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**Coronary Thrombolysis
in the Emergency Department:
Concordance with Clinical Guidelines**

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*A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements of the Master's Degree*

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Table of Contents

Section	Title	Page Number
	List of Tables	iii
	List of Figures	iv
	Abstract	v
	Résumé	vi
	Acknowledgment	vii
1	Introduction and objectives	
1.0	Introduction	1
1.1	Objectives	3
2	Background and literature review	
2.0	The motivation for clinical guidelines	4
2.1	Clinical guidelines and thrombolysis	5
2.2	The evaluation of clinical guidelines	9
2.3	Concordance of thrombolysis decisions with clinical guidelines	9
2.4	Coronary thrombolysis in the Emergency Department	14
3	Methods	
3.0	Design overview	16
3.1	Patient selection	16
3.1.1	Inclusion and exclusion criteria	17
3.2	Assessment of concordance of thrombolytic decisions	17
3.3	Setting	18
3.4	Sample size calculation	18
3.5	Sources of information and data collection	19
3.6	Validity and generalizability	20
4	Analysis	
4.0	Primary analysis	22
4.0.1	Physician-specific concordance rates: hierarchical modeling	23
4.1	Secondary analysis	25
4.2	Computer resources	26

5	Results	
5.0	Eligibility criteria: inclusion and exclusion of patients	27
5.1	Comparison of sampling periods for thrombolysed and non-thrombolysed patients	29
5.1.1	Comparison of charts with missing ECGs	30
5.2	Assessment of concordance with clinical guidelines	32
5.2.0	Consensus assessment of reviewers: inter and intra rater agreement	32
5.2.1	Overall concordance with clinical guidelines	33
5.2.2	Percent concordance by thrombolysis status	34
5.2.3	Analysis of concordance by final diagnosis	34
5.2.4	Physician-specific concordance rates: hierarchical modeling	36
5.2.5	Documentation of contra-indications and concordance	37
5.3	Secondary analysis	38
5.3.0	ED thrombolysis complication rates	38
5.3.1	Time to thrombolysis	41
5.3.2	Use of ASA with acute coronary syndromes	42
5.3.3	Analysis of independent predictors of thrombolysis	42
5.3.4	Survival	46
6	Discussion	
6.0	Thrombolysis in the ED and concordance with guidelines	47
6.0.1	Physician-specific concordance rates	49
6.1	Complications of ED thrombolysis	50
6.2	Time to thrombolysis	50
6.3	Factors affecting the decision to administer thrombolysis	51
6.4	Study limitations	52
6.5	Conclusion	53
Appendix A	Summary of 1994 Canadian Consensus Guidelines on indications for coronary thrombolysis	54
Appendix B	The Kappa and adjusted Kappa statistics	55
References		58

List of Tables

Table Number	Title	Page Number
1	Thirty day mortality and TIMI grade in the infarct-related coronary artery at 90 minutes following thrombolysis	7
2	Studies evaluating thrombolytic use in or via Emergency Departments	12
3	Eligibility, exclusion and inclusion of patients	27
4	Demographics of patients included for concordance analysis	28
5	Distribution of suspected acute coronary syndrome admissions from the Mount Sinai ED to the CCU from August 1, 1994 to August 31, 1995	30
6	Comparison of groups by presence/absence of ECGs	31
7	Concordance with consensus assessment	33
8	Concordance pattern by final diagnosis	35
9	Physician-specific concordance rates and hierarchical model results	36
10	Complication rates for patients thrombolysed in the ED (n=42)	38
11	Spearman correlation matrix of independent variables	44
12	Comparison of selected logistic regression models	45

List of Figures

	Title	Page Number
Figure.	Steps in decision-making for thrombolysis	10

Abstract

Previous studies have shown that mortality reduction with thrombolysis in acute myocardial infarction depends in part on time to thrombolysis, which can be shortened by administering these drugs in the Emergency Department (ED). This study was undertaken to determine the appropriateness of thrombolytic use by Emergency Physicians, and to determine complication rates of ED thrombolysis.

The charts of 137 patients admitted from a tertiary care hospital ED with acute coronary syndromes were assessed for concordance with standard Canadian thrombolytic guidelines, based on a blinded review by two independent assessors. The adjusted Kappa statistic for the overall concordance with the guidelines was 0.85 (95% CI 0.76-0.94). Hierarchical modeling was used to estimate the distribution of physician-specific concordance rates. Complication rates for thrombolysis in the ED were similar to previously reported rates. A logistic regression was also carried out to identify other independent predictors of thrombolysis after controlling for eligibility for thrombolysis; none were found.

The results indicate excellent agreement between Emergency Physicians' clinical decisions regarding thrombolysis and standard Canadian thrombolysis guidelines.

Résumé

Plusieurs études ont démontré que la réduction de la mortalité due à l'infarctus du myocarde traité par thrombolyse est, en partie, reliée au délai où la thrombolyse est initiée. Ce délai peut être réduit en administrant les agents thrombolytiques en salle d'urgence (SU). Cette étude fut effectuée dans le but de déterminer si l'utilisation des agents thrombolytiques par les urgentologues est appropriée, et pour déterminer le taux de complications associé à ce traitement en SU.

Les dossiers de 137 patients admis à partir d'une SU d'un centre de soins tertiaires pour syndrome coronarien aigu ont été révisés. La concordance entre le traitement instauré et les standards Canadiens pour la Thrombolyse fut établie par deux observateurs indépendants, sur une base aveugle. Le Kappa ajusté pour la concordance avec ces standards était de 0.85 (intervalle de confiance à 95%: 0.76 - 0.94). Un modèle hiérarchique a été utilisé pour estimer la distribution des taux de concordance individuels des médecins urgentologues. Les taux de complications en SU furent similaires à ceux rapportés dans la littérature. Une régression logistique a également été effectuée pour identifier d'autres facteurs prédictifs indépendants, après contrôle de l'éligibilité au traitement par thrombolyse: aucun n'a été trouvé.

Les résultats indiquent une excellente concordance entre les décisions cliniques prises par les urgentologues en regard de la thrombolyse et les standards Canadiens.

