# Health Technology Advisory Committee Technology Evaluation Report

# Thrombolytic Therapy for Acute Myocardial Infarction



**May 18, 1994**

CONSULTANT'S REPORT

# Health Technology Advisory Committee

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# Preface

The Health Technology Advisory Committee (HTAC) is convened by the Minnesota Health Care Commission pursuant to the MinnesotaCare Act. HTAC is responsible for evaluating research and assessments regarding health care technologies to provide Minnesota-specific information for consumers, health care providers, group purchasers, and health plan companies.

This report compares the thrombolytic agents tissue plasminogen activator and streptokinase for treating acute myocardial infarctions.

Thrombolytic therapy involves giving a person who is experiencing a heart attack a "clotbusting drug" to break up a blot clot in a coronary artery that is obstructing blood flow. HTAC originally selected one particular thrombolytic drug--tissue plasminogen activator (tPA)--for evaluation. HTAC's evaluation process led to evaluation of a second drug--streptokinase (SK). The process also led HTAC to some conclusions about utilization of thrombolytic therapy generally. HTAC's report was approved by the Minnesota Health Care Commission on May 18, 1994.

In the judgment of the health care commission, the most significant conclusion in the report relates to the present underutilization of thrombolytics generally. Thrombolytics are relatively safe and effective. They should be used more often and earlier in the treatment process, since their benefit diminishes as time passes after the onset of heart attack symptoms. Currently, approximately 30% of patients in Minnesota admitted for acute myocardial infarction receive thrombolytic therapy. Increased use of thrombolytic therapy in appropriate situations will improve treatment outcomes, reduce the risk of permanent disability, reduce health care costs, and allow patients to return home and to work more quickly.

This report does not recommend any one thrombolytic agent over another. Both drugs have advantages and disadvantages that differ from patient to patient. The purpose of this report is to provide objective, Minnesota-specific information that will lead to well-informed decision making. The report evaluates the available research and assessments regarding tPA and streptokinase. Decisions regarding the appropriate thrombolytic agent to administer in a particular situation should be made by the treating practitioner on a case-by-case basis. Cost-effectiveness is one factor among many that must be considered. Because tPA is much more expensive than streptokinase, its use should be confined to patients who, in the treating physician's judgment, are most likely to benefit.

**Minnesota Health Care Commission**

# EXECUTIVE SUMMARY

## *Description:*

Acute myocardial infarction (AMI) results from the sudden obstruction of a coronary artery by a blood clot (thrombus). Thrombolytic therapy is a method of dissolving such blood clots and restoring blood flow to the heart. Tissue plasminogen activator (tPA) and streptokinase (SK) are the two common thrombolytics used in Minnesota. The approximate purchase price of tPA and SK to the provider are $2300 and $300 per dose, respectively. The approximate difference in purchase price to the patient is $2400.

## *Rationale:*

Several of the earlier large clinical trials have found no significant difference between tPA and SK in terms of clinical effectiveness. Smaller trials suggested that the method of administering tPA in those trials was not the most effective. In 1993 a large clinical trial (GUSTO) compared a new regimen for administering tPA (accelerated tPA) with SK and found tPA to be more clinically effective. The difference in the mortality rates experienced by patients treated with the two drugs was small (6.3% vs. 7.3%) but statistically significant. This technology was selected for evaluation because the small increment in clinical effectiveness associated with accelerated tPA (1%) appears to have a high incremental cost ($2000 per patient). It was also selected due to the number of Minnesotans affected by AMI annually (approximately 12,000).

## *Conclusions:*

1. Thrombolytic therapy saves lives.

2. Thrombolytics are under-utilized. In Minnesota we estimate that there are approximately 12,000 hospital admissions for acute myocardial infarction annually. It is estimated that only 30% of these patients currently receive thrombolytic therapy.

3. The benefit of thrombolytic therapy diminishes with time after symptom onset. Providers of health care should make every effort to administer thrombolytic therapy to appropriate patients without delay.

4. Both streptokinase and tissue plasminogen activator are safe and effective thrombolytic agents.

5 Available data appears to indicate that accelerated tissue plasminogen activator confers an additional survival benefit compared to streptokinase, especially for anterior infarcts, or when thrombolytic therapy is initiated within four hours after symptom onset.

6. Available data indicates an increased rate of stroke associated with the use of tPA; approximately 2.5 additional strokes per 1000 patients. The cost associated with treating strokes and the impact on health outcome should be considered in comparing the cost of tPA to SK.

7. Based on a $2000 difference between the cost of tPA and streptokinase, using tPA would reduce mortality at a cost of approximately $200,000 per additional life saved or approximately $29,000 per life year saved (based on an incremental life expectancy of 11 years).

8. Current estimates of the use of thrombolytics in Minnesota vary widely and Minnesota-specific data on the use of thrombolytics is limited. On the basis of the data currently available, it is estimated that using tPA as the thrombolytic of choice in Minnesota would save approximately 35 additional lives annually, when compared with streptokinase, at an additional total cost of approximately $7 million.

9. Physicians should recognize that the cost of tPA is approximately seven times that of streptokinase, and hence, the use of tPA should be confined to patients who, in the treating physician's judgment, are most likely to benefit.

## *Implications:*

If patients are treated with thrombolytics within one hour of the onset of symptoms, their chances of survival are maximized. Counties, health regions, and public health officials may consider health education aimed at decreasing the time it takes a patient to recognize symptoms and get to the hospital.

If patients are treated with thrombolytics within 30 minutes of arrival in the emergency room (as recommended by the National Heart Attack Alert Program), their chances of survival are also increased. Hospitals' emergency room personnel and emergency physicians are encouraged to streamline emergency room procedures with this goal in mind.

Integrated Service Networks may wish to develop standard protocols designed to assure the use of tPA for cases where it will be the most effective.

## *Other Issues/Considerations:*

1. Minnesota-specific data on the use of thrombolytics is limited. More complete data would permit HTAC to draw more specific conclusions.

2. Regional Coordinating Boards (RCBs) may wish to monitor how medical facilities and networks in their regions are addressing the issues raised by this evaluation.

3. The Practice Parameters Advisory Committee (PPAC) may wish to develop guidelines to assist physicians in determining which patients are most likely to benefit from tPA.

4. As additional analysis of the GUSTO data becomes available, a re-evaluation of tPA may be warranted.

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HTAC

# INTRODUCTION

## Legislative Charge

The Health Technology Advisory Committee (HTAC) was established by the Minnesota Legislature as an advisory committee to the Minnesota Health Care Commission (MHCC). HTAC has seventeen members that represent diverse sectors of the health care industry as well as different geographic areas of Minnesota.

HTAC is responsible for conducting "evaluations of existing research and technology assessments conducted by other entities of new and existing health care technologies." Technologies are defined as including "high-cost drugs, devices, procedures, or processes applied to human health care, such as high-cost transplants and expensive scanners and imagers." [§62J.15, Subdivision 1].

The legislature directed HTAC to consider the following criteria in selecting technologies for evaluation:

1) the level of controversy within the medical or scientific community, including questionable or undetermined efficacy;

2) the cost implications;

3) the potential for rapid diffusion;

4) the impact on a substantial patient population;

5) the existence of alternative technologies;

6) the impact on patient safety and health outcome;

7) the public health importance;

8) the level of public and professional demand;

9) the social, ethical, and legal concerns; and

10) the prevalence of the disease or condition [§62J.15, Subdivision 2].

## Definitions

In conducting technology evaluations, HTAC considers safety, clinical effectiveness, improvement in health outcomes, and cost effectiveness [§62J.15 Subdivision 3]. These terms are defined as follows:

> Safety means a judgment of the acceptability of risk of using a technology in a specified situation [§62J.03, Subdivision 9].
> Clinically effective means that the use of a particular medical technology improves patient clinical status, as measured by medical condition, survival rates, and other variables, and that the use of the particular technology demonstrates a clinical advantage over alternative technologies [§62J.03, Subdivision 2].
> Improvement in health outcome means an improvement in patient clinical status, and an improvement in patient quality-of-life status, as measured by ability to function, ability to return to work, and other variables [§62J.03, Subdivision 7].
> Cost effective means that the economic costs of using a particular technology to achieve improvement in a patient's health outcome are justified given a comparison to both the economic costs and the improvement in patient health outcome resulting from the use of alternative technologies [§62J.03, Subdivision 5].

