65 to 75% patency appears to be surpassed by front-loaded dose regimens of rt-PA. Hence, Neuhaus has recently reported in excess of 80% patency rates without an apparent increase in bleeding. These data have recently been confirmed by Neuhaus in a comparative study of rt-PA versus APSAC (10,11). This study revealed 84.4% patency for rt-PA and 70.3% patency for APSAC at 90 mins, whereas 9.4% of rt-PA patients and no APSAC patients reoccluded within 24 to 48 h (11). In this study of 421 patients there was a surprising mortality difference (2.4% for rt-PA, 8.1% for APSAC, $P<0.01$) which, although statistically significant, requires further study and confirmation.

- Combination therapy between nonfibrin specific thrombolytic agents such as SK and urokinase (UK) with fibrin specific agents, such as rt-PA and single-chain urokinase plasminogen activator (scu-PA), might, through theoretical drug synergism, lead to a better balance between thrombolytic efficacy and bleeding as well as a reduced potential for rethrombosis (12). The Kentucky Acute Myocardial Infarction Trial (KAMIT) suggests that half dose rt-PA administered over 60 mins given with conventional dose SK over 60 mins enhances early patency over that provided by rt-PA alone (13). Moreover, combination therapy appears to produce reduced frequency of reocclusion (14).

Translation of the early promise of these novel dosing schemes into clinical benefit is evident from the preliminary presentation of the GUSTO trial which examined both the front-loaded rt-PA regimen as well as combination rt-PA/SK therapy (15). This trial indicated a statistically significant and clinically important benefit on mortality alone and mortality plus nonfatal stroke for the accelerated rt-PA iv heparin regimen compared with combination rt-PA/SK therapy and SK therapy with either iv or subcutaneous (sc) heparin.

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Coronary thrombolysis: Adjuvant medical therapy

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The evidence for benefit with thrombolysis is unequivocal. However, the prospect of achieving still better outcomes has prompted the evaluation of a variety of supplemental therapies. These are discussed in two sections: *Adjuvant therapy* (this section), used in conjunction with thrombolysis (generally within 24 h), to maximize myocardial salvage by maintaining coronary patency and limiting infarction size; and *Postlysis management* (page 541) (generally beyond 24 h), concerned with the goals of prevention and treatment of recurrent myocardial ischemia and the limitation of long term morbidity and mortality. The distinction between adjuvant therapy and postlysis management is blurred, particularly when a therapy is instituted early and continued long term. There are many adjuvant and postlytic therapies which have not been specifically evaluated among patients who have received thrombolytic therapy, nor are they likely to be. In these instances, we have extrapolated data from the prethrombolytic era assuming that mechanisms of benefit (or harm) are similar when thrombolytic therapy is given. Furthermore, most randomized trials address one primary drug or management strategy whereas in clinical practice many drugs and strategies are combined. While not formally tested in randomized controlled trials, the assumption is that the use of two or more drugs of differing drug actions may provide additional benefit. An example of this is the use of ASA for its antithrombotic effect and beta-blockers for their anti-ischemic and antiarrhythmic effects.

PATENCY OF THE INFARCT-RELATED ARTERY

Acute ischemic syndromes and MIs are triggered by the rapid development of an intracoronary thrombus on a ruptured atherosclerotic plaque. The material exposed by the ruptured plaque is highly thrombogenic. Thrombus formation proceeds via platelet adhesion and aggregation, and by activation of the coagulation cascade. When the thrombolytic agent is administered, the stimuli that had initiated thrombus formation are still active. Moreover, thrombolytic agents stimulate the release of substances which promote platelet activation and fibrin formation,

including thromboxane, serotonin, plasmin and thrombin. Hence, the administration of an antithrombotic as adjunctive therapy has two goals: to potentiate the efficacy of the lytic agent by decreasing time to reperfusion and to prevent reocclusion. ASA and heparin are the most commonly used antithrombotic agents.

ASA: ASA is an irreversible inhibitor of cyclooxygenase, blocking thromboxane-induced platelet aggregation and vasoconstriction. The common final step of platelet activation and aggregation is the formation of interplatelet bridges by the binding of fibrinogen to specific receptors, the membrane glycoproteins IIb-IIIa. ASA is ineffective at this step, but new molecules have been designed that specifically block this receptor. Their use is promising but still investigational.

The ISIS-2 trial (1) has unequivocally shown that the early administration of ASA at a dose of 160 mg/day reduces mortality following a MI. The decrease of mortality with ASA alone (13.2 to 10.7%) was of the same magnitude as with SK alone (13.2 to 10.4%). Further, the protective effects of ASA and SK were additive to further reduce mortality to 8.0%. The relative benefit of ASA did not vary with the time interval from pain onset to therapy. The mechanism for benefit appeared related to a reduction in the rate of reinfarction from 3.7% with SK alone to 1.8% with SK/ASA ($P<0.00001$). The joint use of SK and ASA was safe; it caused a 0.3% excess of major bleeds, a 0.1% excess of cerebral hemorrhage but an overall reduction in total stroke of 0.5% ($2P=0.02$).

Heparin: The additional benefit that can be derived from the use of heparin as adjunctive therapy to thrombolysis is still under investigation. In ISIS-2, heparin was prescribed by the treating physician in 65% of the 17,187 patients enrolled, resulting in reductions of mortality from 13.1 to 6.4% used iv, and from 13.5 to 7.6% sc, compared with a reduction from 12.9 to 9.6% when no heparin was used (2). GISSI-2 (3) and ISIS-3 (4) specifically studied the usefulness of sc heparin in conjunction with rt-PA and SK. Heparin was initiated 12 h after thrombolysis in GISSI-2 and 4 h after in ISIS-3. No significant benefits on the clinical outcomes could be demonstrated. In a combined analysis of the results of the two studies, totalling

48,294 patients, mortality at 35 days was 10.0% with heparin and 10.2% without (not significant) and in-hospital reinfarction rates 3.3 versus 3.6% (2P<0.08). The incidence of probable cerebral hemorrhage was slightly increased with heparin (0.6 versus 0.4%) but the incidence of total stroke was unchanged (1.4 versus 1.3%). Bleeding complications requiring blood transfusion were significantly more frequent (1.1 versus 0.8%, 2P<0.001) (1).

The adequacy of the anticoagulation therapy in these trials has been questioned because of the sc regimens of administration resulting in delayed and subtherapeutic anticoagulation. However, the preliminary data from GUSTO showed no differences in 24 h and 30-day mortality with iv or sc heparin administered as an adjunct to SK. Of the patients given SK, 9249 were randomized to iv heparin (5000 U bolus as soon as possible, 1000 U/h infusion commenced immediately and continued for at least 48 h, activated partial thromboplastin time [APTT] 1.5 to 2.0) and 8663 to sc heparin (12,500 U begun 4 h after starting SK and repeated q12h for seven days). The 30-day mortality was 7.4% with iv heparin and 7.2% with sc heparin. A large proportion of patients randomized to sc heparin received an iv infusion by protocol violation. The rt-PA arm of GUSTO included 9222 patients; heparin in this group was used iv in the same regimen as for SK plus iv heparin.

Several angiographic studies have shown that heparin can enhance the efficacy of rt-PA in reperfusing the occluded artery. The TAMI-3 trial specifically studied whether heparin could facilitate the fibrinolytic effect of rt-PA (5). Among the 170 patients randomized, the overall patency of 79% at 90 mins was not different between placebo and heparin. In the Heparin and Aspirin Reperfusion Trial (6), which enrolled 205 patients, patency at 18 h was 82% with rt-PA and heparin compared with 52% with rt-PA and 80 mg of ASA. In the Bleich study (7) of 83 patients, the patency rate at 57 h was 71% with the addition of heparin to rt-PA compared with 44% with placebo; no ASA was given. The European Cooperative Study Group (ECSG-6) (8) recruited 652 patients to a regimen of rt-PA plus immediate ASA, followed by ASA 75 to 125 mg on alternate days, with subsequent randomization to iv heparin (5000 U stat iv, 1000 U/h, no adjustment) or no heparin. Angiography at a mean of 81 h showed slightly improved patency with heparin (83% versus 75%, 2P<0.01). In these studies, benefit of heparin was

greatest when APTT levels were higher than 1.5 times control values (6,8). The National Heart Foundation of Australia Coronary Thrombolysis Group (9) randomized 202 patients 24 h after treatment with t-PA and heparin to heparin or to ASA plus dipyridamole. The one-week patency (about 80%) was not different in the two groups. A recent study has compared front-loaded rt-PA with APSAC in 435 patients (10). Heparin 5000 U iv was administered conjointly with each fibrinolytic regimen, followed by an iv infusion initiated after 1 h in the rt-PA group and after 6 h in the APSAC group, and maintained throughout the hospital stay. ASA 100 mg orally was also given daily. Coronary angiography performed at 90 mins revealed TIMI grade 2 and 3 flow in 84.4% of the patients randomized to rt-PA compared with 70.3% of the patients randomized to APSAC (P=0.0007). Although early reocclusion occurred more frequently with rt-PA, resulting in a higher patency rate at 24 to 48 h with APSAC (93.4% versus 84.9%, P=0.027), in-hospital mortality was significantly lower with rt-PA (2.4% versus 8.1%, P=0.0095). The findings of this level I trial, showing a correlation between early patency and survival may have important clinical implications. The preliminary data from GUSTO confirm this correlation.

MYOCARDIAL PROTECTION

Beta-blockers: Clinical trials performed in the prethrombolytic era have shown that administration of beta-blockers within the first 12 h after MI reduced mortality by 13% with a favouable effect on the rate of reinfarction and of cardiac arrest (11-13). Patients with heart rate below 50 beats/min, systolic BP below 100 mmHg, left ventricular failure, second and third degree heart block, and severe chronic obstructive pulmonary disease were generally excluded.