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Coronary Thrombolysis in the Emergency Department: Concordance With Clinical Guidelines

1.0 Introduction

Despite a gradual decline since the 1970s, cardiovascular disease remains the number one killer of men and women in Canada.¹ Ischemic heart disease and acute myocardial infarctions (MI) account for a large part of these cardiovascular deaths.^{1,2} Since the landmark study by DeWood in 1980 demonstrating that 87% of acute MIs were due to the sudden formation of a thrombus in a coronary artery,³ much research has been focused on “thrombolysis”, or acutely dissolving these clots with thrombolytic drugs such as Streptokinase or Tissue Plasminogen Activator. Recently, several large, randomized controlled trials of thrombolytic drugs have shown clinically and statistically significant reductions in mortality in acute MI with the use of thrombolytic agents.⁴⁻⁸

However, these studies have also shown that the benefit of thrombolysis is greatest in a well-defined subset of patients with acute MI,^{6,7} and that the reduction in mortality in these patients is inversely proportional to the time from the onset of MI to the time the thrombolytic drugs are given.⁶⁻⁸ Furthermore, thrombolytic drugs may have significant adverse effects; they have been associated with stroke, severe bleeding, anaphylaxis, arrhythmias, hypotension and cardiac arrest.⁴⁻⁷ As a result, absolute and relative contra-indications to their use have been defined.^{9,10}

In order to maximize the mortality reduction with thrombolysis, reduce the potential for adverse effects and minimize the inappropriate use of these expensive medications, the 'Canadian Consensus Conference on Coronary Thrombolysis' first published detailed and explicit clinical guidelines for their use in 1993,⁹ in the Canadian Journal of Cardiology. They were updated with minor revisions and re-published in June, 1994.¹⁰

In addition to defining which patients should receive thrombolytic drugs, the Canadian Consensus guidelines further recommend they be given "...as soon as possible...", once the decision has been made, and "...that hospitals establish a target of less than 1 hour from the time of patient arrival to the initiation of thrombolytic therapy." The guidelines also state that this would be facilitated by "...identif[ying] individuals who have the authority to order thrombolytic therapy (in many cases, this will be the emergency room physician independently or in consultation with a Cardiologist/Internist)".¹⁰

Many studies have documented that time to thrombolysis can be significantly reduced when thrombolytic drugs are administered in the Emergency Department instead of waiting to transfer the patient to another critical care area.¹¹⁻¹⁶ As well, studies have shown further reductions in time to thrombolysis when the Emergency Physician independently decides on the use of these drugs, rather than waiting to consult a Cardiologist or Internist.^{11,12,17}

Nonetheless, in many hospitals, restrictive policies persist which limit the use of thrombolytic drugs to Coronary Care Units, and/or only allow Cardiologists or Internists (who see the patient after being consulted by the Emergency Physician) to order the thrombolytic drugs.^{11,17,18,19}

These policies may persist because of perceptions that they can increase appropriate decision-making and potentially decrease complications, but they also increase the time to needle.^{11,12,17} Few studies have assessed the appropriateness of thrombolytic decisions made by Emergency Physicians, and, as will be shown, those that have been done have suffered from methodologic problems.^{14,20-23} Furthermore, no study has specifically examined the safety of thrombolytic drugs when given in the Emergency Department. Demonstrating that thrombolytics can be appropriately, safely and rapidly administered in the Emergency Department may result in more hospitals approving such protocols for their use, and therefore maximize the benefit of these medications by decreasing time to thrombolysis.

Determining the rate of concordance with clinical guidelines will also help to evaluate the impact of guidelines on physician practice.^{24,25} After evaluating how well physicians are complying with these guidelines, feedback can be provided to physicians in a further effort to improve compliance.²⁵ Factors in their design and dissemination which improve compliance may be identified in order to aid the future guideline development.^{25,26}

1.1 The objectives of this study are therefore:

- Primary: To determine the extent to which patients with acute coronary syndromes treated by Emergency Physicians in a tertiary care center receive thrombolytic drugs in accordance with standard Canadian guidelines,
- Secondary: To determine the rate of complications and the time to thrombolysis when thrombolytic drugs are administered in a tertiary care center by Emergency Physicians.

2 Background and Literature Review

2.0 The Motivation for Clinical Guidelines

The clinical guidelines movement began gathering steam in the late 1970s and 1980s.^{24,27,28} Concerns over wide regional variations in the delivery of medical services in the US, as well as the rising cost of health care, prompted policy-makers, researchers and clinicians to begin asking questions about the quality and effectiveness of many common medical procedures and services.^{24,28,29}

This issue was highlighted with the development of so-called “appropriateness” methodology to evaluate health services. One method was to assemble expert physician panels and, after detailed literature reviews, draw up lists of clinical indications for selected medical procedures which were rated by consensus as “appropriate”, “inappropriate” or “equivocal”. Multi-center chart reviews of patients having undergone the selected procedures were then carried out, and the particular indications for the procedure were rated.^{24,30}

The development of this assessment methodology led to a series of studies.³¹⁻³⁴ One study of Coronary Artery Bypass Grafting (CABG) in three US hospitals in 1979-82 revealed “inappropriate” indications for the surgery in 14% of patients sampled overall, and “equivocal” indications in a further 30%. The percentage of patients with “appropriate” indications for this surgery varied from 37% to 78% in the three hospitals.³² According to another study in 1993, only 58% of coronary angioplasty procedures in 15 New York state hospitals were rated as having “appropriate” indications.³¹

Studies done in the UK showed similar results. When coronary angiography procedures done in the UK were rated by British physicians, 21% were considered “inappropriate” and 30% “equivocal”.³³ In Canada, an appropriateness study in Manitoba showed slightly better results, with 10–17% of coronary angiography procedures being rated “equivocal” or “inappropriate”, while 6–17% of CABG surgery was similarly assessed.³⁴

Standardized clinical guidelines were thought by many, including governments, to potentially provide a means to improve medical practice, and reduce inappropriate use of medical procedures.^{24,35} Most explicitly, it was stated that “the motivation to create clinical guidelines lies in the belief that guidelines, if properly constructed, may eliminate inappropriate care, thereby reducing the cost of medical care.”²⁸

2.1 Clinical Guidelines and Thrombolysis

At the same time in the 1980s, interest was being renewed in thrombolytic drugs in acute MI, and several large randomized controlled trials of these agents showed reductions in mortality. The GISSI trial, published in 1986, randomized 11806 acute MI patients to either Streptokinase (SK) or conventional therapy. It showed a reduction in mortality at 21 days from 13% in controls to 10,7% in treated patients, an 18% risk reduction ($p=0,0002$).⁸ In this study, patients were thrombolysed in the CCU.