The legislature defined the terms "evaluate," "evaluation," and "evaluating" to mean "the review or reviewing of research and technology assessments conducted by other entities relating to specific technologies and their specific use and application." [§62J.15, Subdivision 1a]. The legislature also set forth a process for evaluating technology that permits HTAC to "collect and evaluate studies and research findings on the technologies selected for evaluation from as wide a range of sources as needed, including, but not limited to: federal agencies or other units of government, international organizations conducting health care technology assessments, health carriers, insurers, manufacturers, professional and trade associations, nonprofit organizations, and academic institutions. The health technology advisory committee may use consultants or experts and solicit testimony or other input as needed to evaluate a specific technology" [§62J.15, Subdivision 4].

## Prioritization Process for Designating Technologies

HTAC uses a structured, open process for selecting technologies for evaluation, based on a model proposed by the national Institute of Medicine in its report, Setting Priorities for Health Technology Assessment: A Model Process. The technology selection process includes: setting and weighting criteria for selection; soliciting nominations of technologies for evaluation; preliminary winnowing of the initial nominations through group consensus of HTAC; information gathering on the remaining smaller number of technologies of interest; scoring the technologies according to the selection criteria, based on information compiled; and final review and consen-

sus ranking of the scored technologies by HTAC.

HTAC's process for nominating, reviewing, winnowing, and selecting technologies for evaluation was developed during the period April-September 1993 following extensive staff work, HTAC discussions, and briefings of the Minnesota Health Care Commission, both directly and through the Commission's HTAC Liaison Committee. Nominations of technologies for evaluation were solicited from HTAC members and the Minnesota Health Care Commission. Over 100 technologies were initially nominated for evaluation. A number of HTAC meetings and group exercises were devoted to weighting the legislatively mandated criteria for selecting technologies. Cost implications and public health importance were weighted most heavily. HTAC narrowed the preliminary list of technologies to 10 semi-finalists using a structured, iterative winnowing process. The list was further narrowed to 5 technologies following additional research and scoring of the technologies according to the selection criteria. Of the five technologies of greatest interest, tissue plasminogen activator (tPA) for acute myocardial infarction was selected by committee consensus as the first technology for evaluation by HTAC.

## Evaluation Process

Below is a brief summary of the HTAC technology evaluation process. The process described below is a general framework for conducting evaluations and does not reflect the full scope of HTAC's technology evaluation process.

At the outset of the process, notice was published in the State Register announcing that HTAC had selected tPA for acute myocardial infarction for evaluation, and soliciting comments and information.

Literature searches were conducted by staff and reviewed by a working group consisting of four HTAC members. The working group selected the most pertinent articles for initial review (see Appendix A). After developing a list of relevant issues/questions (see Appendix B), additional pertinent articles were identified and reviewed by the working group.

In addition to the working group's review of select articles, an independent review was conducted by ECRI, a non-profit technology assessment firm. The initial list of pertinent articles and the list of questions/issues developed by the working group was distributed to numerous other interested parties. HTAC members and other identified experts were contacted and interviewed during the course of the evaluation. The working group was also assisted by a consultant that participated in all working group activities and was responsible for drafting this report.

Technology assessments conducted by other entities, practice guidelines, institutional protocols, and other information was solicited by making specific requests of national and international technology assessment organizations, health carriers, insurers, managed care companies, various professional societies and associations, Minnesota medical institutions, practicing physi-

cians, and others. Efforts were made to obtain protocols from a representative sample of medical facilities throughout the state of Minnesota. Additional information was solicited directly from the manufacturers of thrombolytic agents and academic institutions. Further efforts were made to solicit input from interested parties by contacting various trade and professional organizations.

National and statewide data were obtained from the American Heart Association, the Minnesota Center for Health Statistics, the Metropolitan Healthcare Council, the Foundation for Health Care Evaluation, and the Myocardial Infarction Registry. Additional data were compiled from surveys and other data collection efforts.

Several pharmaceutical companies that produce thrombolytic agents responded to a solicitation for input on the issues/questions developed by the working group by making presentations to the working group. Public notice of the presentations were provided so that interested parties could attend.

HTAC was kept apprised of the working group activities during regularly scheduled HTAC public meetings, through written communications, and provided input throughout the technology evaluation process. A draft preliminary tPA Technology Evaluation Report was presented to HTAC along with background information and supporting data. The preliminary report was approved by HTAC and has been made available for public comment. In addition, copies of the preliminary report were mailed to members of the Minnesota Health Care Commission (MHCC), individuals identified as experts, and other individuals that expressed interest in the evaluation of tPA.

A State Register Notice was published announcing the availability of the Preliminary tPA Technology Evaluation Report, soliciting written comments, and setting a public hearing date. The Notice also included a summary of a preliminary tPA Technology Evaluation report. A copy of the Notice was mailed to individuals listed on numerous public mailing lists maintained by HTAC and MHCC. Written comments were reviewed by the tPA working group and several revisions were made in the preliminary tPA Technology Evaluation Report. HTAC's final report was presented to the MHCC along with public testimony on April 20, 1994. The MHCC took final action on the report on May 18, 1994.

# BACKGROUND

The annual frequency of acute myocardial infarction (AMI) in the U.S. is nearly 1.5 million, accounting for approximately 750,000 hospital admissions per year, and one-fourth of all deaths in the U.S. (Martin, 1991). Most cases of AMI result from the sudden obstruction of a coronary artery by a blood clot or thrombus at the site of a rupture in the plaque lining the artery. The presence of an AMI can be confirmed by observing a distinctive wave pattern on an electrocardiogram (EKG). Physicians identify this wave pattern by elevated ST segments. Approximately 66% of heart attack victims exhibit this pattern (Gunnar, 1990). As blood flow is restricted, tissue begins to die. The sooner the clot can be removed or reduced, the sooner blood flow is restored, and tissue deterioration halted.

Patients who present with the distinctive pattern of symptoms associated with AMI, such as chest, arm, jaw, neck or back pain, nausea and/or perspiration lasting at least 20-30 minutes typically receive an EKG as soon as possible. If elevated ST segments are observed, the patient is then screened for contraindications.[1] If none are present, the patient is eligible for thrombolytic therapy. If a cardiac catheterization laboratory is readily available, a catheterization may also be indicated, initially for the purpose of confirming the diagnosis, and often for the purpose of opening the blocked blood vessel with angioplasty.

## Treatment for Patients with Acute Myocardial Infarction

Current treatments for AMI all focus on removing the obstruction, restoring blood flow, and preventing new clots from forming. Thrombolytic therapy is the least invasive method of dissolving such blot clots and restoring blood flow to the heart.

### *How Thrombolytics Work*

These agents are administered intravenously, over periods of time varying from a few minutes to three hours. Five thrombolytic agents have been studied over the past forty years in a series of large, controlled clinical trials. Streptokinase (SK), anistreplase (APSAC) and urokinase (UK) are non-fibrin specific agents. That is, they are not able to target the thrombus, so their action is system-wide. Tissue plasminogen activator (tPA) and single-chain urokinase plasminogen activator (scu-PA) are genetically engineered to convert naturally occurring plasminogen into its active form, plasmin, which then breaks down the blood clot. The tPA molecule has a binding site for fibrin, the natural substance that forms the clot, thus tPA in the blood stream will be

[1] Contraindications are described on page 11.

"attracted" to the site of the clot rather than activate plasminogen throughout the body. Additional drugs, such as heparin, are administered in combination with all thrombolytics to prevent additional clotting, once the thrombus is lysed (dissolved) (Anderson and Willerson, 1993).

Because thrombolytic agents dissolve blood clots, and concomitant anticoagulant therapies prevent further clotting, patients who are bleeding, or are at risk for bleeding based on prior health history, are often judged ineligible for such therapy. In the ISIS-3 comparison of SK with tPA, tPA was associated with an increased risk of stroke (ISIS-3, 1992).

While thrombolytic agents are administered intravenously, some other therapies for AMI are more invasive, such as percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass graft surgery (CABG). In many cases, these more expensive procedures are employed *in addition to* the thrombolytic therapy. There is, in fact, some evidence that patients receiving one thrombolytic agent are more likely to receive a surgical procedure than patients receiving other thrombolytic agents. In the most recent large clinical trial (GUSTO, 1993), patients treated with tPA were significantly more likely to receive CABG surgery than patients treated with SK, while rates of congestive heart failure, pulmonary edema and cardiogenic shock appeared to be somewhat lower among the tPA patients (Ridker et al, 1993).

## Current Use of Thrombolytics

Recent national estimates suggest that as few as 10% of patients presenting with AMI receive thrombolytic therapy (Doorey, Michelson and Topol, 1992). Based on currently accepted standards, approximately three times as many AMI patients are eligible for such therapy.