The TIMI-IIB trial (14) has examined the specific question of beta-blockers as adjunctive therapy to rt-PA. A total of 1390 eligible patients were randomly assigned to immediate 15 mg iv metoprolol followed by oral metoprolol or to oral metoprolol begun on day 6. The primary outcome of LVEF at hospital discharge was not different between the groups, nor was the mortality. However, at hospital discharge the rates of nonfatal reinfarction (2.3% versus 4.5%, P=0.02) and of recurrent ischemic episodes (15.4% versus 21.2%, P=0.0005) were less with

early treatment. The finding of a reduced rate of intracranial bleeding suggested in this study has not been corroborated in the subanalysis of the much larger population of the GISSI-2/International Study (15). The reduced rate of myocardial rupture and of electromechanical dissociation reported in ISIS-1 may be important since fibrinolysis can be associated with an excess very early risk (13).

Nitroglycerin and nitrates: The usefulness of nitroglycerin and other nitrates was evaluated in a few randomized trials of small sample size, prior to the fibrinolytic era (16,17). A metaanalysis of seven trials (16,17) of iv nitroglycerin within 24 h found a reduction of mortality from 20.5% in 425 control patients to 12.0% in 426 treated patients (48% risk reduction, $P<0.001$). The largest trial involved 310 patients. Nitroglycerin was administered within 12 h of onset of chest pain at an initial iv dose of 5 m g/min and was progressively increased until mean BP was reduced by 10% but not less than 80 mmHg (18). The infusion was continued, uninterrupted for 39 h. Mortality was reduced from 26 to 14% ($P<0.01$) in-hospital and from 31 to 21% ($P<0.05$) at one year with favourable effects on infarct size, infarct expansion and reinfarction. The benefits were greater in patients with anterior MI.

The gain that may be derived with nitroglycerin as an adjunct to fibrinolysis has not been studied. Early angiographic studies have demonstrated that nitroglycerin will only rarely open an occluded coronary artery (19). One study has shown that intracoronary isosorbide dinitrate could, in some cases, re-establish coronary bloodflow associated with intermittent reocclusion occurring during or after the SK infusion (20). Jugdutt et al (21) reported preservation of LV geometry and function in serial echocardiographic studies of 76 patients with a first MI. LV function recovered within 24 h with the combination of SK and nitroglycerin opposed to one week with SK alone and to no recovery with placebo. However, other investigators have suggested that the benefits of isosorbide dinitrate combined with SK occurred mainly in patients who failed to reperfuse (22).

Nitroglycerin has many potentially beneficial effects in AMI. It produces coronary vasodilatation with a favourable profile on subendocardial flow; it reduces preload, afterload, and LV wall

stress, and thus possibly infarct expansion and LV remodelling (18,21). Two preliminary reports have however suggested that nitroglycerin administered concurrently with rt-PA could reduce its effectiveness (23,24). Nitroglycerine also inhibits platelet aggregation (25). More definitive data on the usefulness of nitroglycerin will be available when the GISSI-3 trial, evaluating nitroglycerin as adjunctive therapy, and the ISIS-4 trial, evaluating isosorbide mononitrate, have been completed.

Calcium antagonists: Experimental models of coronary occlusion and reperfusion have provided strong support for the use of calcium antagonists in human MI (26). These drugs can protect the ischemic myocardium and reduce reperfusion injury, resulting in smaller infarct and better recovery of the stunned myocardium. The effects may be more marked when the medication is started before the coronary occlusion (27) or early during ischemia (28) and when occlusion is of shorter duration (29).

The clinical experience has, however, failed to show any benefit from the use of calcium antagonists in AMI. Thuesen et al (30) randomized 100 patients to double-blind administration of verapamil or placebo a median of 4 h after onset of chest pain. No difference was found in cumulated CK elevation (level II). In a smaller randomized study of 29 patients, the administration of iv verapamil, a mean of 8 h after onset of chest pain, reduced the size of infarct estimated enzymatically (31). Muller et al (32) in a double-blind randomized study observed no benefit with nifedipine in 171 patients with threatened MI or AMI; the incidence of MI was not reduced and infarct size was not modified. Two weeks following randomization, the mortality was higher in the nifedipine-treated patients compared with placebo (7.9% versus 0%, not significant) (level II). The findings of the Norwegian nifedipine multicentre trial (33), a randomized, double-blind, placebo controlled study of nifedipine administered within 12 h of onset of symptoms in 227 patients, also showed no differences in calculated infarct size between the nifedipine and placebo groups (level II).

Calcium antagonists specifically used as adjunctive therapy to fibrinolysis have been evaluated in only a few studies. Erbel et al (34) randomized 149 patients to double-blind administration of

nifedipine or placebo during SK therapy and coronary angioplasty. An unfavourable negative trend for nifedipine was found with more CK-MB release, more frequent reocclusion and higher mortality (13% versus 8%) (level II). Ellis et al (35) retrospectively reviewed 424 consecutive records of patients successfully recanalized by coronary angioplasty within 12 h of symptom onset. Beta-blockers correlated with improved survival (0 versus 8%, not significant), whereas calcium antagonist therapy made no difference (level V). The early administration of diltiazem in patients with non-Q wave MI in one level II study prevented infarct extension (36).

Angiotensin-converting enzyme (ACE) inhibitors: LV function following MI is the most important determinant of long term prognosis and is influenced by many pathophysiological processes, including the size of the infarct zone, the extent of wall motion abnormality and subsequent infarct expansion. It is also influenced by the adaptative changes occurring in the noninfarct myocardium described as LV remodelling. Experimental data in rats have shown that captopril significantly reduces the amount of LV dilation (37) and subsequent mortality (38). Early administration however was not better than late administration (39).

Whether the benefits from the use of ACE inhibitors in patients with more chronic LV dysfunction caused by previous MI (40-43) will be present or enhanced with their early use as adjunctive therapy is still investigational. In a small randomized double-blind study of 38 patients, captopril combined with rt-PA resulted in less deterioration of LV volumes after one week than placebo combined with rt-PA (level II) (44). The second CONSENSUS trial, however, was prematurely stopped because no gain over placebo was observed with enalaprilat begun within 24 h after onset of MI and followed by oral enalapril (45). This trial enrolled 6090 patients with the primary endpoint of mortality at 180 days. Mortality rates were 10.2% in the placebo group and 11.0% in the enalapril group (P=0.26). Only 56% of the patients received thrombolytic therapy. This trial had insufficient power to rule out a modest benefit of early ACE inhibitor therapy. The hypothesis of a beneficial effect of ACE inhibitors coupled with thrombolysis is now being tested in two much larger trials: ISIS-4 and GISSI-3.

Magnesium: Magnesium has been described as a physiological calcium antagonist and possesses many properties that could be beneficial in AMI (46), such as lowering of systemic vascular resistance, dilation of coronary arteries, decrease in platelet aggregation, improvement in myocardial metabolism, protection against catecholamine-induced myocardial necrosis and stabilization of cell membranes. A large randomized, double-blind, placebo controlled study of 2316 patients with suspected MI documented a 24% risk reduction in mortality at 28 days. Mortality was 7.8% in the magnesium group and 10.3% in the placebo group. The drug was administered as magnesium sulphate, 8 mmol over 5 mins followed by 65 mmol over 24 h; 36% of the patients received thrombolysis and 65% received ASA (level I study) (47). No important side effects were noted but flushing was common.

Two meta-analyses of magnesium in MI have provided the same results (48,49); one included 1300 patients and the other 930. Administration of magnesium was associated with a significant 54% reduction in mortality but with wide confidence intervals. The role of magnesium as adjunctive therapy to thrombolysis has not been adequately tested. Investigation of this treatment has been incorporated in one arm of ISIS-4, to be compared in a factorial analysis with nitrates and captopril.

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Coronary thrombolysis: Adjuvant coronary angioplasty

MERRILL KNUDTSON

The routine performance of catheterization as soon as possible after thrombolytic therapy with a view to dilating the culprit lesion if a significant restriction remains is the essence of `immediate angioplasty'. The objectives are: (A) to open the 10 to 25% of occlusions that have not reperfused with thrombolytics; (B) to reduce ongoing ischemia by treating severe residual restrictions; (C) to speed recovery of ventricular dysfunction; and (D) to reduce the risk of reocclusion and its severe consequences (1).

TABLE 1

Randomized trials of interventional approaches after thrombolytic therapy

Reference (number)	Total Number	Angio-plasty	PTCA (%)	CABG (%)	Time	%	(%)	Important limitations	
al (1987) (TAMI) (2)	386	Early Effective	65 52	9.1 15.3	In-hosp	4 1	11 13	High risk groups excluded, eg 25% with IRA occlusion (mortality 10.4%) and 24% with other exclusions (mortality 11%)	With thrombolytic success and no severe mvd or shock routine early intervention not indicated and possibly harmful

Study Group (1989) (3)	3262	18-48 h Conser- vative	56.7 13.3	11.9 10.5	In- hosp	5.2 4.7	6.4 5.8	Patients with occluded IRA, shock and `PTCA not suitable' excluded; 24% of these had CABG in <3 months	After iv thrombolyticsroutine cath +/- PTCA at a mean of 32 h offers no advantage over decisions made on clinical grounds
(1988) (ECSG) (4)	367	Early Elective	91 7	2 1	14 days	7 3	7 4	2 or more lesions dilated during acute procedure in 19%; very low incidence of elective group intervent	After iv thrombolyticsroutine cath +/- PTCA has no benefit over the very conservative ECSG non-invasive strategy
Study Group (1991) (5)	801	Elect- ive Conser- vative	42 3	15 2	12 mnths	5.8 5	15.1 12.9	Randomization after first 24 h	After thrombolytic therapy cath +/- inter-vention is appropriate only when clinically indicated
Study Group (1988) (6)	389	2 h 18-48 h	72 55	16.4 7.7	21 days	7.2 5.7	6.7 4.1	PTCA mandated if feasible	After thrombolysis routine cath +/- PTCA is better per-formed after a few days than acutely
(7)	206	Early Elect- ive	83 3	6.8 3.9	In- hosp	16.5 11.7	29 18	All had urgent cath with intracoronary SK. If poor flow all were `probed' with wire before PTCA random-ization	Following thrombolysis immediate PTCA has no additional positive short or long term (three-year) outcome effect
et al (1990) (8)	201	Delayed Conser- vative	53 19	11 3.8	In- hosp	5 4	16 10	Many `anatomical' PTCA exclusions	After thrombolysis, even late routine cath +/- inter-vention had no advantage over a more conservative approach

ECSG European Cooperative Study Group; IRA Infarct-related artery; MVD Multivessel disease

Table 1 itemizes selected findings of the major randomized trials of immediate angioplasty (2-8). The strategy of routine intervention appears to have no clear benefit over an approach directed by clinical circumstances, and appears to have negative consequences in the very early stages. There is a consistent trend to a higher mortality and an increased need for early bypass surgery with routine early intervention. Further, the predicted lower reinfarction rates with routine angioplasty were not observed.