In 1988, the ISIS-2 study randomized 17187 patients to streptokinase, acetylsalicylic acid (ASA), both or neither. SK alone and ASA alone both produced significant 5 week vascular mortality reductions: SK alone reduced mortality from 12,0% in placebo group to 9,2% in SK group ($p<0.00001$, 25% reduction in odds of mortality).

ASA alone also reduced mortality from 11,8% in placebo group to 9,4% ($p<0,00001$, reduction in odds or mortality 23%). SK and ASA together were even better, with reductions in mortality from 13,2% in placebo group to 8,0% in the group receiving both ($p<0,0001$, odds reduction of 42%).⁴ Whether patients received the thrombolytic agent in the CCU or in the Emergency Department is not specified.

Another large study, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial, reported in 1993 on 41021 patients randomized to one of the following: SK and subcutaneous heparin, SK and intravenous heparin, accelerated Tissue Plasminogen Activator (TPA) and intravenous heparin or SK plus TPA plus intravenous heparin. They found the following 30 day mortality rates: SK and subcutaneous heparin 7,2%; SK and intravenous heparin 7,4%; accelerated TPA and intravenous heparin 6,3%; SK and TPA and intravenous heparin 7,0%. In addition, they showed a significant difference in the combined endpoint of deaths or disabling stroke in the accelerated TPA group versus the SK only groups (6,9% Vs 7,8%, $p=0,006$).⁷ Once again, it is not specified where the patients received their thrombolytic regimens.

In addition, GUSTO provided evidence of the importance of minimizing time to needle, regardless of the agent chosen. When mortality was analyzed according to hours from onset of MI to receipt of thrombolytic drug, the following mortality rates results were obtained for TPA versus SK: 0-2 hours, 4.3% vs. 5.4%; 2-4 hours, 5.5% vs. 6.7%; 4-6 hours 8.9% vs. 9.3%; >6 hours 10.4% vs. 8.3%.⁷

Perhaps the best evidence of the importance of minimizing time to needle was supplied by the GUSTO angiographic substudy.³⁶ In this study, 2431 of the GUSTO trial patients were randomized to undergo angiography at 90 minutes, 3 hours, 24 hours or 7 days following thrombolysis. The primary analysis was based on those patients who underwent angiography at 90 minutes. Thirty day mortality was compared based on the infarct-related coronary artery blood flow (patency) during angiography, as graded by the 'Thrombolysis in Myocardial Infarction' (TIMI) score.

Table 1. Thirty day mortality and TIMI* grade in the infarct-related coronary artery at 90 minutes following thrombolysis

TIMI grade at 90 minutes	Definition of TIMI grade	30-day mortality (p value)
grade 0	Absent antegrade flow	8.4%
grade 1	Partial contrast penetration; incomplete distal filling	9.2% (p=ns)
grade 2	Patent with opacification of the entire distal artery; delayed contrast filling or washout	7.9% (p=ns)
grade 3	Patent with normal flow	4.0% (p<0.01)

*TIMI = Thrombolysis in Myocardial Infarction

Thirty day mortality was significantly reduced with TIMI grade 3 flow at 90 minutes compared to lesser degrees of coronary artery patency (table 1). The relation was further explored by a logistic regression analysis, which found the odds ratio for 30-day mortality to be 0.46 (95% CI 0.25 - 0.86) for TIMI 3 versus TIMI 0 or 1 flow at 90 minutes, even after adjusting for known important risk factors. In simple terms, this means that a patient with TIMI grade 3 flow in an infarct-related coronary artery at 90 minutes following thrombolysis is 0.46 times as likely to be dead at 30 days than a patient with TIMI 0 or 1 flow.³⁶

Finally, the Fibrinolytic Therapy Trialists' meta-analysis of nine thrombolytic trials totaling 58,600 patients, reported in 1994, showed the following reductions in proportional odds of 35 day mortality compared to placebo by time to thrombolysis: 0-3hr (26% $p<0,00001$), 4-6hr (18% $p<0,0001$), 7-12hr (14% $p=0,005$) and 13-24hr (5% $p=ns$). Complication rates for stroke and other bleeds were also estimated; they found a 1% stroke rate, 0,7% other major bleed rate. The benefit of thrombolysis was observed among those patients presenting with specific electrocardiographic patterns (ST elevation or bundle branch block), and was greatest the earlier the treatment was begun.⁶

Despite the demonstrated effectiveness of thrombolytic agents, studies showed that they were not as widely used as they could be, to the potential detriment of many patients.^{9,13,37-39} As well, since the benefit of thrombolysis is inversely proportional to the time delay between the onset of acute MI and the time the thrombolytic drug is given,^{4,6-10} while the risk of adverse effects remains, these agents must be given as quickly as possible to optimize the risk/benefit ratio.

Finally these drugs are not cheap. In Québec, the two most common agents, Streptokinase and Tissue Plasminogen Activator, cost respectively approximately \$385 and \$2400 per patient.⁴⁰ These facts together helped lead to the development of Canadian clinical guidelines in the use of thrombolytic drugs in acute MI, first published following a national Consensus Conference in 1993,⁹ then updated and re-published in 1994.¹⁰

2.2 The Evaluation of Clinical Guidelines

Appropriateness studies have, in some cases, identified inappropriate use of medical procedures and resources, and clinical guidelines have been proposed as a way to improve medical practice.²⁶ Proper implementation and dissemination of guidelines is essential for them to have adequate impact, but dissemination alone is unlikely to alter clinical practice.^{24-26,35} As Lomas points out, “words, whether credible or not, rarely flow into action.”²⁵

An important, though difficult, step in the implementation of guidelines is the evaluation of their use after dissemination, to determine whether physicians are practicing in accordance with the recommendations.²⁵ Such evaluations help to determine physician compliance with guidelines, and may help identify barriers which impede improved compliance.^{25,26,41} The findings can help with the future refinement of thrombolytic guidelines, and also provide feedback to the practitioners using them.

2.3 Concordance of Thrombolysis Decisions with Clinical Guidelines

Previous studies have attempted to assess thrombolysis in the Emergency Department, but they have suffered from three main methodological problems. First, they have used the wrong denominator.

The Figure represents the steps involved in the decision to administer thrombolysis and the areas for potential errors. Decision 1 is interpretation of the electrocardiograph (ECG); decision 2 is deciding whether a patient with an ECG meeting thrombolysis criteria meets other criteria (time since onset of pain and absence of contra-indications).