The University Hospital Consortium (UHC), a not-for-profit alliance of academic medical centers throughout the U.S., surveyed its members regarding their use of thrombolytic therapy. According to the UHC report, in 1992 tPA accounted for 53% of all thrombolytics used in the U.S. A 1991 survey of UHC members reported that 86.7% of the money spent on thrombolytics was spent on tPA, compared with 4.2% for SK and 9.2% for APSAC (Behal, 1993). These usage patterns have occurred during a period prior to the release of the GUSTO findings, when large-scale clinical trials, GISSI-2 and ISIS-3, suggested no meaningful difference in mortality between tPA and SK.

## Minnesota Experience

Based on a statewide analysis of Medicare claims, combined with hospital data provided by the Metropolitan Healthcare Council, it is estimated that Minnesota hospitals treated 12,000 AMIs in 1992. Although these data sources indicate that 5-12% of AMIs in Minnesota receive

some thrombolytic agent, Genentech, the manufacturer of tPA, estimates that 30% of AMIs receive a thrombolytic agent. Information obtained from Minnesota physicians indicate that the use of thrombolytic therapy in the state may be as high as 60%. In sixteen Minnesota hospitals where Genentech maintains an infarct registry, 30.5% of AMIs admitted in 1992-3 received thrombolytic therapy. Genentech estimates that tPA accounts for 52% of thrombolytics used in Minnesota, with SK accounting for 47% and APSAC 1%. Since tPA and SK account for 99% of thrombolytics used in Minnesota, this report is focused on those two drugs

Table 1

Total AMIs in Minnesota, 1992

| | Medicare | Non-Medicare | Total |
|---|---|---|---|
| Metro | 2332 | 2804 | 5136 |
| Non-Metro | 3487 | 2970* | 6457* |
| Total | 5819 | 5774* | 11593* |

*Estimates based on the assumption that 54% of non-metro hospital patients are reimbursed under Medicare.

# FDA APPROVAL

Both tPA and SK are approved by the Food and Drug Administration for use in the treatment of myocardial infarction. However, current FDA approval for tPA is based on a three-hour regimen for administering the drug. In the GUSTO trial, and in treatment protocols currently used in most hospitals, tPA is administered according to an accelerated or front-loaded regimen, whereby most of the dosage is administered in the first thirty minutes. The accelerated regimen is not yet approved by the FDA. Meanwhile, past practice indicates that administering a drug in a manner other than that specifically approved by the FDA is often accepted as a matter of physician discretion.

# REVIEW OF EVIDENCE

## *Safety*

All large-scale clinical trials of thrombolytic therapies have found them to be safe when used in conjunction with appropriate protocols, and when contraindications are observed. Four of these trials are described and appropriately cited below. The contraindications and associated

risks continue to be evaluated with increased clinical experience. As mentioned above, the primary contraindications are associated with bleeding.[2]

### *Absolute contraindications*

- Active internal bleeding within previous 10 days
- Other major bleeding event within 6 weeks
- Head trauma or surgery within one month
- Stroke within six months
- Pregnancy
- Suspected aortic dissection
- Intracranial neoplasm (tumor), arteriovenous malformation, or aneurysm
- Known bleeding diathesis (tendency)
- Blood pressure greater than 200/120

### *Relative contraindications*

- Puncture of a non-compressible vessel
- Recent non-head trauma or surgery (within 2 weeks)
- Cardiopulmonary resuscitation for more than 10 minutes
- History of hypertension (high blood pressure)
- Active peptic ulcer
- Significant liver dysfunction
- Age greater than 75 years
- More than six hours since onset of pain

### *Contraindications for Streptokinase*

- Previous allergic reaction to SK
- Prior exposure to SK or APSAC in past 6-9 months

## Risks

For patients with no contraindications, thrombolytic therapy is not without risks. While all AMI patients have some risk of stroke (1-2% in large trials), there is some indication that this risk is slightly higher for patients treated with tPA as compared with patients treated with SK. In the ISIS-3 study, this difference was small but significant. Of approximately 13,500 patients

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[2] These contraindications are based on the American College of Cardiology's Guidelines for the Early Management of Patients with Acute Myocardial Infarction. Since that list was compiled in 1990, they have been modified slightly to reflect current practice (Gunnar,1990).

treated with each drug, there were 141 strokes among those treated with SK and 188 among those treated with tPA. In the GUSTO trial, there was a greater incidence of stroke in patients that received tPA (1.55% versus 1.3% for combined SK groups, p = .09). In drawing conclusions from the subsequent GUSTO trial, non-fatal strokes are added to deaths as negative outcomes to account for this increased risk.

Since all thrombolytics suppress the blood's ability to coagulate, there are additional risks for other types of bleeding. The GUSTO trial found that patients treated with SK were significantly more likely to suffer moderate non-stroke bleeding that is not life threatening than patients treated with tPA (5.7% for combined SK groups versus 5.1% for tPA, p = .04). Overall, non-fatal strokes occurred in approximately 1.5% of all patients, and other moderate bleeding occurred in approximately 5.5%.

It should also be noted that SK has certain risks not associated with tPA. Because SK is derived from bacteria, there is an increased risk of allergic reaction and hypotension.

## Clinical Effectiveness

While there are an estimated 4000 publications on the subject of thrombolytic therapy for acute myocardial infarction, comparisons of the major drugs used for such therapy have been made in several large controlled clinical trials, each of which is summarized in a small number of publications. As each of these trials has been published, new questions have been raised and new regimens have been included in subsequent trials. Because of the large numbers of patients treated in these trials, the HTAC believes that a reasonable evaluation of the relative efficacy of tPA as compared to SK can be made on the basis of a relatively small number of articles. The primary trials include GISSI-1, GISSI-2, ISIS-2, ISIS-3 and GUSTO-1 (see bibliography for full citations). While these studies have been focused on short-term mortality outcomes, smaller studies have been focused on specific clinical outcomes such as the degree to which the occluded artery is opened (patency) within 90 minutes or within three hours, and the degree to which left ventricular function is restored.

A series of large-scale trials during the 1980s produced evidence of the effectiveness of thrombolytic therapy. In GISSI-1, a control group, not treated with any thrombolytics, had a 13% 21-day mortality, while patients treated with thrombolytics experienced a significantly lower rate of 10%. (This amounts to a relative mortality reduction of approximately 20%.) ISIS-2 confirmed the GISSI-1 mortality findings, and demonstrated that adding aspirin to the thrombolytic regimen significantly improved treatment outcomes, although it was associated with a small increase in rates of bleeding requiring transfusion. Short term mortality rates reported in ISIS-2 were as follows: aspirin and SK 8.0%; aspirin-only 10.7%; neither aspirin or SK 13.2%. Long term follow-up of patients from these and several smaller early trials indicated

that the mortality benefit associated with thrombolytics is maintained for several years. Because of the indisputable benefit of thrombolytics, subsequent large-scale trials did not include a control (placebo) group. In fact, one small study was stopped early when a 50% reduction in mortality was observed for patients in the treatment group (AIMS, 1988).

GISSI-2 was the first large-scale trial (20,891 subjects) to compare two thrombolytics, tPA and SK, on the basis of their effects on mortality and left ventricular function. This study used a combined endpoint of death or extensive left ventricular damage. No significant differences were found between tPA and SK on the combined endpoint, and an overall 21-day mortality rate of 8.8% was observed. However, tPA was associated with significantly more strokes (1.33% vs. .94%, p = .008).

ISIS-3 set out to assess the balance between the increased risk of hemorrhagic stroke or other bleeding associated with some thrombolytics, and the clinical advantages of these drugs as established in earlier large-scale trials, as well as the early patency established by small-scale trials. In addition, ISIS-3 added a third drug, APSAC. Again, no clear difference was observed between the three thrombolytic agents on the major endpoint of 35-day mortality. However, other findings included a significantly higher rate of allergic reaction and hypotension requiring treatment for SK, and a significantly lower rate of stroke and cerebral hemorrhage for that drug. In addition, ISIS-3 found no significant benefit from adding the anticoagulant heparin, administered subcutaneously, in addition to aspirin, although heparin was associated with increased risk of non-cerebral bleeding.

The GUSTO trial, results of which were released in mid-1993, was the first large-scale trial to use an accelerated regimen of tPA. Earlier trials administered tPA over a three-hour period, while the accelerated regimen administers 65% of the dose in the first thirty minutes. The accelerated regimen was shown to achieve greater patency 90 minutes after administration in two small trials (Neuhaus et al, 1989; Carney et al; 1990). The GUSTO evaluators reasoned that, by opening the artery earlier, an accelerated regimen of tPA might achieve lower mortality rates than SK.