That adequate early reperfusion is a strong indicator of subsequent ventricular function recovery has strong support in the literature (9-11) although it is clear from the studies reported in Table 1 that the routine use of percutaneous transluminal coronary angioplasty (PTCA) is not the way to achieve this objective. The recent report of Ito et al (11) demonstrates that inadequate tissue perfusion can exist despite the apparent restoration of an adequate epicardial coronary artery lumen by postinfarction thrombolysis or PTCA.

Despite this compelling indictment against routine action, early catheterization and appropriate intervention can be performed with safety and effect when the need is there.

Combined TIMI-II data show that 60% of patients in the conservative categories received catheterization during the first 12 months because of clinical need, and by the end of this period the number of interventions in the invasive andconservative groups by PTCA and/or surgery was the same. Further, there were 40% more hospital admissions in the conservative group than the invasive group during the first year (12).

The unfavourable mortality trends reflect more on the approach of routine intervention than on the angioplasty procedure per se. Only five of the 14 deaths in the TIMI-IIB invasive group actually had PTCA (13).

The exclusion criteria used in trials of angioplasty (Table 1) have led to a population of patients who is fundamentally different from the overall infarction patient population. Patients with

multivessel disease, for example, were frequently excluded from thrombolytic intervention trials. Two-thirds of postthrombolysis angioplasty trial patients had single vessel disease whereas more than two-thirds of prethrombolytic era patients had multivessel disease (12). Other reasons for exclusion included, inter alia, advanced age (>>75 years), shock, cerebrovascular disease and other perceived `high risk' patients, all groups that have a higher incidence of multivessel disease and a higher infarction mortality. Overall, only 15% of patients admitted with infarction to the thrombolysis study centers were randomized (14). The trials listed in Table 1 do not provide guidance as to the management of excluded patients.

TABLE 2

Effect of PTCA failure on mortality in postlysis randomized intervention trials Mortality (%)

Reference (number)	PTCA success randomization group	Per cent	PTCA	No PTCA	All attempts	Failed	PTCA + No PTCA
Topol et al (1987) (2)	Early Elective	86 92	11	29.4	2.5	23.5	7
SWIFT Study Group (1991) (5)	Elective	87	0	26	1.1	8.3	4.9
TIMI IIB Study Group (1989) (3)	Planned Conservative	85.1 85.6	6.5	9	0.7	4.9	4.9
TIMI IIA Study Group (1988) (6)	2 h Late	84.4 93.5	6.5	8	1.6	13.8	6.4
Simoons et al (1988) (4)	Early	61	2	1	7.1	11.7	4.6

PTCA (Percutaneous transluminal coronary angioplasty) success defined as angiographic success without in-hospital death

Table 2 expands on some of the trials referred to in Table 1 addressing the issue of angioplasty safety. With the exception of the ECSG Trial, mortality in patients receiving angioplasty, whether by randomization or by later perceived clinical need, was low (0.7 to 2.5%). The ECSG Trial angioplasty mortality of 7% stands out. Possible explanations include the questionable practice of multiple vessel PTCA during acute infarction PTCA and the rigid protocol adherence with a much lower incidence of treatment cross-overs than reported in other trials. PTCA in ECSG was performed in 91 and 7% of the early catheterization and conservative groups, respectively (4).

There may be clinical subgroups where a lower threshold for early catheterization and intervention are indicated. Further analysis of the TIMI-II data demonstrated that patients in the conservative group with prior MI had a higher mortality than those without prior MI (11.5% versus 3.5%), which persisted at one year (15,16). There was no difference in the invasive group. On the other hand, diabetes without prior MI had a higher mortality in the invasive than the conservative group (14.8% versus 4.2%), suggesting even greater caution before intervening in diabetics. The strength of these observations is open to question as patients were not prospectively stratified by these features (15).

The need for vigilance in a conservative post-thrombolysis approach is highlighted by the report of Muller et al (17) on data from the TAMI-5 trial. Of 288 patients treated conservatively, by the end of day 1 and day 4 urgent catheterization was deemed to be required in 19 and 26%, respectively, leading to angioplasty in 49% and surgery in 3%. Advanced age and anterior infarction were the only clinical variables that correlated with urgent study. The mortality in the group requiring symptom-driven intervention was 7% compared with 3% if they remained asymptomatic (17).

Cardiogenic shock and its lethal clinical course has not been influenced by thrombolytic therapy alone (18); mortality rates are not appreciably different from the predictions of Killip and Kimball (19) of a 81% mortality. There is growing enthusiasm for the adjunctive or primary role of angioplasty and/or surgery (20). Table 3 summarizes findings of the more recent large

series describing the experience with angioplasty in cardiogenic shock (21-29). Included in this tabulation is a summary of earlier small trials summarized by O'Neill (29). The overall mortality rates in these nonrandomized trials (level IV and V) of 27 and 73% are lower than pre-interventional reports, and the mortality observed with an angiographically successful angioplasty of 19 to 49% are particularly encouraging. Whether this is a true revascularization influence or whether it reflects a combination of astute patient selection and aggressive management with assist devices such as intra-aortic counter-pulsation will remain unclear until a randomized trial of intervention and medication is available. This assistance is not expected soon, hence most centers will continue to be swayed be the encouraging data in Table 3 in light of the horrible prognosis of shock (30).

TABLE 3

Experience with PTCA in cardiogenic shock

Reference (number)	Number of patients	PTCA success (%)	CABG post PTCA (%)	IABP use (%)	Prior lytics (%)	Success	Failure	PTCA and/or CABG	Duration	Mortality
Moosvi et al (1992) Detroit (21)	38	71.8	9.9	84	50	NA	NA	44	21 months	
Lee et al (1988) Lausanne (23)	24	54	17.4	88	0	23	81.8	50	NA	NA
Ghitis et al (1991) Columbia, MO (24)*	62	77.4	0	32	16	19	62.5	27.4	NA	NA
Gacioch et al (1992) Ann Arbor (25)	50	NA	15	70	46	49	93	49	1 year	NA

Hibbard et al (1992) Rochester, MN (26)	45	62	28.9	68	28.8	29	71	44	2.3 years	20
O'Keefe et al (1989) Kansas City (27)	39	NA	NA	NA	0	NA	NA	NA	NA	NA
Ellis et al (1989) Ann Arbor (28)	61	59	NA	NA	80	14.3	72.2	32.2	NA	NA
O'Neill (1988) (review) (29)	98	67	NA	NA	NA	24	78	NA	NA	NA

*AHA/ACC Joint Task Force definition os successful percutaneous transluminal coronary angioplasty (PTCA) used for column 'PTCA success (%)'; column 'success' under 'Angioplasty mortality' refers to patients with angiographic success without procedural mortality only. *Definition of cardiogenic shock is weak Ð could be hypotension for a variety of reasons; Estimated; CABG Coronary artery bypass graft; IABP Intra-aortic balloon pump; NA Not available*

In summary, the routine use of the immediate angioplasty approach cannot be supported. There are significant portions of the acute infarction population that have been excluded from the randomization process; therefore the potential role of intervention by angioplasty and bypass surgery has yet to be defined. When intervention is perceived to be clinically required in experienced centres, angioplasty and urgent bypass surgery can be performed safely (31-34).

DIRECT ANGIOPLASTY

The emergent performance of angiography and PTCA without prior thrombolytic therapy, referred to as 'direct angioplasty', has been assessed in three randomized trials comparing angioplasty alone with thrombolytic therapy alone (35-37). Two of these trials (35,36) concluded that immediate PTCA reduced the combined incidence of nonfatal reinfarction and

death with a lower incidence of intracranial hemorrhage (level I). Whether this intervention results in improved LV function is not clear, but a higher patency rate, more rapid establishment of patency and a less severe residual stenosis on average seems achievable by the interventional approach. Table 4 outlines most papers describing a large experience with direct angioplasty that appeared prior to publication of the above randomized trials (27,38-43). It is clear that the higher mortality with direct angioplasty suggested in Table 4 was not substantiated in the randomized trials.

The pursuit of approaches that will achieve a higher patency rate continues to be important as patency is a principal determinant of mortality (44,45). Retrospective data on the influence of artery patency on subsequent mortality is available from Cigarroa et al (46) who report a twofold increase in 10-year mortality in those with occluded infarct-related arteries. This mortality information is supported by the study of Brodie et al (47) who, along with Marino et al (48), report more favourable ventricular remodelling with ongoing perfusion even in the absence of demonstrable ischemia. Two of the three randomized trials showed that a higher rate of vessel patency can be achieved by direct angioplasty compared to thrombolytic therapy (35,36).