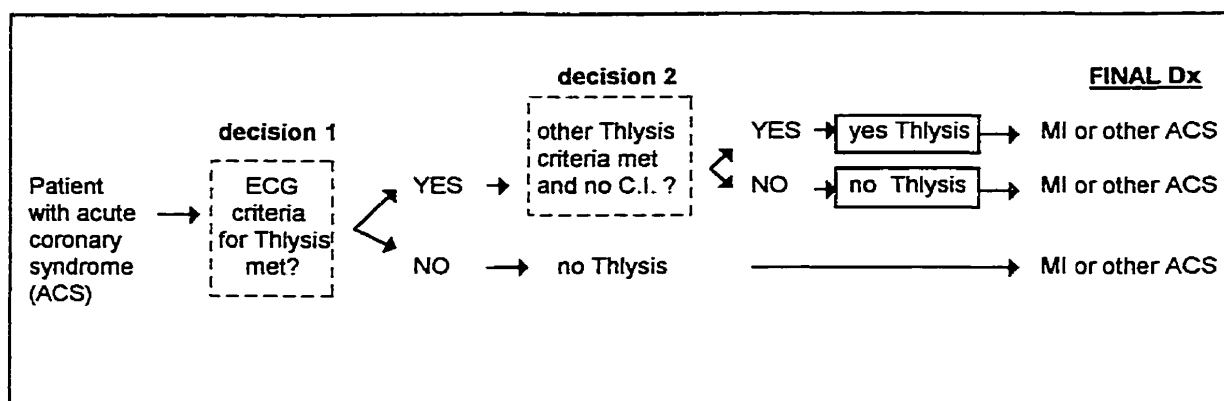


Figure. Steps in decision-making for thrombolysis. **Decision 1:** interpretation of the ECG. **Decision 2:** consideration of other thrombolysis criteria and contra-indications. ("ACS"=acute coronary syndrome; "ECG"=electrocardiogram; "Thlysis"=thrombolysis; "C.I."=contra-indications; "yes Thlysis"=thrombolysis given; "no Thlysis"= thrombolysis not given; "Final Dx"=final diagnosis).

All three outcome arms may include patients having had an MI, or patients with other acute coronary syndromes (angina, unstable angina, other cardiac chest pain).

There are two possible errors in decision-making with regard to thrombolytic drugs: first, to withhold it from someone who meets the guidelines (underuse) , or, second, to give the drug to someone who does not meet the guidelines (overuse). Since both of these errors are potentially associated with a worse outcome, both should be evaluated to properly estimate concordance with guidelines. The overall percent concordance with guidelines is then:

$$\text{Concordance} \% = \frac{(\# \text{ patients considered}) - (\# \text{ underuse errors} + \# \text{ overuse errors})}{\# \text{ of patients considered}} \times 100$$

The crucial point here is that the denominator is not only patients who are eventually shown to have had an MI; the true denominator is *all patients with acute chest pain of presumed cardiac origin*. Because the definitive diagnosis of acute MI is sometimes not made until 12 to 18 hours after the patient presents to hospital, the decision whether to give the drug must be made hours before.¹⁰ As a result, all patients who present to the hospital with an 'acute coronary syndrome', that is, acute chest pain of presumed cardiac origin and the *potential* to be having an acute MI, should be considered for thrombolysis. All these patients should be included in any study evaluating decision-making, not just those patients who received thrombolytics or only those with acute MI. Overall and sub-group analyses can then be carried out to look at concordance among particular patient groups.

Despite this, studies that have looked at appropriateness of physicians' thrombolysis decisions have not used this denominator. Some studies have looked only at those who received thrombolysis; this strategy can miss those patients who meet the criteria, but who do not receive thrombolytics (underuse).

Other studies have looked instead at all patients with acute MIs; this strategy can miss those patients who are given thrombolysis, but whose final diagnosis is not MI (overuse). Table 2 shows the main studies looking at thrombolysis in the emergency department. Pell looked at a series of patients with suspected acute MI, and found a rate of 93% of "appropriate" thrombolysis (127/136). However, the criterion for appropriateness was simply that the final diagnosis be acute MI.¹⁴

Table 2. Studies evaluating thrombolytic use in or via Emergency Departments

Author, Date (ref)	Denominator	n	Time to Thrombolysis* (min) by Location	Appropriateness of Thrombolysis	Definition of Appropriate Thrombolysis	Complications
Sharkey, 1989 (16)	consecutive suspected MI given Thlysis ψ	236	ED: 47 $\pm$ 23** CCU: 82 $\pm$ 34** [mean $\pm$ SD]	not assessed	n/a	"No bleed or arrythmia" in the ED
Dalton, 1989 (13)	consecutive suspected MI given Thlysis	57	ED: 61 (30-105) CCU: 141(45-614) [mean (range)]	52 of 57 (91%)	unblinded; criteria not defined	not assessed
McKendall, 1992 (24)	consecutive suspected MI given Thlysis	188	ED: 46.6 CCU: 84.5 [mean]	32 of 32 (100%) of ED physician administered Thlysis	not defined	not assessed
Pell, 1992 (14)	consecutive admitted suspected MI	359	ED: 49 min CCU: 93 min (p<0.001) [median]	127 of 136 (93%) thrombolysed patients	unblinded; if final diagnosis MI, then Thlysis appropriate	"no hemorrhagic stroke and no..bleeding complications"
Birkhead, 1992 (15)	consecutive admitted suspected MI	1934	ED: 31 (25-35) CCU: 80 (75-85) median(95% CI)	not assessed	n/a	not assessed
Gonzalez, 1992 (11)	consecutive suspected MI given Thlysis	210	ED: 49 (33-66) CCU: 50(39-87) ξ [median (25-75 percentile)]	not assessed	n/a	not assessed
Sharkey, 1994 (20)	consecutive suspected MI given Thlysis by ED MD	93	ED: 45 (32-63) [median (25-75 percentile)]	83 of 93 (89%)	unblinded; review by cardiologist (criteria not listed)	not assessed
Tsuyuki, 1994 (21)	consecutive confirmed MI	372	not assessed	79 of 79 (100%) thlysis patients; "adjusted" rate	unblinded; if met ECG criteria, <6 hrs, & not "poor prognosis"	not assessed

* Time from arrival in ED until thrombolysis unless otherwise specified, "ED": thlysis in ED, "CCU": Thlysis in CCU **Time from initial EKG in ED until thrombolysis