In addition to these treatment regimens, GUSTO included a SK group treated with subcutaneous heparin, as was used in ISIS-3, and a fourth group, consisting of a combination of SK and tPA with IV heparin.

GUSTO was the first large-scale clinical trial to find significant differences in short-term

mortality outcomes between different thrombolytic agents. The most significant finding was a 6.3% mortality rate for the accelerated tPA group as compared with a 7.3% combined mortality rate for the two SK groups. However, the SK group given subcutaneous heparin had slightly better results than the SK group given IV heparin. Since ISIS-3 had reported a higher rate of strokes associated with the use of tPA (1.1% versus 1.4%, p <.01), the GUSTO investigators used both deaths and strokes as major endpoints. When the regimen of SK with subcutaneous heparin is compared with the regimen of accelerated tPA with IV heparin, on the combined endpoints of death or disabling stroke, tPA remains significantly clinically superior (6.9% vs. 7.7%, p=.006). The use of tPA accounted for an additional eight persons per thousand surviving without a disabling stroke. The increased incidence of stroke and bleeding associated with tPA did not offset the significant difference in mortality. In addition, the tPA group had significantly fewer allergic reactions (1.6% vs. 5.7%, p <.001), and a lower incidence of sustained hypotension (10.1% vs. 13.3%, p < .001). The GUSTO investigators concluded that accelerated tPA with IV heparin "is the best thrombolytic strategy to date for patients with acute myocardial infarction."

## Table 2

### Short-Term Mortality Rates (and Stroke Rates) in Large-Scale Clinical Trials of Thrombolytic Therapy

| Study | Year | # of Patients Randomized | Aspirin-only | SK + Aspirin | tPA + Aspirin |
|---|---|---|---|---|---|
| ISIS-2 | 1988 | 17,187 | 10.7 (.5) | 8.0 (.6)* | na |
| GISSI-2 | 1990 | 20,891 | na | 8.5 (.9) | 8.9 (1.3)** |
| ISIS-3 | 1992 | 41,299 | na | 10.6 (1.0) | 10.3 (1.4)** |
| GUSTO-1 | 1993 | 41,021 | na | 7.3 (1.3) | 6.3 (1.55)*** |

* Difference in mortality rates significant at p < .01

** Difference in stroke rate is significant at p < .01

*** Difference in mortality rate is significant at p < .001. Difference in stroke rate is marginally significantly at p = .09.

The GUSTO investigation has been criticized as potentially biased in favor of tPA patients (Ridker et al, 1993). Critics site the fact that participating physicians were not "blinded," that is, they knew which drugs their patients received. GUSTO included physicians and patients in twelve European countries, Australia and New Zealand, as well as the U.S. Since most American physicians favored tPA, critics suggest that they may have treated their tPA patients more aggressively. As evidence of this bias, they point out that mortality differences between tPA and SK in

other countries were smaller (6.9% vs. 7.3% for the SK with SC heparin group), and larger in the U.S. (5.9% vs. 7.1%). They also point out that a greater proportion of the tPA group received potentially life-saving CABG surgery than the SK group (9.5% vs. 8.5%, p<.01). While a 1% difference in the frequency of CABG is not sufficient to explain the difference in mortality outcomes, it may be an indication that participating physicians treated tPA patients differently.

Some critics have suggested that all large-scale trials involving tPA and SK should be combined in a meta-analysis. The resulting data set of over 100,000 patients would undoubtedly lead to conclusions more in keeping with the earlier trials, GISSI-2 and ISIS-3. Defenders of the GUSTO findings claim that these trials cannot be combined, due to the substantially different tPA regimen used in the GUSTO trial. The accelerated tPA regimen has been shown to achieve earlier coronary artery patency and superior left ventricular function when compared to the tPA regimen used in the earlier trials, and when compared to SK.

Prior to the GISSI-2 trial, the major rationale for using tPA rather than SK had been higher patency (the degree to which the artery is opened) achieved at 90 minutes as observed in the TIMI trials (Chesebro et al, 1987). Many cardiologists subscribe to the "open artery hypothesis," which states that the earlier the artery is opened the better are the patient's chances of survival. GISSI-2 raised some doubts about this hypothesis, since the earlier patency assumed to be achieved by tPA did not result in significantly lower mortality.

To establish the connection between early patency and patient survival, the GUSTO investigators conducted angiographic analysis of a small group of patients (GUSTO Angiographic Investigators, 1993). They tested the open artery hypothesis by breaking it down into three parts:

- Accelerated tPA achieves greater patency within 90 minutes of treatment.
- Greater early patency results in improved heart function.
- Improved heart function is associated with lower mortality

Each of these statements was supported by their analysis. Approximately 2400 patients were randomly selected from each of the four treatment groups (Two SK groups, one tPA group and one tPA + SK group). 81% of the group treated with tPA had partially or fully open arteries (TIMI Grades 2 and 3) 90 minutes after treatment compared with 60% of the SK + IV heparin group (p< .001). A different group of patients, whose patency was measured after 180 minutes, showed no significant differences between drugs. When early patency is indicated only by fully open arteries (TIMI grade 3), the results were similar, in favor of tPA, with 54% versus 32% (p < .001) of patients with complete (TIMI grade 3) flow at 90 minutes, but similar degrees of TIMI 3 flow at 180 minutes.

## Table 3

## GUSTO ANGIOGRAPHIC STUDY: PATENCY

| | SK + SC Heparin % | SK + IV Heparin % | Accelerated tPA % | tPA + SK % |
|---|---|---|---|---|
| *Angiography at 90 minutes* | | | | |
| Open vessel (TIMI Grades 2 and 3 combined) | 159/293 (54%) | 170/283 (60%) | 236/292 (81%)* | 218/299 (73%)* |
| Complete reperfusion (TIMI Grade 3) | 85/293 (29%) | 91/283 (32%)* | 157/292 (54%)* | 114/299 (38%) |
| *Angiography at 180 minutes* | | | | |
| Open vessel (TIMI Grades 2 and 3 combined) | 77/106 (73%) | 72/97 (74%) | 71/93 (76%) | 77/91 (85%) |
| Complete reperfusion (TIMI Grade 3) | 37/106 (35%) | 40/97 (41%) | 40/93 (43%) | 48/91 (53%) |

* $p < .001$ when compared with both SK groups

The second part of the open artery hypothesis was supported by observing that a fully open artery (TIMI Grade 3) was associated with better heart function. For five different measures of heart function[3], fully open arteries performed significantly better than partially opened arteries (TIMI Grade 2). Similarly, each of these measures of heart function was significantly associated with survival. That is, patients with better heart function by these measures were significantly less likely to die within the 30-day study period.

Although the significant differences in 90-minute patency appeared to disappear after 180 minutes, the effects of 90-minute patency on mortality were significant as shown in Table 4.

The study establishes a statistically significant relationship between getting the artery opened within 90 minutes and survival of myocardial infarction, thus supporting the open artery hypothesis.

[3] 1)Ejection fraction; 2)end-systolic volume index; 3) wall motion (standard deviation per chord) ; 4) abnormal chords; and 5) preserved regional wall motion.

Table 4

## 90-MINUTE PATENCY AND 30-DAY MORTALITY

| Degree of Patency at 90 minutes | 30-day mortality (%) |
|---|---|
| TIMI 0 or 1 | 8.9 |
| TIMI 2 (partially opened artery) | 7.4 |
| TIMI 3 (fully opened artery) | 4.4 |

TIMI 3 vs. TIMI 2, p = .08 TIMI 3 vs. TIMI 0 or 1, p = .009

### *Differential Effectiveness for Subpopulations*

The GUSTO investigators specified three groups of patients for subgroup analysis according to age (>75 years vs. ≤75 years), infarct location (anterior vs. inferior), and the time to treatment.

Several protocols currently in use by Minnesota hospitals indicate that patients over age 75 are considered poor candidates for thrombolysis. While it is true that older patients have higher mortality rates, the GUSTO investigators found that the reduction in deaths associated with tPA was repeated for the over age 75 group (20.6% vs. 19.3%). Among ISIS-2 patients over 70, those treated with thrombolytics had a 6% absolute reduction in mortality when compared with the control group (22% vs. 16%). While successful treatment for the elderly may yield a lower gain in life years compared to successful treatment of a younger person, there is no evidence to suggest that such treatment is less clinically effective for the elderly.