TABLE 4

Experience with 'direct' angioplasty

Reference (Ref. No.)	No. of patients	Mean time to PTCA (h)	Shock (%)	PTCA success(%)	Over-all	Failed	Re-occlusion	Repeat PTCA	CABG	Length of follow-up	PTCA	CABG	Comments including LV fuunction data
Rothbaum et al (1987) Indianapolis (38)	151	3.1	12	83.4	9	52	5	1.5	3.3	20 months	22.2	5.9	EF improvement by infarct vessel: LAD +0.13; RCA and Cx +0.10
Brodel et al (1991) Greensboro, NC (39)	383	4.1	5.7	84.3	9.1	61.4	6	3.7	6.8	NA	NA	NA	Most LV function improvement seen in ant MI and high thrombolytic risk group

Beachamp et al (1990) Kansas City (40)	214	`<6'	NA	81.8	7.9	69.2	NA	NA	5.6	57 weeks	15	15.5	NA
Ellis et al (1989) Ann Arbor (41)	254	10.3	13	73.6	13.7	55.6	NA	NA	5.5	NA	NA	NA	Shock, EF <30% and advanced age predicted poor outcome
O'Keefe et al (1989) Kansas City (27)	500	5.2	8	88.6	7.2	63.1	9.4	3.2	2	33 months	24	13	In patients restudied at discharge (50%) EF increased from 0.53 to 0.59
Lee et al (1990) Kansas City (42)	105	5.2	11	76	17.1	72	26.3	5.7	7.6	12 months	13.8	0	In 51 patients restudied at discharge EF increased from 0.54 to 0.61
O'Neill et al (1986) Ann Arbor (43)	29	4.1	Excl	83	6.9	NA	14.3	3.4	20.7	NA	NA	NA	Greater EF increase with direct PTCA versus lysis alone

*Modified AHA/ACC Joint Task Force definition of percutaneous transluminal coronary angioplasty (PTCA) success used (freedom from myocardial infarction not required). All nonrandomized data except for O'Neill. *Patients older than 75 years; ant MI anterior myocardial infarction; CABG Coronary artery bypass graft; Cx Circumflex; EF Ejection fraction; Excl Exclusion; LAD Left anterior descending artery; LV Left ventricular; NA Not available; RCA Right circumflex artery*

Reclosure rates with direct angioplasty appear to be lower than with either thrombolytic therapy alone or thrombolysis n combination with PTCA. Grines et al (49) analysed a series of 50 patients who had received both thrombolysis and angioplasty in a search of angiographic predictors of reocclusion and found that a sub-optimal lumen size and TIMI-I or -II flow were strong predictors. Ellis et al (50) evaluated a larger series of 240 patients at the University of Michigan, all had received PTCA and 59% had been given a thrombolytic agent. Recurrent ischemia was associated with an in-hospital mortality of 15% and was responded to by PTCA

in 51% and coronary artery bypass graft (CABG) in 13%. Again the strongest predictors were angiographic appearance and flow parameters.

Based upon two level I studies, as well as many level IV and V studies, the use of the direct approach may be supported among patients who have contraindications to thrombolytic therapy and when there is rapid access to an interventional laboratory with experienced interventionalists. The strength of this grade A recommendation holds only when catheterization can be undertaken within approximately 1 h from presentation to hospitalization (35,36). Based upon level IV and V studies, those in cardiogenic shock may also benefit from early direct angioplasty (13,43).

ELECTIVE ANGIOPLASTY

Postinfarction angina is currently the strongest and most frequent indication for early intervention (51). TIMI-II reported that 23% of conservative-assigned patients received PTCA within one year, the majority during the initial hospitalization. In the report of Bassand et al (52) of a trial with PTCA done only as clinically indicated, angioplasty was performed in 33% of cases. Postinfarction angina can present in many ways, from threatened reclosure with hemodynamic instability and new ECG changes, to late-stage treadmill test angina. The benefit of revascularization in each circumstance has not been tested.

The utility of angioplasty with thallium scintigraphic evidence of ongoing ischemia was demonstrated by Lew et al (53). De Feyter et al (54) earlier had reported their experience with angioplasty performed in 53 patients with unstable postinfarction angina. There were no deaths and the success rate seemed to improve as the time to PTCA from the acute event increased. By six months 26% had required repeat PTCA or CABG for recurrence of symptoms.

Prediction of ischemic events in the postinfarction period is seldom possible by exercise testing or by angiographic features. Unfortunately ischemic events usually occur before functional tests are performed. Further, in TAMI-I and -III patients without revascularization, 21.3% had a predischarge clinical event that could not be predicted by detailed angiographic assessments (55).

In contrast to immediate or direct angioplasty, elective angioplasty has a high (93 to 96%) primary success rate, a low incidence of reocclusion and a low complication rate (56,57). The decrease in complications of angioplasty later after thrombolysis is understandable from the pathological studies of Waller et al (58). PTCA performed early after thrombolysis tended to be associated with significant perivascular hemorrhage, whereas postinfarction angioplasty without lytic agents was not. Postlysis PTCA, particularly of the RCA, continues to have increased risks over noninfarction PTCA, likely due to the influence of incompletely resolved thrombus (59,60).

Cardiac catheterization early in the course of MI provides information relative to patient treatment and prognosis. Early reports from the Western Washington Trial stated that 60% of patients with acute infarction had an underlying lesion of less than 60%, suggesting that angiography provides information of limited value prior to resolution of the clot (61). Nevertheless, significant prognostic value of angiography may be present early. Lesion morphology has been shown to correlate to a higher incidence of acute events (62), minimal lumen diameters of less than 0.6 mm are associated with a less favourable outcome (9) and inadequate reperfusion is associated with blunted recovery of ventricular function (10). In addition to coronary morphology, the location and extent of coronary collaterals, the extent of ventricular dysfunction in relation to coronary anatomy, and the location and extent of coronary lesions provide important clues as to prognosis and the most appropriate means of revascularization (63-67).

Based upon known clinical risk factors, one could support a lower threshold for early angiography for patients with: (A) previous infarction; (B) signs of heart failure or hemodynamic instability; (C) recurrent angina and new ECG changes; as well as (D) all candidates for direct angioplasty mentioned above. A later time frame would be suitable for: (A) patients with a positive exercise test; (B) patients unable to exercise and for whom dipyridamole testing is not suitable; (C) non-Q infarction; (D) where the prognostic data possible from catheterization would be critical to the patient's management; (E) where thrombolysis created clear early reperfusion with a threatened large infarction; and (F) with recurrent ventricular tachyarrhythmias.

A compelling argument against liberalization of criteria for postinfarction angiography is the observation that once angiographic anatomy is known, it is often hard for clinicians to exercise restraint concerning revascularization, a phenomenon labelled as 'reperfusion momentum' (68).

RESCUE ANGIOPLASTY

The attempt to open an artery by angioplasty after thrombolysis failure has theoretical appeal if it can be performed quickly. Acceptable mortality rates have been reported in the small number of series published. Abbotsmith et al (69) compared clinical outcome in 169 successfully `rescued' patients with 607 with thrombolytic success. Mortality was 5.9% compared with 4.6% in the thrombolytic group, the PTCA reocclusion rate was high (21%) and CABG was needed in 8%. The small series of Holmes et al (70) also reported a low mortality (3%) and an excellent long term result. The only randomized data available are those of Belenkie et al (71), who randomized 28 patients 3 to 6 h post-MI. Mortality in the rescue group was 6.3 and 33% in the conservative group. Other series are summarized in the article by Ellis et al (72) who review the points for and against this approach. Identification of patients in need of 'rescue' and the logistic difficulties associated with facilitating the rescue process are the two most formidable obstacles limiting this approach. The matter would be open for review should rapid noninvasive indices of vessel patency and closure become available.

The impact of a failed PTCA attempt is an issue that remains unresolved with respect to rescue and direct angioplasty, and perhaps immediate angioplasty. From the tabulations presented, it is clear that failed PTCA carries with it a substantial risk. Whether those patients in whom PTCA fails were already at high risk of death or whether the patients would have survived had it not been for the PTCA attempt remains unresolved. Wherever the data were available, mortality rates have been presented in this document for all patients with a PTCA attempt in addition to angiographically successful and unsuccessful procedures. The procedural success rates quoted in the articles have been amended to comply with current success definitions, ie, excluding patients with in-hospital mortality.

Table 5

Exclusion criteria for postfarction intervention

Absolute	Relative
Nonculprit lesions	Operator inexperience
Nonsignificant lesions	Small culprit vessel
Lesion distal to LM lesion >50%	Diabetes
Culprit not known	Intraluminal clot
	No surgical backup

FACILITY AND INTERVENTIONAL CARDIOLOGIST ACCESS

There has been concern that the availability only in regional centres, of facilities and personnel capable of providing early angiography and revascularization may not allow optimal access for all to needed treatment. The report of Feit et al (73) comparing outcomes of those patients in the TIMI-II study who lived remote from a catheterization facility with those close to a study centre is somewhat comforting in this regard. There were no important differences in mortality, complications or ventricular function recovery in patients cared for in the community hospitals, although a smaller number of these patients received interventions (74,75).

One set of guidelines cannot be established for all of Canada, not only because of geographic factors, but because of physician-related factors as well. It is clear that one's threshold for performing interventional procedures is conditioned in part by the experience of local physicians, cardiologists and surgeons, and a procedure appropriate in one area may not be so in another. In a report of clinical outcome in TAMI patients, 22% of all patients enrolled in this trial eventually had bypass surgery. Despite the fact that the surgical group had a higher number of patients with features associated with poor outcome, the surgical mortality was the same as those who were not operated upon (76). In addition, patient selection for intervention in all the studies reported herein was performed by skilled interventionalists who exercised a great deal of judgement as to angioplasty candidacy in that particular centre. It would be

inappropriate to propose very specific patient-related criteria for intervention that did not take into account local practice differences. From a surgical point of view some centres have more experience in operating in acute coronary situations than others (77).

EXCLUSION CRITERIA FOR POST-MI PTCA

Although there are no randomized trials supporting the list shown in Table 5, careful review of current interventional practice would support the adoption of several absolute and relative contraindications to PTCA in the setting of AMI.

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Coronary thrombolysis: Adjuvant revascularization surgery

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Coronary reperfusion therapy in ami is an evolving strategy that seeks to limit infarct size and preserve myocardial function, and has been shown to decrease early mortality after AMI (1,2). It has been demonstrated that the restoration of patency early on is likely to result in the recovery of function (3,4) since LV functional reserve is closely related to the rapidity with which coronary bloodflow is restored, particularly in patients with anterior wall MI and to a lesser extent in cases of posterior wall infarction (5,6). In studies where mortality was evaluated in relation to perfusion status of the infarct-related artery, early patency was associated with survival benefit, and in most of these studies an improvement in LV function was also observed (7-10). However, in 15 to 35% of patients, thrombolytic therapy fails to achieve patency.