ψ "Thlysis": Thrombolytic therapy

ξ Thrombolytics here administered by cardiologists in the ED

γ "ED MD": Emergency Department physician independently of consultants

Sharkey et al in 1994 (Table 2) studied 93 consecutive patients treated by Emergency Physicians with thrombolytics and found a 89% concordance rate with guidelines, but patients who did not receive thrombolysis were not included.²⁰

Tsuyuki et al (Table 2) found that out of a series of 104 patients admitted with acute MI, 100% of those eligible for thrombolysis were correctly treated. This impressive figure was obtained only after the reviewers agreed with the clinicians' decisions that in 10 patients the prognosis was "poor", and therefore the patients should not have received thrombolysis. In this study, the thrombolytic decisions were made by consultants.²¹

In a large European trial of pre-hospital physician-administered thrombolysis, 92% of 4767 patients randomized to receive pre-hospital or in-hospital thrombolysis were "confirmed" to have been eligible for thrombolysis by a second physician in the hospital. Again, however, this study included only those patients who received thrombolysis.²² This pre-hospital study and those by Gonzalez¹¹ and Sharkey (1994)²⁰ were the only ones in which the thrombolytic decisions were made by Emergency Physicians independently of consultants (Table 2).

A second methodological problem of previous studies is that in none were the evaluators of appropriateness of thrombolysis blinded as to which patients actually received thrombolytics. This could lead to bias.

Finally, the statistic used to measure appropriateness of thrombolysis in all previous studies was a simple percentage. This statistic cannot take into account agreement by chance, which, in a dichotomous outcome such as a yes/no decision, will be at least 50%.⁴²

The overall effect of these methodological problems on the estimate of thrombolytic appropriateness is difficult to predict, and makes their results difficult to interpret. Failure to account for chance agreement would tend to overestimate appropriateness, while using unblinded reviewers could lead to bias in either direction, depending on the personal biases of individual reviewers. Finally, choosing the wrong denominator may also bias the estimate in either direction, since including all patients in whom thrombolytics are considered impacts both the numerator and denominator of the estimate of thrombolytic appropriateness.

2.4 Coronary Thrombolysis in the Emergency Department

Maximizing the benefit of thrombolytics requires minimizing the time to thrombolysis.⁶⁻¹⁰ This priority is reflected in the guidelines published by the Canadian Consensus Conference, which “...strongly recommend that...thrombolytic therapy...be started as soon as possible after the clinical impression of evolving MI is formed...”. The guidelines go on to recommend a one hour target and state that this “...can only be achieved by ensuring...the safe administration of thrombolytic therapy in the emergency room”.¹⁰

Many studies now have shown that administering thrombolytics in the Emergency Department is significantly faster than transferring the patient first to Coronary Care Units (CCU) (Table 2). Dalton et al showed a decrease in the mean time from arrival in the ED to thrombolysis from 141 minutes (range 45-614) when given in the CCU to 61 minutes (range 30-105) when given in the Emergency Department.¹³ Pell found the median time from ED arrival to thrombolysis to decrease to 49 minutes when thrombolysis was given in the Emergency Department from 93 minutes when it had been given in the CCU.¹⁴ Birkhead et al found that thrombolysis was more quickly given in the Emergency Department than when patients with suspected MI were admitted directly to the CCU from the community.¹⁵

As well, some studies have demonstrated that delays are associated with policies which insist on Cardiologist or Internist approval before initiating thrombolysis, even when the drugs are given in the Emergency Department.^{11,12,15,19} This effect, however, can be lessened when the consultant is not required to physically see the patient first.^{11,12}

Nonetheless, in many hospitals policies limiting the use of thrombolytic agents to the Coronary Care Unit persist, and some require a consultant's approval first.^{17,19} These policies persist despite the Consensus recommendations, and despite several calls for the relaxing of these stipulations in order to speed delivery of thrombolytics.^{10,18,19,43}

It may be that the reluctance to do so may stem from a perception that thrombolytic agents are safer when kept in specialists' hands. Adverse effects do occur with thrombolysis. Bleeding complications of thrombolytic therapy, including hemorrhagic strokes, are estimated to occur in 0.3 - 1% of cases, and are higher among the elderly. Severe allergic reactions to SK are reported in 0.2 - 0.3% of cases. Hypotension requiring treatment has been estimated to occur in 4 - 7% of patients following thrombolysis.⁹ As a result, some may feel that the Coronary Care Unit itself is a safer place than the Emergency Department for the use of thrombolytics. Despite this, no study to date has looked specifically at complication rates following thrombolysis in the Emergency Department.

3.0 Design Overview

The study was designed as a retrospective review of records of patients admitted from the ED with a diagnosis of an acute coronary syndrome (angina, unstable angina, acute MI, “rule-out” cardiac chest pain) during the study period of August 1st, 1994, to August 31st, 1995. Within this group of patients there are two sub-groups, those who were thrombolysed and those who were not. Abstracted data (see below) from the charts were assessed independently by two blinded reviewers, a Cardiologist (FRCPC) and an Emergency Physician (FRCPC). Each assessed independently whether the patient should or should not have received thrombolysis, based explicitly on Canadian Consensus guidelines. Agreement of the reviewers' decisions with the actual clinical decisions was then determined.

3.1 Patient Selection

Patients were selected from a master list of all patients admitted from the ED with an acute coronary syndrome during the study period of August 1st, 1994, to August 31st, 1995. This master list was generated by the hospital medical records department. It has been estimated that of all patients presenting to the ED with acute chest pain, only between 2 to 4% are eligible to receive thrombolysis.²⁰ Therefore, given the importance of including an adequate number of patients who received thrombolytics, all patients who received thrombolysis in the ED during the study period were included (approximately 30-40 patients per year receive thrombolysis in the ED at Mt. Sinai).⁴⁴ These patients were initially identified from an Emergency Department log book of all thrombolysed patients, then confirmed to have received thrombolysis when their charts were reviewed.

After selecting all thrombolysed patients from the master list, a consecutive series of the remaining patients were included (those admitted from the ED with an acute coronary syndrome, but who were not thrombolysed), starting from the beginning of the study period. A consecutive series rather than a random sample was used for reasons of convenience. Enrollment of patients into the study ended when a sufficient total number of charts have been collected, based on the required sample size calculation.