The GUSTO investigators found that the difference in mortality rates between tPA and SK was greater for patients with anterior infarcts (8.6% vs. 10.5%) than for other infarct locations (4.7% vs. 5.3%).

All large-scale clinical trials have indicated that the earlier a patient receives treatment, the better are his or her chances of recovery. In GISSI-1, thrombolytics achieved a 50% reduction in mortality for patients presenting within one hour, as compared to a 20% reduction in mortality for those presenting from 3-6 hours after the onset of pain. In GUSTO, the tPA treatment group experienced significantly lower mortality than the SK groups among patients presenting within two hours (4.3% vs. 5.4%), and among patients presenting within 2-4 hours (5.5% vs.

6.7%). For patients treated more than four hours after onset of pain, the tPA group had non-significantly lower mortality (8.9% vs. 9.3%), and for those presenting after six hours, the SK group had lower mortality (8.3% vs. 10.4%). Since all of these mortality rates are lower than the 10.7% rate observed for the aspirin-only group in ISIS-2, it seems likely that thrombolytics continue to have some clinical benefit up to at least six hours after onset of pain, possibly longer, but that any clinical advantage favoring tPA appears to decline significantly after four hours.[4]

Table 5

30-DAY MORTALITY BY TIME THROMBOLYTIC THERAPY

| Hours to thrombolytic therapy | % of patients | SK % | tPA % |
|---|---|---|---|
| 0 to 2 | 27 [5] | 5.4 | 4.3 |
| 2 to 4 | 51 | 6.7 | 5.5 |
| 4 to 6 | 16 | 9.3 | 8.9 |
| > 6 | 4 | 8.3 | 10.4 |

*Source: GUSTO-1

## Ability to Improve Health Outcomes

Aside from the major endpoints discussed under clinical effectiveness (mortality and disabling stroke), published literature on the health outcomes of thrombolytic therapy is sparse. With an average age at the time of treatment of 62 years, long-term follow-up studies suggest an average of approximately 10 years of life for those who survive the 30-day period used in GUSTO. There have been no studies commenting on the quality of life of these survivors, although one small study reports that 69% of those holding white-collar jobs were able to return to work (Machecourt et al, 1993).

[4] Since the GUSTO sample was not designed to afford sufficient power for subgroup analysis, conclusions regarding subgroups should be confirmed by further research before major policy recommendations can be made.

[5] Combined SK arms.

# CONCLUSIONS: CLINICAL EFFECTIVENESS AND HEALTH OUTCOMES

1. Thrombolytic therapy (both tPA and SK) is safe and clinically effective.

2. The less time that elapses between the onset of pain and treatment for myocardial infarction, the more effective that treatment is likely to be.

3. Accelerated tPA has been shown to achieve earlier coronary artery patency and improved left ventricular function 90 minutes after administration, when compared with SK.

4. If the release of additional data from the GUSTO trial dispels claims of bias, tPA should be considered more clinically effective than SK for patients presenting within four hours of onset of pain, and for patients with anterior infarcts.

5. GUSTO's finding that tPA achieves better mortality outcomes than SK should be interpreted with caution until questions concerning its validity have been dispelled by the release of additional data.

# COST EFFECTIVENESS

A technology will meet cost-effectiveness criteria if it is:

1. At least as effective as alternatives, and less costly, or

2. More effective and more costly than alternatives, but resultant health outcomes justify the additional expenditure, or

3. Less effective and less costly than alternatives, but resultant health outcomes from use of alternatives do not justify additional expenditures.

In conducting this evaluation, HTAC did not consider any treatment modalities for AMI other than thrombolytic agents, such as angioplasty. Nor did HTAC consider the cost of thrombolytic agents in comparison to treatment modalities for other conditions.

One of the major reasons for evaluating tPA and SK is the significant difference in cost between the two drugs. If the two drugs were similarly priced, the small but significant mortality advantage of tPA would suggest broad adoption of that drug. GUSTO reports a price to the provider of $2300 per dose for tPA compared with $300 for SK. Thus, if tPA is to be deemed cost-effective, it must fall into the second category above. The $2000 difference in cost must be justified by improved health outcomes. Since we have discussed clinical effectiveness primarily in terms of mortality, we will address cost-effectiveness using mortality as the patient health outcome.

The simplest approach to a consideration of cost-effectiveness is a calculation of the cost of each life saved by using tPA instead of SK based solely on the difference in price between tPA and SK. Based on GUSTO mortality outcomes, for every 1000 patients treated with SK, 73 will die. For every 1000 patients treated with tPA, 63 will die. The cost of 1000 doses of tPA exceeds the cost of 1000 doses of SK by $2 million. Ten lives are saved at a cost of $200,000 per life saved.

The GUSTO investigators have conducted a somewhat more sophisticated analysis, not yet published (Mark, 1993). They have estimated that, on average, each person saved by the use of thrombolytics will live an additional eleven years. Calculating expected additional health care costs, and discounting future dollars at a rate of 5% (net present value), they have arrived at a

cost per life year of approximately $29,000.[6] MHCC may wish to compare this estimate with similar data for other medical therapies.

The GUSTO investigators indicated that any cost effectiveness estimates would vary with subgroups. Using GUSTO mortality rates for subgroups, Table 6 presents approximations of the cost per life saved if tPA were used only for subgroups for whom it is known to be most effective, with SK used for subgroups for whom the difference between the two drugs is not significant. Since data on combinations of subgroups, such as anterior infarcts for patients under age 75, are not available, each subgroup must be considered separately in this analysis.

[6] This analysis uses a difference in cost between SK and tPA of $2400.

## Table 6
## Cost Effectiveness Estimates for Thrombolytic Agents per 1000 Acute Myocardial Infarctions Treated: Subgroups

| Strategy | Deaths/ 1000 Patients | Total Cost of Thrombolysis (per 1000) | Additional Lives Saved[1] | Cost per Additional Life Saved [1] | Total Annual Cost in Minnesota[2] |
|---|---|---|---|---|---|
| No use of thrombolytics | 107 | 0 | 0 | | |
| SK only | 73 | 300,000 | 34[1] | 8,824[1] | 1,080,000 |
| tPA only | 63 | 2,300,000 | 10[1] | 200,000[1] | 8,280,000 |
| **SUBGROUP ANALYSIS** | | | | | |
| *INFARCT LOCATION* (Treat anterior infarcts with tPA, other infarcts with SK) | | | | | |
| Differential treatment by *location* | 65.8 | 1,080,000 | 7.2[1] | 150,000[1] | 3,888,000 |
| *TIME TO TREATMENT* (Treat patients who present within four hours with tPA, others with SK) | | | | | |
| Differential treatment *time to treatment* | 64 | 1,860,000 | 9[1] | 173,000[1] | 6,696,000 |
| *AGE* (Treat patients under age 75 with tPA, others with SK) | | | | | |
| Differential treatment by *age* | 63.4 | 2,060,000 | 9.6[1] | 183,000[1] | 7,416,000 |

Assumptions based on GUSTO Trial

*Mortality rates*

| | |
|---|---|
| Streptokinase (SK) | 7.3 % |
| tPA | 6.3 % |
| SK within 4 hours of onset of pain | 6.25% |
| tPA within 4 hours of onset of pain | 5.1% |
| tPA anterior infarct | 8.6% |
| tPA age <75 | 4.4% |

*Time to therapy*

| | |
|---|---|
| within 4 hours | 78% |
| more than 4 hours | 22% |

*Location*

| | |
|---|---|
| anterior | 39% |
| other | 61% |

*Age*

| | |
|---|---|
| <75 | 88% |
| ≥75 | 12% |

Assumption based on ISIS-2

*Mortality rate*

| | |
|---|---|
| without thrombolytic therapy | 10.7% |

1 For all strategies other than SK only, comparison group is SK only.

2 Based on estimated 3,600 AMIs treated with per year (30% of 12,000).

# CONCLUSIONS: COST EFFECTIVENESS

The extra cost of tPA relative to SK may be justified in the treatment of subgroups for whom the clinical advantage of tPA is greatest. Based on the literature reviewed for this evaluation, these subgroups include:

- Patients with anterior infarcts;
- Patients treated within four hours of the onset of pain; and
- Patients under 75 years of age.

The extra cost of tPA, when used for patients not included in any of these subgroups is not normally indicated, while it is most clearly indicated for patients who fall into all three subgroups. A substantial number of AMI patients will fall into one or two of these subgroups, but not all three. While physician discretion should be the final determinate in selecting a thrombolytic agent for AMI, differences in cost effectiveness for these three subgroups may inform clinical practice.