The importance of failure to reperfuse per se remains unresolved. Previous studies have demonstrated a poor prognosis for patients who fail to respond to thrombolytic therapy (11). Failure to reperfuse could simply be a marker for patients who have a poorer prognosis for other reasons, such as infarct location, age, LV function or extent of coronary artery disease.

Indeed differences in the biology of the vascular endothelium or of the coagulation system or in the reaction to various drugs that may affect it can be factors that influence which patients are likely to reocclude and suffer additional ischemic events (12). PTCA has been advocated as a method of salvaging patency in patients in whom thrombolysis has failed (13). `Rescue' angioplasty in this setting may offer benefit (14). Failure to reperfuse within 90 mins of thrombolytic therapy has led, in some cases, to surgical revascularization which resulted in the restoration of flow to the infarcted zone in the great majority of cases but the clinical course of these patients was markedly different from that of patients with successful thrombolytic therapy (12).

TABLE 1

Long term outcome of PTCA (n=198)

	Emergency CABG (n=96)	Elective CABG (n=34)	Medical (n=66)
Myocardial infarction at follow-up	3%	1%	5%
CABG	1%	2% (n=2)	16% (n=10)
PTCA	0%	6% (n=2)	8% (n=5)
Cardiac death	0%	3% (n=4)	6% (n=4)
Cardiac survival at four years	97%	100%	86%

Cause of failure: Unsuitable anatomy; inability to pass or dilate; dissection; acute occlusion. Tuzcu et al (16) (level V trial)

Early coronary bypass grafting after failed thrombolysis may offer certain advantages including prevention of the consequences of rethrombosis, treatment of postlysis angina caused by a remaining critical lesion, maintenance of myocardial salvage resulting from reperfusion, augmentation of bloodflow to the infarct zone allowing optimal recovery of function and infarct prevention. These potential benefits must be weighed against the risks of an early bypass procedure, including increased risk of hemorrhage because of the persisting effects of thrombolytic agents, risk of hemodynamic unstability because of a recent MI and emotional trauma among patients already sustaining the effects of AMI (15). Tables 1 and 2 illustrate the

results of a study published by Tuzcu et al (16) and pertain to the late outcome of unsuccessful PTCA treated by different means and the factors that affect survival in their patients (level V).

TABLE 2

Long term outcome of unsuccessful PTA: Factors that affect cardiac survival unfavourably

	P	Relative risk	Confidence interval
No CABG	0.003	6.2	1.7-22.4
Female sex	0.02	4.6	1.4-15.5
Moderate or severe ventricular dysfunction	0.04	4.3	1.3-14.7

Tuzcu et al (16) (level V trial)

TABLE 3

Medical and surgical management of MI in the prethrombolysis era

	Medical*(%)	Mortality P (%)	Surgical (%)
In-hospital	11.5	P<0.08	5.8
If Killip IV excluded	9.3	P<0.003	1.2
At 18 to 56 months	20.5	P<0.03	11.7
If Killip IV excluded	18.1	P<0.005	7.1
Early surgery (<6 h)	11.5	P<0.01	2.0
Surgery performed late (>6 h)	11.5	NS	10.3
Early surgery normal enzymes	11.5	P<0.001	2.6
In-hospital	20.5	P<0.001	3.6
Late			
Early surgery – elevated enzymes	11.5	NS	8.1
<6 h			2.1
0-10 h			4.6
>10 h			20.4
Survival at 10 years			
All	59	P<0.0007	74

Early reperfusion	59	P<0.0003	83
Late reperfusion	59	NS	66

*De Wood et al (17,24) (level III trial); *Conventional; NS Not significant*

Several groups have shown excellent results in level V (17,18) and level III (19) trials of bypass surgery practiced within 6 h after the onset of chest pain in patients who also had electrocardiographic, coronary angiographic and retrospective enzyme changes consistent with MI. Berg et al (20) reported 227 patients who underwent coronary artery bypass grafting an average of less than 6 h after the start of chest pain, with in-hospital mortality of 1.76% and a first year mortality of 1.44%; there was 94.3% patency of grafts and the EF was normal, unchanged or improved in 86.3% of patients (level V). A similar group of 200 patients treated conventionally in the same hospital experienced a hospital mortality of 11.5%. These results support the affirmation that in acute evolving MI, early coronary artery bypass surgery can be superior to conventional management (17,20,21). Table 3 outlines the short and long term outcomes of medical and surgical management of AMI in the level III study of DeWood et al (19). Table 4 summarizes the results of what is the only randomized controlled study of urgent surgical revascularization versus conventional medical treatment (prethrombolysis era) of acute evolving transmural MI (level I) (22).

The benefits of bypass surgery are most marked when surgery is undertaken within 6 h following the onset of symptoms. Mortality is higher when surgery is performed between 6 and 24 h and there is less improvement of ventricular function (18,19,23). Although there are no published randomized comparisons of bypass surgery with PTCA, coronary bypass offers the theoretical advantages of being carried out under safe and controlled conditions with complete revascularization and excellent long term efficacy. In the surgical setting, hypothermia reduces metabolic demands and is accompanied by complete sedation, cardioplegia, and topical myocardial cooling. The nonbeating, nonworking heart, and the vented and decompressed LV have minimal oxygen demand.

A report from the TAMI study group (19) has shown that emergency bypass surgery, practised after failed thrombolysis and where angioplasty was unsuccessful or not feasible because of anatomical considerations, could be performed with a low mortality and morbidity (level V). Patients that came to surgery in a stable hemodynamic condition fared much better than those who were in cardiogenic shock. There were no deaths in the stable group and in that small series of patients, the comparison of preoperative and late ventriculograms demonstrated preservation of global and regional LV function. Other reports have shown similar results (22,24-27). Emergency surgical intervention has also been practised as a `salvage operation' following abrupt closure of the infarct-related artery post-PTCA. In the TAMI study emergency coronary bypass was performed in eight patients in cardiogenic shock and five survived (19). Similar outcomes in other studies suggest that as a life saving procedure, this aggressive approach is defensible (28-30). Tables 4 and 5 depict the indications for emergency bypass surgery after unsuccessful thrombolysis or angioplasty. The basic principle governing the persuit of this emergency operation is that optimal results are achieved when the time of infarct onset to that of reperfusion is less than 6 h (31,32).

Even though thrombolytic therapy results in reperfusion in the majority of patients, there is often a severe residual stenosis. Residual stenosis following thrombolysis is an important determinant of rethrombosis. Harrison and colleagues (33) have shown that vessels with residual stenotic cross sectional areas less than 0.4 mm2 are at high risk for rethrombosis. Remodelling due to ruptured atherosclerotic plaque (such as seen following angioplasty), persistent coronary spasm, or lysis of persistent thrombi are other factors that may change the residual size of the lumen significantly (34-38). Although PTCA is an effective means of optimizing patency of the infarct-related vessel, its routine practice within 18 to 48 h following the onset of MI in patients having already received an early thrombolytic treatment does not offer greater benefit than a conservative (ie, noninterventionist) therapy and is often associated with a higher risk of adverse clinical events (39). While infrequent, abrupt vessel closure complicating coronary angioplasty has important clinical repercussions. A review of the PTCA Registry of the Heart Lung and Blood Institute reveals that in the 6.8% of patients who had periprocedural coronary occlusion, 20% died, 40% suffered a MI and 25% had to undergo bypass operation (40,41). Abrupt closure by coronary dissection and rethrombosis following

angioplasty may occur within a very short time after an apparently successful coronary dilation. This type of reocclusion is usually refractory to repeat dilatation as well as intracoronary infusion of tissue plasminogen activators (42).

Decisions as to the appropriateness of surgery should be based upon an assessment in each patient of hemodynamic data, the extent of jeopardized myocardium and the severity of multivessel disease. This assessment should be made keeping in mind that the residual stenosis may be difficult to assess and is often underestimated (43). Patients with a small infarct-related artery and a limited infarct territory should not be treated with surgery after unsuccessful angioplasty (19). Patients who have undergone PTCA and in whom ischemia can be easily provoked on a treadmill test should be evaluated angiographically to determine the extent of their coronary atheromatous process. Although these patients are not necessarily candidates for immediate or delayed surgery, they should be carefully evaluated.

Some patients who have been excluded from thrombolysis studies because of factors, such as history of a recent stroke, predisposition to hemorrhage, high blood pressure, recent (two weeks) surgery or severe trauma within the previous six months, might benefit from early PTCA or bypass surgery and should be considered (44).

It is now recognized that patients who have received thrombolytic therapy do not generally warrent angiography on a routine basis. Randomized trials have demonstrated that angiography and revascularization should be reserved for patients who develop hemodynamic instability or recurrent ischemia either spontaneously or induced by stress testing. Angiography in such patients will determine whether revascularization is possible and whether PTCA or surgery is preferable. Generally surgery is preferable for patients with significant stenosis of the left main coronary artery, all three major vessels, or the left anterior descending artery plus the right or circumflex coronary arteries, or who have a tortuous, calcified or narrow infarct-related artery deemed unsuitable for PTCA (20,35). Evaluation of these patients should be on an individual basis, taking into account previously mentioned clinical, hemodynamic and laboratory criteria (12). If myocardial ischemia persists, revascularization surgery may be

helpful. Although in many of these cases, the ideal time limit of 6 or 7 h may have elapsed, surgery can still be performed with a very acceptable morbidity and mortality (21,26,45-48). However, patients are at higher risk than those in whom thrombolysis has succeeded or in whom PTCA was successful. Although restoration of perfusion is possible and may be beneficial (16,49-51), improvement of ventricular function is not certain (19,24,25,47).