3.1.1 Inclusion and Exclusion Criteria

All patients who were admitted from the Emergency Department to the CCU with a diagnosis of acute coronary syndrome between August 1st, 1994 and August 31st, 1995, were eligible for inclusion. Only those charts in which a substantial proportion of the required information is missing or illegible were excluded. Of particular note are missing ECGs: if the ECGs from the period of time the patient spent in the ED were missing, then the case could not be assessed for appropriateness of thrombolysis.

3.2 Assessment of Concordance of Thrombolytic Decisions

The Emergency Physicians' thrombolytic decisions were compared with the "gold standard" assessment of the two blinded reviewers. In cases where the two reviewers agreed, the comparison with the ED physician's decision was straightforward. In cases where the two reviewers did not agree, they were reconvened to review the case, this time together, though still blind to the ED thrombolytic decision. If any cases could not be resolved in this manner, a final decision was to be made by the study director (MS); this did not occur, however.

3.3 Setting

At present, in only a few hospitals are thrombolytic decisions made independently by Emergency Physicians, and in still fewer is this done routinely.^{17,19} As a result, this study collected patients from only one site, the Mount-Sinai Hospital in Toronto, Ontario, a tertiary care center where Emergency Physicians routinely administer thrombolysis independently of consultants. This policy has been in place since January, 1991.⁴⁴

3.4 Sample Size Calculation

The required sample size was calculated such that adequate precision would be obtained for the primary objective, that of estimating the percent overall concordance of thrombolytic decisions made by Emergency Physicians with those of the reviewers:

$$\text{\% Concordance} = \frac{(\# \text{ patients considered}) - (\# \text{ discordant cases})}{\# \text{ of patients considered}} \times 100$$

The required sample size estimate was generated from the formula for desired confidence interval width for a proportion,⁴⁵ $n = (2z^*/w)^2 p^*(1-p^*)$. The following assumptions were made: 'w', the desired total width of the 95% confidence interval is 12%; 'p*', the "best guess" for the true concordance proportion based on published studies is 0.95,^{13,14,20,21} however in order to be more conservative we used a best guess of 0.85; and 'z*', the critical z score for a 95% CI is 1.96. With these assumptions, the required sample size was 136 patients.

3.5 Sources of Information and Data Collection

Data were gathered from the patients' charts, using primarily the Emergency Department record and nursing notes from the day of admission. Since the main objective was to determine whether the decision to give or withhold thrombolysis was the correct one, the information necessary for a reviewer to make that decision was collected.

A **"Standard Data Sheet"** was collected which included the patient's age, sex, duration of chest pain, presence of chest pain in the ED, initial vital signs, history of cardiac risk factors or previous ischemic heart disease and the documented presence of any relative or absolute contra-indications. As well, all ECGs taken in the ED from the time the patient presented up until the time the patient was transferred to the CCU or received thrombolysis were photocopied. If the ED record documented that an old ECG was available to the ED physician, then the most recent old ECG in the chart was also photocopied. This data sheet and the ECG copies were available to the reviewers.

An **"Additional Data Sheet"** was also completed, but was NOT made available to the reviewers in order to maintain blinding. It recorded whether the patient received thrombolysis and who ordered it. In order to assess safety of ED thrombolysis, the following adverse events in the first 24 hours following thrombolysis in the ED were recorded: major arrhythmia, hypotension, allergic reaction, cardiac arrest, stroke, or severe bleeding.

Final diagnosis, peak cardiac enzyme levels (creatinine kinase (CK) and CK isoenzyme (CKMB)), and survival to discharge were also recorded. Final diagnosis was recorded as listed in the chart, with the exception of acute MI, which was defined as chest pain, ECG changes and *one* of the following:

- 1- a peak CK level of greater than the upper limit of normal
AND a CKMB/CK ratio of greater than 6%
- or 2- a peak CK greater than twice the upper limit of normal.

The treating ED physician was identified by code. Data relating to the Emergency Physicians such as age, sex, training, number of years practicing in the ED and the average number of ED shifts per month were collected through a self-administered questionnaire of Mount-Sinai Emergency physicians, in order to assess how physician related factors affected thrombolysis decision-making.

3.6 Validity and Generalizability

The gold standard for determining whether study patients met the Canadian consensus guidelines for thrombolysis was the reviewers' decision based on the abstracted patient information, ECGs and the consensus recommendations. In order to increase reliability in data collection, all information was abstracted in a standard manner by one physician (MS). Furthermore, to ensure validity and avoid any potential biases of the reviewers, *they were instructed to make their decisions about eligibility for thrombolysis based only on the explicit criteria laid out by the guidelines (see appendix A), and not on their personal opinions.* Reliability and reproducibility of reviewers' decisions was assessed by inter and intra rater variability using the adjusted Kappa statistic.⁴⁶

By using one tertiary teaching site, generalizability may have been limited. However, there was little choice since in very few centers are Emergency Physicians routinely giving thrombolytics. This limitation is also one of the motivations behind the study: if we can show that thrombolytics can be appropriately and safely administered in this ED, then their use by Emergency Physicians may broaden, allowing multi-center studies to be performed.

4 Analysis

4.0 Primary Analysis

The primary outcome consisted of calculating the overall concordance of Emergency Physicians' thrombolytic decisions with reviewers' decisions, and a 95% exact confidence interval based on that estimate.⁴⁷ Since such a proportion does not take into account the likelihood of chance agreement, an adjusted Kappa statistic for agreement of binary outcomes was also calculated.⁴⁶

The adjusted Kappa statistic will be used in preference to the standard Kappa. Unlike a simple percentage, the Kappa statistic corrects for agreement expected to have occurred by chance, and is a standard measure of agreement for reliability studies.⁴² Agreement for binary outcomes may occur simply due to chance, or for cause (both reviewers knew what they were doing and therefore agreed). Ideally, the calculation of "expected" agreement in the standard Kappa formulation should include only agreement by chance, but, in fact, also tends to include some of the agreement for cause.