# OTHER ISSUES/CONSIDERATIONS

## Scope of HTAC's Technology Evaluation

In conducting this evaluation, HTAC did not consider any treatment modalities for AMI other than thrombolytic agents, such as angioplasty. Nor did HTAC consider the cost of thrombolytic agents in comparison to treatment modalities for other conditions.

## Data Needs

The data presented in Table 6 are based on assumptions about the number of AMIs in Minnesota and the number of patients eligible for and receiving thrombolytic therapy. These assumptions are based largely on statewide Medicare data provided by the Foundation for Healthcare Evaluation and twin cities hospital data provided by the Metropolitan Healthcare Council. No data were available for non-metropolitan non-Medicare patients. In addition, the most reliable source of data on the actual number of patients receiving thrombolytic therapy comes from the 16 hospitals included in the MI registry, initiated and maintained by Genentech, the manufacturer of tPA. This data set includes the number of patients receiving tPA, but those receiving SK are grouped with all other patients. This data set also includes data on time to treatment, infarct location, and age. For accurate statewide estimates of the total cost of various treatments it is necessary to have data at the level of Genentech's MI registry for all Minnesota hospitals, with an additional variable added for other thrombolytics.

## Regional Coordinating Boards (RCBs)

RCBs may wish to monitor how hospitals and networks in their regions are addressing some of the issues raised by this evaluation:

- Public education to reduce the time from onset of symptoms to treatment
- Early response by emergency medical service
- Minimal delays in the emergency room
- Uncompensated care associated with the treatment of AMI

## Practice Parameters Advisory Committee (PPAC)

Analysis of the GUSTO data does not yield confident conclusions regarding contraindications and differential treatment of subgroups. It does, however have implications for guidelines for the use of tPA and SK. An examination of treatment protocols used by several Minnesota hospitals indicates that several hospitals do not use the term "absolute contraindications" thus allowing greater discretion in assessing relative risks. Most protocols are silent on the issue of choice between tPA and SK. While these strategies allow maximum physician discretion, the PPAC may wish to develop guidelines to assist physicians in determining which cases are most likely to benefit from tPA.

## Re-Evaluation

It is likely that additional analysis of the GUSTO data will be available in 1994, enabling an updated determination regarding validity. If such publications do not support the previously published GUSTO findings, tPA should be re-evaluated. In addition, it is hoped that a data base will be developed that will enable more precise calculations of total costs, of the sort presented in Table 6. As these become available, it may be useful to prepare an addendum to this evaluation with current data on the frequency of AMI, number of patients treated with thrombolytics, time to treatment, infarct location, and revised cost projections.

# CONCLUSIONS

1. Thrombolytic therapy saves lives.

2. Thrombolytics are under-utilized. In Minnesota we estimate that there are approximately 12,000 hospital admissions for acute myocardial infarction annually. It is estimated that only 30% of these patients currently receive thrombolytic therapy.

3. The benefit of thrombolytic therapy diminishes with time after symptom onset. Providers of health care should make every effort to administer thrombolytic therapy to appropriate patients without delay.

4. Both streptokinase and tissue plasminogen activator are safe and effective thrombolytic agents.

5. Available data appears to indicate that accelerated tissue plasminogen activator confers an additional survival benefit compared to streptokinase, especially for anterior infarcts, or when thrombolytic therapy is initiated within four hours after symptom onset.

6. Available data indicates an increased rate of stroke associated with the use of tPA; approximately 2.5 additional strokes per 1000 patients. The cost associated with treating strokes and the impact on health outcome should be considered in comparing the cost of tPA to SK.

7. Based on a $2000 difference between the cost of tPA and streptokinase, using tPA would reduce mortality at a cost of approximately $200,000 per additional life saved or approximately $29,000 per life year saved (based on an incremental life expectancy of 11 years).

8. Current estimates of the use of thrombolytics in Minnesota vary widely and Minnesota-specific data on the use of thrombolytics is limited. On the basis of the data currently available, it is estimated that using tPA as the thrombolytic of choice in Minnesota would save approximately 35 additional lives annually, when compared with streptokinase, at an additional total cost of approximately $7 million.

9. Physicians should recognize that the cost of tPA is approximately seven times that of streptokinase, and hence, the use of tPA should be confined to patients who, in the treating physician's judgment, are most likely to benefit.

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# APPENDIX A

## *HEALTH TECHNOLOGY ADVISORY COMMITTEE*
## *tPA WORKING GROUP*
## *LIST OF MEDICAL JOURNAL ARTICLES (11/30/93)*


Anderson HV, Willerson JT
Thrombolysis in Acute Myocardial Infarction
The New England Journal of Medicine 1993; 329:703-709

GUSTO Investigators
An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction (GUSTO)
The New England Journal of Medicine 1993; 329:673-682

Doorey AJ, Michelson EL, Topol EJ
Thrombolytic Therapy of Acute Myocardial Infarction: Keeping the Unfulfilled Promises
JAMA 1992; 268:3108-3114

International Study Group. ISIS-3: A Randomised Comparison of Streptokinase vs Tissue Plasminogen Activator vs Anistreplase and of Aspirin Plus Heparin vs Aspirin Alone Among 41,299 Cases of Suspected Acute Myocardial Infarction
Lancet 1992; 339:753-773

Maggioni AP, Maseri A, Fresco C, Franzosi C, Franzosi M, Francesco M, Santoro E, Tognoni G
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# APPENDIX B

## *HEALTH TECHNOLOGY ADVISORY COMMITTEE*
## *tPA WORKING GROUP*
## *QUESTIONS/ISSUES*

**Please review the following points using the eight enclosed articles.**

1) tPA as used in the GUSTO trial appears to save one additional life per 100 acute myocardial infarction patients when compared to streptokinase (of all acute myocardial infarction patients, 25% die after no intervention, 12.5% die after aspirin or heparin, 7.3% die after streptokinase, and 6.3% die after tPA)

2) comparing current prices of tPA and streptokinase, there appears to be a cost of approximately $200,000 per additional life saved, and a cost ranging between $23,000 and $45,000 per additional life year saved, associated with the use of tPA in comparison to streptokinase

**Do you concur?**

3) The literature suggests that thrombolytic therapy could be extended to groups currently contraindicated, for example:
    1) by decreasing elapsed time between onset of pain and treatment
    2) by treating the elderly
    3) by improving EKG diagnosis
    4) by using only the most compelling contraindications to rule out thrombolytic therapy

**Please comment - which of these areas require further attention?**

# APPENDIX C

*SUMMARY OF PUBLIC COMMENTS HTAC - tPA PRELIMINARY TECHNOLOGY EVALUATION REPORT APRIL 12, 1994*

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**4/06/94**

## Carl A. Sirio

- The large sample provides statistical power to detect small, yet significant, differences whose clinical importance may in fact be difficult to assess.
- Should estimate the total number of patients who will require treatment in order to produce the observed therapeutic difference in one person. The GUSTO results suggest that 91 to 111 patients would require treatment with accelerated tPA to produce one additional survivor 30 days after MI.
- Given the natural history of ischemic heart disease and AMI, it is by no means certain that survival at 30 days confers any long-term benefit.
- References recent guidelines issued for treatment of infarcts and unstable angina. Compliance with these guidelines will likely do more to save lives in MN than will the selection of a particular thrombolytic.

**4/06/94**

## Michael B. Higginbotham, M.D.

- One problem with the GUSTO study, not specifically addressed by HTAC and an inherent drawback of "megatrials" - was that it was unable to indicate what subgroups may benefit most from tPA versus SK. Their stratification into age/time of administration/site of MI could not really be expected to adequately identify a subgroup not needing the added benefits of tPA.

**4/04/94**

## William R. Bell, M.D.

- HTAC recommendations rely heavily on GUSTO.
- GUSTO shows a maximum survival difference of 0.7% for tPA versus SK.
- Many more tPA patients require surgery (CABG). Is increase in survival attributable to tPA or to surgery?
- Why was the marginally minimal difference of 0.7% only seen in the U.S.?
- The 0.7% difference was only seen in patients presenting within less that 2 hours after onset of symptoms.
- Must consider/add the additional cost of surgery for tPA patients.

- Should not focus on the more recent smaller study (GUSTO) but on the larger study (ISIS-3).
- Using tPA escalates cost and does not save additional lives.