TABLE 4

Surgical reperfusion in acute evolving MI in the prethrombolysis era (n=68)

	Medical* (%) (n=34)	Surgical (n=34) <6 h from the symptom onset
Early mortality	8.8% (n=3)	2.9% (n=1)
Late mortality	11.8% (n=34)	0
Survivors	79.4%	97.0%

*Koshal et al (22) (level I trial); *Conventional*

TABLE 5

Indication for emergency bypass surgery after unsuccessful thrombolysis or angioplasty

Clinical and electrocardiographic signs of ongoing uncontrolled ischemia in patients with any of the following:
>50% left main coronary artery stenosis with left anterior descending or circumflex as infarct-related artery (IRA);
>75% left main coronary artery stenosis with right coronary as IRA; left main coronary artery equivalent
Unsuccessful angioplasty (dissection/rethrombosis)
Failure to recanalyse IRA either pharmacologically or mechanically within 6 h from onset of symptoms

Kereiakes DJ et al (19); ACC/AHA (60)

Patients with severe hemodynamic instability following extensive MI are likely to have seriously impaired LV function, often involving more than 50% of the myocardium, and may have life threatening ventricular arrhythmias. Some of these patients may benefit from surgical revascularization providing that operation can be performed early. However, this group of patients remains at high risk, particularly if they suffer the added complications of massive mitral regurgitation or septal rupture (52).

Thus urgent or emergent operation for complications of coronary artery disease is dictated by conditions where myocardial necrosis is threatening or ongoing; failed thrombolysis, failed angioplasty and unstable angina are conditions in which the extent of necrosis may be minimal if revascularization is performed within 4 to 6 h from the onset of ischemia (53). There are other conditions associated with MI that are characterized by myocardial necrosis of varying extent, including rupture of the ventricular septum, papillary muscle or LV free wall, and cardiogenic shock.

Early mortality ranged from 12 to 66% (mean 34%) of the 101 patients operated upon by Balooki (54) for shock from MI (level V). Mortality in patients operated upon for failed angioplasty, failed thrombolysis or unstable angina varied from 3.6 to 44% in comparable series. These results have remained constant for the past five years and changes in therapy should be considered. Logistically, it is often difficult to offer a surgical treatment within the 4 to 6 h ideal time to prevent ischemia from evolving to necrosis. The intra-aortic balloon pump has generally been used only when failure or hypotension were present. Akin (55) reports excellent results with less than 1% mortality and a 2% infarction rate, when the intra-aortic balloon was inserted in 86% of 127 patients undergoing emergency bypass. A recent report by Naunhein et al (56) strongly supports this approach. LV assist devices have also been tried (57); even though they are more physiological, the published mortality statistics do not show improvement.

In a recent publication (58), the cardiovascular surgeons from the University of Toronto have revealed the results of a study on over 12,000 patients operated upon between 1982 and 1990 (level V). An analysis of risk factors has shown that among patients with an EF which varied between 20 and 40%, the predictors of operative death were urgency of operation, re-operation, sex, myocardial protection and age. In patients with an EF of less than 20%, the sole predictor of the risk of operative death was the urgency of operation. This report therefore suggests that patients with poor ventricular function following MI should be treated more aggressively by means that aim at myocardial protection before surgery is attempted.

CONCLUSION

For failed thrombolysis and persisting ischemia, angioplasty is a better alternative than surgery, primarily for logistic reasons. Angioplasty in such situations carries its own risks as previously mentioned. Bypass surgery should be restricted to cases of unstable angina where other means have failed or are not possible, keeping in mind that the time limit for `reversible ischemia' is 6 h. Hemodynamic instability remains not only a risk factor for operative mortality but also for death within the following six months (59).

RECOMMENDATION

Emergency coronary bypass grafting should be considered only in those patients with signs or symptoms of continued or recurrent ischemia, or who have hemodynamic instability and in whom other means, such as thrombolysis and/or percutaneous transluminal angioplasty (PTA), have failed, cannot be performed or have resulted in threatening complications such as acute thrombosis and plaque dissection (grade C, level III).

Surgery for failed thrombolysis or failed angioplasty practised electively in patients with residual ischemia demonstrated on the treadmill carries the same risk as that of elective coronary surgery and its indications are identical, ie, left main disease, proximal left anterior descending (LAD) with proximal right or circumflex, triple vessel disease and failure of medical treatment (grade C, level III).

Surgery for complicated MI, particularly for patients in cardiogenic shock, should be carefully evaluated taking into account that patients in this subgroup should be considered individually and that consideration should be given to techniques that improve coronary perfusion prior to surgery (grade C, level V).

We could find only one randomized controlled study that evaluated the results of immediate surgical reperfusion and those of conventional medical treatment. Urgent surgical reperfusion in acute evolving MI can be a safe and effective procedure when practiced within 6 h from the onset of symptoms (grade B, level II) (60).

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1992 CANADIAN CONSENSUS CONFERENCE ON CORONARY THROMBOLYSIS

Part IV: Economics

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Cost-effectiveness of inravenous thrombolytic drugs for acute myocardial infarction

The cornerstone of clinical policy-making is solid evidence about the efficacy and effectiveness of the treatment strategies being assessed. Economic analyses draw on efficacy and effectiveness evidence to determine the comparative efficiency of alternative treatments in monetary units. Since all physicians operate in a world of constrained resources, there are good reasons for considering economic issues in clinical policy development. However, the methodologies for cost-effectiveness analysis are still controversial, and the level of detail required for a full economic analysis is often lacking even for therapies that have been exhaustively evaluated through multiple clinical trials (1). No acceptable grading system for economic evidence has been proposed, and no consensus has emerged on how exactly cost-effectiveness analysis is to be incorporated into the policy-making process (1). Thus, the following cost-effectiveness analyses of thrombolytic therapy must be viewed as a secondary element in the formulation of policies and guidelines about these potentially life-saving drugs.

PLACEBO OR STREPTOKINASE: WHICH IS THE POINT OF REFERENCE?

Most economic analyses rely on the concept of incremental cost-effectiveness, or additional net cost per additional unit effect. The question immediately arises: Additional costs and effects compared with what? Economic analyses of thrombolytic drugs have compared these drugs

with conventional care in the prethrombolytic era. Data for those analyses are accordingly derived primarily from placebo-controlled trials. However, for clinical situations where thrombolysis is established as standard therapy, and where we wish to compare two agents, a new baseline is needed. The logical baseline is intravenous (iv) streptokinase (SK). This is because SK is the oldest, best-established and cheapest drug. If present studies show newer, more expensive regimens to be superior to SK, the issue then becomes: how much better than SK must these drugs be if their cost-effectiveness is to be similar to other cardiovascular interventions that are routinely funded in Canada?

In this paper we report the results of two related cost-effectiveness analyses. We start with a comparison of thrombolysis to placebo (ie, conventional care without thrombolysis). The primary rationale for this analysis is that there are some subgroups of patients where the cost-effectiveness of thrombolysis has been questioned, eg, middle-aged persons with inferior wall myocardial infarction (MI) who have a very low baseline mortality even without thrombolytic drugs. The next analysis deals with the comparison of recombinant tissue-type plasminogen activator (rt-PA) and SK. If the drugs are truly equivalent the analysis is unnecessary; SK would inevitably be the preferred agent owing to its price. However, well-known concerns about the adequacy of heparinization in GISSI-2 and ISIS-3 have led to the initiation of the GUSTO trial. GUSTO is comparing a `front-loaded' regimen of rt-PA, the now-standard regimen of SK, and a combination of SK and rt-PA. Thus, the second analysis is intended to assist with policy decisions that will be needed after the GUSTO trial reports its findings. Note that we deal here only with SK and rt-PA, not with the combination arm (which has costs intermediate between the single agents).

Because any advantage of rt-PA over SK is uncertain, the model uses a technique known as sensitivity analysis to project a range of possible differences in outcome that might be demonstrable in GUSTO. A sensitivity analysis varies the value of a variable to determine its impact on the results. This allows assessment of the effects of uncertainty about the true value of that variable. Two variables can also be assessed simultaneously with two-way sensitivity analysis.

METHODS

Overview of the model: The analysis extends and updates our previously published economic evaluation of the potential incremental benefits of iv rt-PA versus SK for treatment of MI (2). Readers are referred to that article for more details on methodology. A brief summary of the previous methods follows, together with a description of revisions made in the current update.

We use a third-party payer perspective (Ontario Ministry of Health). That is, we include only health care costs directly incurred by the insurer, and have not allowed for costs and benefits related to employment income, direct out-of-pocket costs incurred by patients and so forth. Hospital costs include appropriate allocations for overhead. We draw on costs for cardiovascular procedures and hospitalization for MI, as obtained anonymously for four Ontario teaching hospitals between 1986 and 1988. Professional charges were taken from the provincial health insurance fee schedule and drug costs obtained from the manufacturers. Only short term costs are included owing to uncertainty about the magnitude and direction of longer term incremental cost differences.

Potential clinical yields from treatment are estimated only with respect to survival. We have not attempted to estimate improvements in quality of life that might occur through, say, superior left ventricular (LV) preservation with improved functional status.

TABLE 1

Summary of costs and charges in 1991 dollars

Type of procedure	Professional	Hospitalization and/or procedure	Total*
Myocardial infarction	$430.86	$5,712.69	$6.144
Angiography	$382.23	$560.23	$942
Angioplasty	$357.91	$2,714.02	$3,072
Bypass surgery	$2,821.13	$11,027.22	$13,848

*Procedure costs for angiography and angioplasty exclude hospitalization costs and apply for the procedure alone. *Rounded to nearest dollar*

Survival benefits can be considered in two dimensions. First, one can calculate additional life-years from the continuing survival of persons who would have died in the first few weeks after myocardial infarction, but were spared. For persons treated with thrombolysis rather than placebo, this difference ranges from less than one to as many as four or five extra survivors per 100 persons treated with these drugs. For comparisons of two agents, however, the marginal yields are smaller. We would be surprised to find differences between SK and rt-PA that are greater than one or two survivors per 100 persons treated.