This results from the fact that in the standard Kappa statistic, the "expected" agreement is calculated based on the marginal probabilities of each possible outcome category, which occur in a model in which both agreement for chance and for cause are present. For example, the marginal totals of a 2 by 2 agreement table are used to calculate "expected" agreement, and these totals include both agreement for chance and agreement for cause. Therefore, if two observers are observed to agree more, their "expected" agreement will also rise. In essence, it is often "unfair" to reviewers who tend to agree.⁴⁶

For these reasons, an “adjusted Kappa” has been proposed, in which the expected agreement is based on a more realistic probability model, and is not affected as much by observed agreement, or the marginal probabilities of individual categories (see appendix B, for further details and an example).⁴⁶

In addition to calculating the concordance for the overall study group, the analysis was repeated for the two subgroups, those who received thrombolysis and those who did not. For each group, percent concordance was calculated. Kappa statistics could not be calculated for the subgroups since there was no variation; all patients either were, or were not, thrombolysed. Given the smaller size of the thrombolysis group, the confidence intervals around these estimates were necessarily wider. Nonetheless, the rationale for including non thrombolysed patients in the overall group was that concordance with guidelines must be assessed for *all patients with acute chest pain of presumed cardiac origin*, not only those who received thrombolysis. This is especially true given that errors of underuse (i.e. not giving thrombolysis to a patient who should receive it) in acute MI are associated with higher mortality since these patients do not receive the benefit of thrombolysis.⁶ These errors cannot be assessed without including non-thrombolysed patients.

4.0.1 Physician-Specific Concordance Rate: Hierarchical Modeling

The overall percent concordance was arrived at by pooling all the thrombolytic decisions made by all the Emergency physicians. However, concordance was also analysed using the ED physician as the unit of analysis, by stratifying by physician and calculating individual physicians' concordance rates.

If we simply used the pooled figure as an estimate from which to infer the average performance of individual Emergency physicians, then we would be assuming that all Emergency physicians have exactly the same concordance rate, so any observed variation between physicians was simply due to sampling (random) error. That is, that the observed concordance rates of MD1 to MD n follow a binomial distribution (since it is a dichotomous outcome) with parameters θ and n , where θ is the same for each physician;

$$MD1, MD2, MD3, \dots, MDn \sim b(\theta, n)$$

This would imply that, with large enough sample sizes, all Emergency physicians would have almost identical concordance rates. This clearly would be inappropriate, as some physicians will simply be better than others, and will have differing concordance rates beyond sampling error.

A more appropriate way to model the concordance rates and arrive at an estimate for individual physicians is to use *hierarchical modeling techniques*. Here, instead of assuming that all physicians' concordance rates follow a single distribution, we assume that there are true differences between different physicians, and that each physician has his or her own concordance rate. This can be represented in the following manner:

$$MD1 \sim b(\theta_1, n); \quad MD2 \sim b(\theta_2, n); \quad \dots; \quad MDn \sim b(\theta_n, n)$$

The distributions of individual physician concordance rates are governed by the θ_i parameters, and the observed data allow us to then model the distribution of θ_i , assuming it follows a normal distribution with parameters μ and σ (that is, $\theta_i \sim N(\mu, \sigma)$). The mean ED physician concordance rate will then be represented by our estimate of μ , and its standard deviation by our estimate of σ . One can then also derive the proportion of physicians whose concordance rates are above a given rate, and a 95% confidence interval representing a range of concordance rates which would include 95% of Emergency physicians.^{48,49}

4.1 Secondary Analyses

Several secondary analyses were carried out. Safety of ED thrombolysis was assessed based on the rates of occurrence of adverse events in the first 24 hours following ED administered thrombolysis. These were calculated as the number of each adverse event (major arrhythmia, severe hypotension, allergic reaction, stroke (ischemic and hemorrhagic), cardiac arrest, severe bleeding other than stroke) divided by the total number of patients thrombolysed in the ED. Exact 95% percent confidence intervals were calculated based on these estimates.

A logistic regression analysis was also carried out to determine whether certain patient or ED factors influenced the decision to thrombolysed a patient after controlling for concordance with guidelines. In particular age, sex and past medical history of the patient, day of week and time of day, as well as physician experience were analysed to see if any were independent predictors of thrombolysis.

4.2 Computer Resources

Descriptive statistics and logistic regression were calculated using Statistical Analysis Software (version 6.1, SAS Institute, North Carolina). Adjusted Kappa statistics were calculated with Splus (version 3.3, Mathsoft, Seattle). Hierarchical modelling was carried out with FastPro (Version 1.0, Academic Press, 1992),⁴⁹ and exact confidence intervals with CIA (version 1.0, British Medical Journal)⁵⁰ software.

5 Results

5.0 Eligibility Criteria: Inclusion and Exclusion of Patients

The charts of a total of 196 patients from the study period of August 1, 1994 to August 31, 1995, were reviewed: 42 were thrombolysis cases and 154 non-thrombolysis cases. All thrombolysis patients from the study period were eligible for inclusion in the study. Non-thrombolysis patients were eligible for inclusion consecutively from the start of the study period until a sufficient total number of patients had been collected (of a total of 317 non-thrombolysis cases over the study period, 154 (or 48.6%) were eligible for inclusion).

Seventeen of 154 (11.0%) non-thrombolysis cases were excluded because their charts were unavailable or because of coding errors which resulted in admission diagnoses being incorrectly coded as an acute coronary syndrome (see Table 3).

Table 3. Eligibility, inclusion and exclusion of patients

Description	ED Thlysis* Cases n (%)	ED Non-Thlysis* Cases n (%)	Total Remaining (after Exclusions)
Eligible for inclusion	42	154	196
Excluded from all analyses: Coding error or chart unavailable	0 of 42 (0%)	17 of 154 (11.0%)	179
Excluded from concordance analysis:			
No ECG	10 of 42 (23.8%)	31 of 137 (22.6%)	138
Drug error**	1 of 32 (3.1%)	n/a	137
Total included for analysis of concordance	31	106	137

*Thlysis= thrombolysis

**See text for explanation

Ten of the 42 (23.8%) thrombolysis cases were excluded *from the analysis of concordance* because the ECGs from the patient's stay in the ED were missing from the chart. Thirty-one of the 137 (22.6%) non-thrombolysis cases were also excluded from assessment of concordance because of missing ECGs.

One thrombolysis case was excluded from the analysis of concordance because of a drug administration error; the patient was thrombolysed by mistake following a mix-up of two patients' ECGs in the ED. It is important to note that *all 42 thrombolysis cases were retained for the analysis of complications resulting from thrombolysis in the ED*. Table 4 provides the demographics of the final 137 patients included in the analysis of concordance.