## 4/06/94
## Sunil Gupta, M.D.

- Thrombolytic therapy saves lives and should be administered without delay to all patients not specifically contraindicated.
- SK and tPA are safe and effective thrombolytic agents.
- ISIS-3 is the landmark clinical trial in thrombolytic therapy.
- The GUSTO trial is an investigative study of a new regimen.
- Cost-effectiveness conclusions drawn from GUSTO are premature.
- SK should be regarded as the gold standard. However, younger patients presenting early 2-4 hours might derive more benefit from treatment with tPA.
- Considering the significant risk of stroke and cerebral hemorrhage associated with tPA, it should not be recommended in treatment of elderly patients over the age of 70.

## 4/06/94
## Gideon Bosker, M.D.

- GUSTO is not as clean of a study as one would like to base such broad decisions that have staggering financial consequences.
- GUSTO, however, is an important study and its limitations must be weighted against the body of statistically significant results that have appeared in the literature that preceded it.
- The often-cited criticisms of GUSTO are valid criticisms.
- In subsets where tPA and SK produce equal survival results in GUSTO, or have tended to produce equal survival results in previous large trials, SK should be recommended because, considering price and outcome, it represents the better value, from a cost-efficacy and pharmaco-economic perspective.
- Recommendation for tPA:

  tPA should be considered the initial thrombolytic agent of choice only in the following subgroup of patients:

  Patients with a history strongly suspicious of AMI who meet all of the following criteria:

  (i) They have an anterior MI and

  (ii) They have presented within 4 hours of chest pain and

  (iii) They are less than 65-70 years of age.

- Recommendations for SK

  SK should be considered the drug of choice for all other patients presenting with a history strongly suspicious of AMI, and these subsets include:

  (i) All elderly patients (i.e., greater than 65-70 years of age), regardless of time of presentation.

  (ii) All patients with inferior or lateral MIs, regardless of time of presentation.

  (iii) All patients presenting greater than four hours after onset of symptoms.

## 4/05/94

## Victor J. Marder, M.D.

- Executive Summary does not mention the major complication of therapy, "stroke"...Strokes are the major cost...In exchange for a 16% reduction in non-stroke mortality, tPA causes a 48% increase in the risk of lethal or deficit stroke.

- Scientific Design
  - -Only one control group in the four arm study (SK w/SQ heparin as in ISIS-3)
  - -the other three arms must be compared with the SK/SQ heparin arm
  - -no tPA control arm using a standard tPA regimen
  - -CABG was applied significantly more often in tPA patients than in SK patients.
- Strokes
  - -The most serious clinical complication of thrombolytic therapy.
  - -Occur more commonly with tPA than with SK.
  - -GUSTO fails to separate deaths resulting from therapy and deaths resulting from MI.
- CABG
  - -CABG was applied five-fold more often in the U.S.than in other countries.
  - -CABG was applied significantly more often in patients who had received tPA than in those who had received SK/SQ heparin -one must consider the possibility that the greater application of the procedure in tPA patients contributed to the overall difference in mortality of the tPA and SK/SQ heparin arm.
  - -The numbers of patients who underwent CABG according to the original report to the Steering Committee are different than the numbers presented to MN.
- U.S. vs Non-U.S. Experience
  - -Mortality results with the accelerated tPA arm were significantly different in U.S. versus non-U.S. patients.
  - -The world-wide results showing the advantage of the tPA arm over the SK-SQ heparin arm were totally dependent upon the data in the U.S., the results from the rest of the world showing no difference between the treatment arms.
- Cost

| SK | tPA | |
|---|---|---|
| 60 | 69 | -lives saved per 1000 |
| $5000 | $36,000 | -cost per life saved |

  - -$245,000 per extra life saved.
  - -The total cost (of using tPA) is probably higher than the $7 million estimate.

- Summary
  - -Is the accelerated regimen of tPA better than prior regimens? - there was no direct comparison in the GUSTO trial.
  - -tPA must be considered with SK/SQ heparin and not with the combined SK groups
  - -The compounding factor of extra CABG procedures with tPA rather than with SK contributed to the mortality advantage in the tPA arm.
  - -Strokes are more common with tPA.

## Raymond J. Gibbons, M.D.

- Re: Conclusion #5 - The only patient groups for which thrombolytic therapy has been demonstrated to reduce mortality are those patients with ST elevation and LBBB.
- Direct or primary angioplasty is at least as efficacious as thrombolytic therapy.
- Exec Summary/Implications - "within one hour of the onset of symptoms, or within 30 minutes of arrival in the emergency room" - lumping of these two issues is not advisable - it is far more important to encourage patients to come the emergency room early after the onset of symptoms.
- Pg 8 - 66% of heart attack victims have elevated ST segments - is probably closer to 45%.
- Table 6 - use of age criteria - results of GUSTO subgroup analysis for age greater than 75 years were not significant - few patients were studied.
- GUSTO - the absolute net benefit with respect to mortality and disabling stroke was similar in both younger and older patients.

### 3/30/94

## Guy S. Reeder, M.D.
## David R. Holmes, M.D.

- The cost per additional life year saved of $29,000 was based on a cost difference of $2400.
- Due to the widespread current use of aspirin in acute infarction, the mortality figure of 10.7% (from ISIS-2) should be used rather than the 13% figure derived from GISSI-1.
- The questions of blinding, differences in treatment between US and non-US countries and differences in rates of CABG have been addressed in "Holding GUSTO Up to the Light".

### 3/30/94

## Lyle J. Swenson, M.D.

- That anterior infarcts derive more potential benefit from tPA compared to SK is quite clear. The four hour time frame is less clear...The group that was treated between four and six hours was a small group and the differences were not statistically significant.
- I don't believe that all patients suffering an AMI should receive thrombolytic therapy in the absence of specific contraindications. The only patients who benefit are those with ST segment elevation.
- The GUSTO information has been analyzed quite extensively and repeat evaluations of the initial GUSTO data will not lead to other conclusions.
- It is inappropriate to give the impression that bias could invalidate the GUSTO Trial.
- Table 6 - deaths per 1000 patients for those not receiving thrombolytics should be 90-100 based on current therapy with aspirin, as reflected in the ISIS-2 Trial. This would affect the calculations of cost per additional life saved with SK and tPA.
- Conclusions on cost-effectiveness are based on mortality only and not on morbidity or long-term outcome. Advantages of tPA may affect long-term outcome and in-hospital costs.

### 3/30/94

## David C. Pang, Ph.D.

- Too much weight is being put on the unconfirmed suggestion of bias by investigators in the GUSTO trial.
- The basis used in the cost analysis is too simplistic. There was no consideration of possible cost(s) for additional medication, physician and hospital care for treatment of patients following SK as a result of more extensive cellular injury during the critical 90 minutes that SK was less effective in reopening the occluded arteries.

## 3/30/94
## Paul M. Ridker, M.D., M.P.H.

- Increased risk of allergic reaction and hypotension with SK explain lack of an accelerated SK regimen - not true - must consider the actual magnitude of the allergic reaction - the absolute levels are very low - see ISIS-3.
- Disputes summary of GUSTO angiographic study: "Data shows ventricular function is not improved - left ventricular ejection fraction is the measure and it's identical for all 4 treatment groups.
- The most consistent finding from GISSI-2, ISIS-3, and GUSTO-1 is that in all three trials, rates of total stroke and cerebral hemorrhage - the most important and feared side effects of thrombolysis - were higher for tPA than for SK.
- The data quoted are for mortality only, thus exaggerating the true "benefit" of tPA.
- There still is no evidence in the GUSTO data that accelerated tPA has a statistically significant mortality advantage over SK for the elderly or for those arriving after 4 hours, the time frame when in fact most infarctions come to the emergency department.
- For 60% to 80% of all infarctions where there is no data to demonstrate mortality efficacy of one regimen over another, it is not clear how any cost effective ratio can be calculated since the more expensive agent also has more serious side effects.
- The $200,000 per life saved is likely an underestimate of using accelerated tPA with IV heparin since it does not appear to take into account the long term costs of caring for the excess strokes.
- Accelerated tPA with IV heparin is compared to the combined SK arms of the GUSTO trial, a comparison which artificially increases the mortality difference in favor of tPA while simultaneously decreasing the stroke difference against tPA.
- It is unfortunate that almost all of the discussion among clinicians has focused on which agent to give rather than on the fundamental issue that thrombolytics are under-utilized in the U.S.
- Four major conclusions can be drawn from a thoughtful review of the thrombolytic literature:

  -Findings from the GISSI-2, ISIS-3, and GUSTO-1 trials consistently indicate that the choice of thrombolytic therapy is much less important to ultimate survival than is the delay time to onset of treatment.