The second dimension involves an assumption that there might be better LV preservation and improved longer term survivorship with thrombolysis rather than placebo, or with one agent versus another. These gains would not be adequately reflected in immediate survival differences because most patients survive the index MI. Instead, they would be manifest in divergent survival curves over time. We have not incorporated this dimension in the present analyses for various reasons. First and foremost, longer term follow-up of placebo controlled thrombolysis trials has generally shown parallel survival curves (3), with only the Netherlands Interuniversity Trial indicating that the initial benefits from thrombolysis were substantially greater over time (4). If nonparallel survival curves have been unusual in placebo controlled trials, they are even less likely to be seen in interagent comparisons where the margin for gains in left ventricular preservation is smaller. Moreover, we earlier modelled the impact of divergent survival curves on the cost-effectiveness of rt-PA compared with SK. If rt-PA did not save any additional patients in the first few weeks after MI, the annual hazard rate difference would need to be at least 0.5% per year for its cost-effectiveness to be comparable to other common interventions. This extent of survival advantage is smaller than seen in the Netherlands Interuniversity Trial, but larger than demonstrated in any other placebo controlled study and thus very unlikely when two agents are compared.

Data are presented as incremental costs per additional short term survivor, ie, accounting for differences in mortality in the first few weeks after MI. We assume that survival curves track in parallel, and that in the absence of an initial survival advantage, no additional life-years are gained in the ensuing years of follow-up. Long term survival data following thrombolysis are still

limited, but a mean survival of at least 10 years seems entirely feasible based on: (A) treatment of a wide variety of patients, young and old; and (B) use of standard secondary preventive manoeuvres, ie, acetylsalicylic acid (ASA) and beta-blockers, with or without lipid-altering agents. For conservatism we suggest that readers divide the costs per additional short run survivor first by 5, and then by 10, to obtain estimates of the potential marginal costs per life-year gained. (Discounting has only a minimal impact in this context.)

Specific features of the present model: To carry out the present analyses, we first updated costs and prices from the earlier published work (2). Pharmacy acquisition costs for the thrombolytic agents are currently $460/1.5 million units for SK - an increase of about $170, and $2,900/100 mg for rt-PA - unchanged since the drug's release in the Canadian market. The 1991 Ontario Health Insurance Plan Fees Schedule was used to update all professional costs; these fees are comparable to those in other provinces. All percentages and ratios that were outlined earlier to calculate professional costs were kept the same, except that for coronary artery bypass surgery we assumed 70% of patients would receive a left internal mammary artery graft and that there would be an average of 3.5 grafts per patient. All costs were inflated to 1991 dollars with the Health and Personal Care component of the Canadian Consumer Price Index. Hospitalization costs for 1988 were inflated to 1991 dollars as well (Table 1). New professional, procedure and hospitalization costs were then summed to provide new total costs.

A meta-analysis of placebo controlled trials has indicated that use of thrombolytic therapy leads to a short term increase in the occurrence rate of mechanical revascularization procedures (5). We drew on that meta-analysis and on benchmarks suggested by the TIMI-IIB (6) trial to project procedure volumes for the previous cost-effectiveness analysis. We developed procedural projections as follows:

- The ratio of angiograms to revascularization procedures was taken from the TIMI-IIB trial. The overall six-week angiography rate was 636/1461=43.5%, with a corresponding revascularization rate of 391/1461=26.8% for percutaneous translumnal coronary

angioplasty (PTCA) plus coronary artery bypass graft (CABG). Hence the ratio is 636/391. In community hospitals the ratio was 94/55 whereas in teaching hospitals it was 542/336. Thus, the ratios of angiography to revascularization were very similar even though the actual rates of intervention differed substantially between the two types of settings. Since the ratios were so similar, the overall ratio was used.

- Various benchmarks were considered for use of revascularization after rt-PA or SK. ASSET (7) and GISSI-1 (8,9) were unrealistically low. Table 2 presents the data felt to be more pertinent (10-12).

Since there was no demonstrated advantage to the more aggressive use of procedures in tertiary hospitals in TIMI-IIB, the community hospital benchmarks were preferred. In fact, even these lower rates of intervention were deemed likely to overstate current Canadian practices. The ratios of PTCA: CABG in TIMI-IIB (6) and TPAT (11), a Toronto-based trial, were similar (1.50 and 1.67). Therefore, we assumed that in any scenario, the ratio would be 3:2 for PTCA:CABG. Universal angiography in TPAT, with two separate angiograms for a major subgroup of patients, led us to decide against accepting those data as typical. For more realistic estimates, we therefore took the data from the ECSG-III (12) trial and reallocated the procedures on a 3/2 basis: 35/355 PTCA and 23/355 CABG.

- To back-allocate procedures across rt-PA, SK and placebo, we used the revascularization ratios in the above-noted meta-analysis (5): rt-PA, 87 : SK, 51 : placebo, 35. These ratios may be partly attributable to the location and timing of the trials. However, it is intuitively reasonable to assume that if rt-PA shows any advantages over SK, it must do so by achieving a greater rate of sustained infarct artery patency. This in turn presupposes a higher probability of finding viable myocardium subserved by an arterial conduit in which there is residual atherosclerosis. The latter scenario would be expected to lead to some excess in revascularization. Beyond this rationale we have maintained these ratios for two reasons: (A) as noted below we have not found that procedure rates make a major difference in the results of such analyses; (B) as

explained in the original publication, we sought to incorporate consistent assumptions about cost inputs, so that we would, if anything, overestimate the costs associated with rt-PA. Attributing higher procedure rates to this drug helped ensure the consistent directionality of bias, especially as it appeared inconceivable that procedure rates would ever be lower than SK (unless, of course, a large amount of salvage angioplasty was undertaken for failed lysis).

These steps allowed us to generate Table 3.

The baseline cost-effectiveness of thrombolytic agents versus placebo was then estimated, and a two-way sensitivity analysis performed varying placebo mortality rates and the extent of relative risk reduction expected when thrombolytic drugs were used. By varying initial baseline placebo mortality rates, anterior and inferior infarcts can be represented (inferior infarct typical placebo mortality 4 to 12%, anterior infarct typical placebo mortality 12 to 20%). The interval 20 to 50% is assumed to represent the percentage reductions in relative risk compared with placebo that might occur when either drug is used in conjunction with ASA and heparin.

The cost-effectiveness of rt-PA versus SK was next examined by determining the incremental cost of using rt-PA per short term survivor. A one-way sensitivity analysis was performed by varying the absolute risk reduction in mortality rate that might hypothetically occur when rt-PA is used instead of SK.

TABLE 2

Number of short term revascularization procedures for patients treated with rtPA in some randomized trials

Trial	Followup	PTCA	CABG	Total
TIMIIIB (overall)	6 weeks	235/1461	156/1461	391/1461
TIMIIIB (10)*	6 weeks	32/306	23/30	55/306
TPAT (11)	12 weeks	10/59	6/59	16/59
ECSGIII (12)	12 weeks	24/355	34/355	58/355

**In community hospitals: 94/306 subjects underwent anglograms for a rate of 32% (versus 48% in tertiary centres)*

TABLE 3

Summary of short term procedure volumes used in the model

	Angiography	PTCA	CABG
rt-PA	29.23%	10.46%	7.52%
SK	17.13%	6.13%	4.41%
Placebo	11.76%	4.21%	3.03%

RESULTS

In the original publication costs were varied widely (typically halved at the low end and doubled at the high end) for sensitivity analyses. Results were relatively insensitive to changes in any factors apart from the short term and longer term mortality rates, costs of the more expensive drug and, to a small extent, the volume of procedures associated with one treatment versus another. Hence, we felt comfortable generating results that focused on the mortality advantages or disadvantages of various treatment strategies.

Thrombolysis versus placebo: The results of the comparison of thrombolysis to placebo or conventional care are shown as two-way sensitivity analyses. Tables 4 and 5 display the variable cost-effectiveness ratios associated with using thrombolytic therapy in different clinical scenarios. Recall that these results are short term cost-effectiveness analyses for no more than the first three months post-MI and should be divided by a number between 5 and 10, depending on how many years of survival one believes will accrue to the extra survivors generated by thrombolytic therapy.

Even use of rt-PA (Table 4) in scenarios with a low baseline mortality, eg, small inferior infarct, could be associated with cost-effectiveness ratios similar to some funded interventions (eg, $98,200 per life-year gained in the very worst case scenario of 4% baseline mortality, 20% relative risk reduction and only five years of life expectancy for any extra survivor in that subgroup!). For any scenario, SK will be more efficient than rt-PA given similar effectiveness of these two agents. These advantages for SK become especially dramatic when baseline event rates are low.

More important, however, is the observation that there is virtually no scenario wherein SK (Table 5) is not a cost-effective treatment. Take the case of a small inferior infarct, with a baseline mortality of 4% and the 20% relative risk reduction. This means that the mortality in the SK group is 3.2%, i.e., 125 persons must be treated for every death prevented. As shown here, even in the worst case where the extra survivor lives only five years the cost per life-year gained is about $20,000 - similar to bypass surgery for triple-vessel disease, and could be lower if we assume, variously, longer survival for the extra survivor, LV function benefits for other persons treated with SK or greater similarity in the rates of intervention with angiography and PTCA or CABG.

rt-PA versus SK: The results of the one-way sensitivity analysis updating the previous model continue to indicate that rt-PA is cost-effective as a substitute for SK if the absolute risk reduction in short term mortality rates is large (Table 6). Very minor survival advantages would render rt-PA cost-effective provided those advantages were sustained for at least five years on average. The cost-effectiveness ratios could become even more favourable if we made changes in the model similar to those that would optimize cost-effectiveness of SK relative to placebo: i.e., longer survival, LV function benefits to persons who would have survived anyway, and similar rates of intervention with angiography and revascularization procedures.

TABLE 4

Twoway sensitivity analysis for rtPA versus placebo: Cost per additional shortrun survivor

Relative reduction in mortality (%)

PBMR	20	30	40	50
0.04	$490.987.68	$327,325.12	$245,493.84	$196,395.07
0.06	$327,325.12	$218,216.75	$163,662.56	$130,930.05
0.08	$245,493.84	$163,662.56	$122,746.92	$ 98,197.54
0.10	$196,395.07	$130,930.05	$ 98,197.54	$ 78,558.03
0.12	$163,662.56	$109,108.37	$ 81,831.28	$ 65,454,02
0.14	$140,282.19	$ 93,521.46	$ 70,141.10	$ 56,112.88
0.16	$122,746.92	$ 81,831.28	$ 61,373.46	$ 49,098.77
0.18	$109,108.37	$ 72,738.92	$ 54,554.19	$ 43,643.35
0.20	$ 98,197.54	$ 65,465.02	$ 49,098.77	$ 39,279.01

PBMR Placebo baseline mortality rate (divide by expected duration of survival for cost per life-year gained)

TABLE 5

Twoway sensitivity analysis for SK versus placebo: Cost per additional shortrun survivor

Relative reduction in mortality (%)

PBMR	20	30	40	50
0.04	$102,824.21	$ 68.549.47	$ 51,412.10	$ 41,129.68
0.06	$ 68,549.47	$ 45,699.65	$ 34,274.74	$ 27,419 79
0.08	$ 51,412.10	$ 34,274.74	$ 25,706.05	$ 20,419.79
0.10	$ 41,129.68	$ 27,419.79	$ 20,564.84	$ 16,451.87
0.12	$ 34,274.74	$ 22,849.82	$ 17,137.37	$ 13,709.89
0.14	$ 29,378.35	$ 19,585.56	$ 14,689.17	$ 11,751.34
0.16	$ 25,706.05	$ 17,137.37	$ 12,853.03	$ 10,282.42
0.18	$ 22,849.82	$ 15,233.22	$ Il,424.91	$ 9,139.93
0.20	$ 20,564.84	$ 13,709.89	$ 10,282.42	$ 8,225.94

PBMR Placebo basellne mortality rate (divide by expected duration of survival for cost per life-year gained)

TABLE 6

Oneway sensitivity analysis for rtPA versus SK: Cost per additional shortrun survivor

Absolute risk reduction	Marginal cost per short term survivor
4.00%	$69,465.25
3.50%	$79,388.85
3.00%	$92,620.33
2.50%	$111,144.39
2.00%	$138,930.49
1.50%	$185,240.65
1.00%	$277,860.98
0.50%	$555,721.96

DISCUSSION

Limitations of the model: Any exercise such as the foregoing analysis has multiple limitations. First and foremost, we have chosen to ignore some parameters, and had to estimate many other inputs and outputs. As one example, differences in side effects are not specifically modelled. Trials comparing SK with rt-PA have shown statistically significant differences in major side effect profiles, but the differences are small and in opposing directions, ie, more hemorrhagic strokes with rt-PA and more bleeding events with SK. Minor side effects also differ, but their cost implications are unclear.

We have excluded not only noncardiac care costs in the short term model, but also long term costs. Even in our earlier work where we explicitly projected longer term survival (2), we did not

include differences in costs of medical care in the added years of life. As noted above, since the long term effects of the treatments are still largely unknown, the magnitude and even direction of these costs is uncertain. Improved cardiac function could be expected to result in fewer hospitalizations for cardiac pump failure, thus lowering costs; however, if there are more survivors with either drug versus placebo, or with rt-PA versus SK, treatment of those survivors could lead to medical care costs that would offset savings from treatment of pump failure. The third-party payor perspective also means that the model does not include productivity gains or losses because of early or late death.

Lastly, we have not explicitly considered treatment in the windows from 6 to 12 h and 12 to 24 h after onset of symptoms. However, reference to the tables should assist estimation of cost-effectiveness ratios for treatments in any time-window.

Relationship to other models: Laffel et al (13) have published a cost-effectiveness model for reperfusion therapy that explored subgroups according to time to treatment and other risk factors for in-hospital death. However, the model included now-questionable assumptions about a continuous and graded relationship between time to treatment from symptom onset and both extent of LV damage and in-hospital mortality. Treatment effects were assumed to disappear by 6 h from symptom onset. In the absence of a pricing structure, rt-PA was costed at $1,500 per dose. While this model is outdated, its strength was the explicit consideration of time from symptom onset.

Silberberg and McGregor (14) examined cost-effectiveness calculated as the incremental cost per one-year survivor with various strategies for iv SK. They assumed no increase in invasive procedures compared with conventional therapy, an assumption that will lead to an underestimate of the incremental costs of the reperfusion strategy. Cost-effectiveness ratios were only a few thousand dollars per additional survivor in most scenarios - a result similar to those shown here.

Steinberg et al (15) used trial evidence and a delphi process to generate inputs for a detailed model of the cost-effectiveness ratios for a conservative revascularization strategy after thrombolysis. Major increases in the use of invasive procedures were projected for both SK and rt-PA compared with placebo. The incremental cost per additional life saved in this model was based on a 1.3% absolute mortality advantage over placebo for SK, and a further 0.7% advantage for rt-PA. As in our analysis, these ratios would need to be divided by a factor of between 5 and 10 to generate costs per life-year. Unfortunately, the model was built using American Medicare charges and payments, and neither rt-PA (at $2,200) nor SK (at $190) were specifically reimbursed under Medicare. Thus, the incremental costs were $52,796 per life saved for SK versus conventional treatment, barely higher at $56,900 for rt-PA versus conventional treatment, and only $64,571 for rt-PA versus SK. The problematic costing of inputs means that these are not generalizable results.

Simoons, Vos and Martens (16) have provided a particularly useful analysis of the cost-effectiveness of thrombolytic therapy, based on three- to five-year follow-up data from the Netherlands Interuniversity Trial of SK. The generalizability of this model is limited by the fact that all the patients presented less than 4 h from symptom onset, ASA was not used and the intracoronary lysis regimen was atypical. The strength of the model is that survival out to three to five years, hospital days, reinfarction, procedure and medication use, and morbidity were all empirically derived. However, as noted earlier, the divergence in survival curves was far greater than has been seen in other trials. Very long term survival was projected based on appropriately matched subjects in published life tables. With appropriate discounting of deferred benefits and costs, the cost per year of life gained was only $2,690, rising to $2,940 after adjustment for quality of life. For anterior MI the cost per year of life gained was $2,000 while for inferior MI it was $7,030. These findings are in line with estimates generated by the present model, and underscore the comparative efficiency of thrombolytic therapy, even when treating modest-sized inferior MIs.

Krumholz et al (17) have recently addressed the specific question of the cost-effectiveness of treating elderly patients. Pooled data from elderly subgroups in large randomized controlled

trials were used to generate a baseline estimate that iv SK within 6 h would reduce mortality by 13%. This relative risk reduction is modest, but is associated with a high absolute mortality reduction because the baseline case fatality rate is so high for older persons with MI (estimated by Krumholz et al to be 29%). The authors used a published model to estimate post-MI life expectancy of older persons and factored in potential costs of complications from treatment. They estimated the incremental cost per year of life saved for an 80-year-old patient with suspected acute MI to be US$21,200 in 1993 dollars, and found that over "a wide range of assumptions about risks, benefits, and costs, the cost per year of life saved remained less than $55,000".

TABLE 7

Comparative costeffectiveness ratios of some interventions to reduce mortality from coronary heart disease in middleaged males (1988 Canadian dollars)

Intervention	Approximate marginal cost per lifeyear gained
Betablockers postMI in 55 yearold male at medium risk	$5,000
CABS for left mainstem disease	$9,000
CABS for threevessel disease	$20,000
Treatment of severe hypertension (diastolic BP ³105 mmHg)	$20,000
Treatment of moderate hypertension (diastolic BP 95104 mmHg)	$45,000
CABS for twovessel disease	$120,000
Lifelong cholestyramine, serum cholesterol = 6.85 mmol/L after diet; average risk profile	$250,000

From reference (2); adapted from references (1820). Exact costeffectiveness ratios will vary according to methodology of analysis. choice of index to inflate costs to current dollars and the exchange rate, hence ratios are rounded for ease of comparison. None of these studies made allowance for Indirect benefits in the form of wages and salaries, hence there are reasonable grounds for comparison with the costeffectiveness projections shown above.

Relationship to other cardiovascular interventions: Table 7 summarizes the comparative cost-effectiveness ratios for a variety of other interventions that are routinely provided in the cardiovascular sector. Note that these are shown in 1988 Canadian dollars; however, changes owing to inflation would be small. On a comparative basis it appears that SK is a highly cost-effective intervention in virtually all patient subgroups. SK is the agent of choice given its lower price and the lack of evidence that more expensive alternatives are superior. However, substitution of rt-PA for SK could lead to justifiable incremental expenditures for any subgroup where the absolute mortality advantages associated with the substitution are expected to be at least 1% in the first few weeks after MI. Empirical data from the GUSTO trial are obviously necessary before offering a final verdict on the role of rt-PA.

RECOMMENDATIONS

Economic analyses can complement but never supplant the appraisal of clinical risks and benefits of various treatment policies. Our findings underscore the clinical rationale for widespread adoption of thrombolytic drugs for patients with acute MI. The elderly and persons with small infarcts are sometimes denied thrombolytic therapy on the grounds that risks outweigh benefits, and the economic costs cannot be justified. While we have not considered clinical risk-benefit ratios here, suffice it to say that there are no economic grounds for witholding iv SK from patients with acute MI who present early after the onset of symptoms. SK is much less expensive than rt-PA and there is no proof of superior effectiveness of rt-PA for any subgroup of patients (although resistance is a serious concern for the tiny minority of patients who have previously received SK). Thus, SK is also uniformly more cost-effective than rt-PA and is the agent of choice on economic grounds. However, our projections using SK as a baseline show that modest short term gains in absolute mortality with rt-PA compared with SK

would lead to cost-effectiveness ratios that are competitive with commonly provided cardiovascular interventions.

ADDENDUM

Full results from GUSTO, including a detailed cost-effectiveness study mounted in conjunction with the trial, have yet to appear. The preliminary overall results show an absolute mortality advantage of 1%, with no obvious divergence of survival curves in the short run. For a 1% advantage the cost per extra short-run survivor in the foregoing model is $277,861. If mean survival of short-term survivors of AMI were five years, the cost per year of life gained would be about $56,000 before discounting. If mean survival were 10 years, the cost per year of life gained would be about $28,000. Accelerated rt-PA compared with SK therefore appears to have a cost-effectiveness profile similar to those calculated for other funded therapies. However, a definitive verdict, including cost-effectiveness profiles for various subgroups of patients, must await publication of the full GUSTO results with comparative cost data and longer term follow-up.

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