  -Any potential differences in efficacy among thrombolytic agents are at most small in absolute benefit and are unlikely to pertain to most patients with MI who present more than four hours after onset of pain.

  -All thrombolytic agents appear effective when given up to 12 hours after the onset of symptoms.

  -The development of local programs in emergency departments designed to decrease delay time to thrombolysis are probably the most cost-effective way to save the greatest number of lives.

3/24/94

## Karl Matuszewski, R.Ph., M.S.

- I believe the recommendations miss the mark. They should be:
  - -Treat more patients with thrombolytic therapy.
  - -Preserve limited health care resources for other highly effective uses by using the lowest cost effective technology.
- There is an over emphasis on GUSTO.

3/21/94

## James I. Thompson, M.D.

- Over 75 years in age there appears to be a significant risk for the accelerated tPA program combined with aggressive heparin therapy.

# APPENDIX D

## *SUMMARY OF PUBLIC TESTIMONY TAKEN BY THE MINNESOTA HEALTH CARE COMMISSION ON APRIL 20, 1994 REGARDING HTAC'S FINAL TECHNOLOGY EVALUATION REPORT*

## Victor Marder, M.D.

- tissue plasminogen activator is less safe than streptokinase - not cost effective
- early treatment is the major factor in saving lives
- critical analysis of issue has not been resolved/evaluated by the FDA - HTAC's report is premature

### Design of Trial

- no control group of the standard tissue plasminogen activator regimen - no direct comparison of standard and accelerated regimens
- two streptokinase groups - 1) streptokinase with subcutaneous heparin (standard therapy, control group) and 2) streptokinase with intravenous heparin (experimental method of administration - not as good as streptokinase with subcutaneous heparin)
- streptokinase with intravenous heparin has a higher mortality and stroke rate than streptokinase with subcutaneous heparin - any comparison with combined streptokinase groups, as was done in the New England Journal of Medicine article and in the HTAC report, expands the patient base and artificially expands the database and show data that puts streptokinase at a disadvantage.
- the data needs to be reworked
- the trial was open label - could produce bias on the part of the physician - it could have been a blinded study

### Coronary Artery Bypass Graft Surgery

- 8 or 10 patients per 1000 that received tissue plasminogen activator underwent coronary artery bypass graft surgery - this is the same order of magnitude as the difference in mortality between streptokinase and tissue plasminogen activator - this is statistically significant
- what is the potential impact of coronary artery bypass graft surgery on the study
- what would the mortality have been in those patients who underwent coronary artery bypass graft surgery had they not been afforded coronary artery bypass graft surgery - how many lives might have been saved in the tissue plasminogen activator group because they underwent coronary artery bypass graft surgery
- if only 1 per 1000 was saved in the tissue plasminogen activator group by coronary artery

bypass graft surgery, it has a very significant impact on the overall statistical significance of the two groups

Strokes

- there is an excess of strokes with tissue plasminogen activator - generally thought to be one additional severely disabling stroke with tissue plasminogen activator
- there are really 4 additional strokes of clinical importance in GUSTO with tissue plasminogen activator
- you must consider mortality and stroke as the major clinical downside of therapy and it is more with tissue plasminogen activator than with streptokinase
- depending how you count the strokes, you have quite a difference in benefit/risk ratio
- many patients would prefer not to live with a stroke
- average delay before treatment in the U.S. is more than 4 hours -there is no difference between the agents no matter how you look at it in the published reports (for those presenting within 4 hours)
- greater than 6 hours there's actually an advantage for streptokinase
- we don't know if patients treated between 2 and 4 hours received coronary artery bypass graft surgery
- benefit/risk -for a 16% reduction in mortality there is a 48% increased risk of a lethal or deficit inducing stroke

U.S. versus Non-U.S. Experience

- tissue plasminogen activator mortality in U.S. is 5.9% (22,000 patients) - non-U.S. mortality is 6.9% (18,000 patients) - this is statistically significant - p value is .04
- for some reason patients who got tissue plasminogen activator in the U.S. did better than patients in the rest of the world
- if you compare tissue plasminogen activator with streptokinase in the U.S. you have a significant difference - p is .007
- outside the U.S. between tissue plasminogen activator and streptokinase the p value is .42 - it is not significant
- HTAC report says that the difference between tissue plasminogen activator and streptokinase is less impressive outside the U.S. than in the U.S. - this is misinformation - it is not different outside the U.S. - the difference is not significant - you have a p value of .42
- the only difference is in the tissue plasminogen activator group

Dollar Cost of Agents

- if you save 35 lives (as presumed by GUSTO), you will cause 14 strokes that either kill or cause permanent deficits
- this will add $9 million per year

Summary

- the front loaded tissue plasminogen activator is not better than streptokinase
- more strokes will be induced by tissue plasminogen activator
- the benefit/risk ratio is not acceptable
- the dollar cost is high for dubious clinical benefit

## Gideon Bosker, M.D.

- overall the report ought not to rely as heavily on the GUSTO trial as it does
- GUSTO has 40,000 patients - there were 65,000 patients preceding it - there are some differences - should look at all the trials together
- both are good drugs
- patients should be brought in earlier
- the GUSTO trial has some serious pitfalls that were not addressed by previous speaker:
    - more and more heart attacks occur in older patients-they are more expensive to treat and tend to be supported by public dollars
    - study arbitrarily looks at a cut off of 75 years of age
    - GUSTO says there is no difference between patients treated with tissue plasminogen activator versus. streptokinase when they're over 75
    - why was the cut off of 75 years of age made?
    - until we know at what age streptokinase and tissue plasminogen activator are equivalent, we cannot adequately assess
- is it 4 hours or 3 hours at which point tissue plasminogen activator appears to be better than streptokinase?
- report says patency is equivalent at 180 minutes (3 hours)
- approximately 20% of acute myocardial infarctions present between 3 and 4 hours
- if you take your Minnesota statistics, and take the patients presenting between 3 and 4 hours and give them to the streptokinase group, you save $1.44 million
- we can't say that patients presenting less than 3 or 4 hours do better with tissue plasminogen activator - must consider age of patient

### Summary

- Report should say: Patients that have anterior myocardial infarctions and who are less than 65-70 years of age and present less than 3-4 hours should get tissue plasminogen activator.

## David Holmes, M.D.

- angiographic substudy - at 90 minutes, if reperfusion was full, you had a better outcome w with tissue plasminogen activator it was 54%, with streptokinase it was 30%
- the best drug available to achieve full reperfusion is accelerated tissue plasminogen activator
- there are 6 other studies that document that if you get full reperfusion at 90 minutes, your outcome is better - your heart function is better and your mortality is improved
- this does not mean that tissue plasminogen activator should be used in every patient
- physicians take numerous factors into consideration in order to identify the best therapy
- urged flexibility in the specific regimen that can be selected for the patient
- in the lower risk patients, streptokinase is very reasonable

### Difference Between U.S. and Non-U.S. Populations

- there are substantial differences in patient expectations in the U.S. as compared to abroad
- there are differences in practice patterns
- patients in the U.S. have more catheterizations, more angiograms and more procedures done during that first year

- FDA Analysis of Tissue Plasminogen Activator
- tissue plasminogen activator has been approved by the FDA
- the accelerated dose regimen has not been approved by the FDA
- GUSTO selected the accelerated method because it is the best method of administration
- accelerated tissue plasminogen activator is the standard of care in the U.S.

## Ted Love, M.D.

- taking into consideration strokes, tissue plasminogen activator still saves 8-10 additional lives per 1000 patients
- subgroup analysis may erroneously identify patients as not benefiting from tissue plasminogen activator because the analysis measures where the confidence intervals overlap, rather than whether the patients benefited from treatment
- Victor Marder said that patients treated with streptokinase beyond 6 hours get better - this is incorrect
- coronary artery bypass graft surgery - if you remove patients that had coronary artery bypass graft surgery, the benefit of tissue plasminogen activator is even greater - mortality for patients getting coronary artery bypass graft surgery was slightly higher
- stroke - for every 1 person that suffers a disabling stroke, you save 10 lives
- U.S. versus non-U.S. - a rigid statistical analysis of the data would show no difference in mortality - the p value is .3 - there is a 30% chance that this is random
- the magnitude of stroke is relatively small
- patency - opening the artery early accounts for the improved mortality

## David Fuhs, Pharm.D.

- there is a large difference in the price of the drugs and a small difference in their effectiveness
- it is most important to treat patients with thrombolytics
- Genentech has spent equal amounts on research and development, and marketing

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