Table 4. Demographics of patients included for concordance analysis

Characteristic	All Patients included in analysis of concordance (n=137)
Age (yrs) mean $\pm$ SD range	68.1 $\pm$ 13.0 29 to 91
Female n (%)	57 (41.6)
Thrombolysed n (%)	31 (22.6)
Final Diagnosis n(%):	
Acute MI	45 (32.8)
Unstable Angina	70 (51.1)
CP-NYD*	14 (10.2)
Other cardiac	7 (5.1)
Non cardiac	1 (0.8)
Survival n (%)	
yes	125 (91.2)
no	12 (8.8)

* "CP-NYD"=chest pain, not yet diagnosed

5.1 Comparison of Sampling Periods for Thrombolysed and Non-Thrombolysed Patients

Since non-thrombolysis patients were identified consecutively, they were included from August 1, 1994 to January 13, 1995, while thrombolysed patients were included over the entire study period. This could bias the results only if the non-thrombolysed patients in the second period (those not included) were systematically different from those in the first, or if practice patterns of the physicians treating them changed significantly in the two periods.

A review of the log of thrombolysed patients as well as the master list for the whole year revealed no systematic variations in either the monthly total of acute coronary syndrome patients admitted, the admitting diagnoses, the number of patients thrombolysed, or their age and sex distributions, indicating it is unlikely that there were significant differences in the patients over the two periods (see Table 5).

Practice patterns over the two contiguous periods were most likely unchanged. The thrombolysis guidelines were first published in 1993 and re-published in 1994 with no significant revisions of the criteria for patient selection for thrombolysis.^{9,10} As well, discussions with the ED director suggested there were no changes in practice patterns with regard to patient selection for thrombolysis for the two periods, and there were no significant physician staff changes in the Emergency Department over the year, nor any changes in protocols for dealing with cardiac patients.⁴⁴

Table 5. Distribution of suspected acute coronary syndrome admissions from the Mount Sinai ED to the CCU from August 1, 1994 to August 31, 1995

MONTH	Total No. Admitted	No. Thlysed	No. Female	Age Group (years)				ADMITTING Diagnosis ^ψ			
				<40	40-59	60-80	>80	Acute MI	Angina	Other ACS*	Chest Pain**
Aug 94	24	3	7	0	4	16	4	11	11	0	2
Sep 94	32	1	15	0	8	16	8	8	16	1	7
Oct 94	26	5	14	0	6	14	6	6	9	4	7
Nov 94	30	2	10	1	8	17	4	3	21	1	5
Dec 94	32	2	17	1	6	19	6	8	19	1	4
Jan 95	30	4	11	1	11	16	2	3	14	3	10
Period Total (average)	174 (29 per month)	17 9.7%	74 42.5%	3 1.7%	43 24.7%	98 56.3%	30 17.3%	39 22.4%	90 51.7%	10 5.7%	35 20.2%
Feb 95	20	2	6	0	5	8	7	4	8	6	2
Mar 95	22	1	9	0	4	14	4	2	14	1	5
Apr 95	39	5	16	0	8	23	8	11	25	1	2
May 95	33	8	14	1	8	18	6	11	13	2	7
Jun 95	23	2	10	0	7	12	4	5	16	0	2
Jul 95	30	5	16	0	11	14	5	8	16	2	4
Aug 95	18	2	10	0	7	8	3	4	12	1	1
Period Total (average)	185 (26 per month)	25 13.5%	81 43.8%	1 0.5%	50 27.1%	97 52.4%	37 20.0%	45 24.3%	104 56.2%	13 7.1%	23 12.4%

^ψ Admission diagnosis codes as assigned by medical records; may differ from final diagnosis

* "Other ACS" = other acute coronary syndrome ** "Chest Pain" = chest pain, not otherwise specified

5.1.1 Comparison of Charts with Missing ECGs

Because of concern that excluding charts with missing ECGs might introduce a bias in the concordance analysis, all 10 thrombolysis charts with missing ECGs and 14 of the 31 non-thrombolysis charts with missing ECGs (the 14 charts for which all data except ECGs were available) were compared to those with ECGs present to ensure they were not different (table 6).

Table 6. Comparison of groups by presence/absence of ECGs

Characteristic	Thlysis*, no ECG n=10	Thlysis, with ECG n=31	Non Thlysis, no ECG n=14	Non Thlysis, with ECG n=106
Age (mean $\pm$ SD)	63.1 $\pm$ 8.1	67.7 $\pm$ 13.9	66.9 $\pm$ 10.7	68.2 $\pm$ 12.8
Female n (%)	3 (30.0)	15 (48.4)	7 (50.0)	42 (39.6)
Final Diagnosis n(%)				
Acute MI	9 (90)	26 (83.9)	3 (21.4)	19 (17.9)
Unstable Angina	1 (10)	3 (9.6)	8 (57.2)	67 (63.2)
CP-NYD**	0	0	3 (21.4)	14 (13.2)
Other cardiac	0	2 (6.5)	0	5 (4.8)
Non cardiac	0	0	0	1 (0.9)
Survival n (%)				
yes	10 (100)	27 (87.1)	13 (92.9)	98 (92.5)
no	0	4 (12.9)	1 (7.1)	8 (7.5)

Thlysis=thrombolysis; **CP-NYD*=chest pain, not yet diagnosed

Among the non-thrombolysed charts, no systematic differences can be seen in mean age, sex, final diagnosis or survival among the patients with ECGs missing from the charts and those with ECGs present.

Among thrombolysed patients, mean age, sex distribution, final diagnoses and survival among patients with ECGs present in their charts and those without are very similar. Of the 10 thrombolysed patients with missing ECGs, 9 had a final diagnosis of acute MI (90.0%; 95% CI 55.5 - 99.7), and 1 had unstable angina (10.0%; 95% CI 0.25 - 44.5). All 10 patients in this group survived (100%; 95% CI 69.2 - 100).

Of the 31 thrombolysed patients with ECGs, 26 had acute MIs (83.9%; 95% CI 66.3 - 94.5), 3 had unstable angina (9.6%; 95% CI 2.0 - 25.8), and two had other cardiac diagnoses.

Twenty-seven patients of the 31 survived (87.1%; 95% CI 70.2 - 96.4).

These differences may simply represent chance variation, since they are not statistically significant. There is also no indication that there was any clustering of the attending ED physicians or admission dates for these 10 thrombolysed patients with missing ECGs; five different ED physicians treated the 10 patients, and they were admitted during 8 different months ranging from August, 1994 to August, 1995.

5.2 Assessment of Concordance with Clinical Guidelines

5.2.0 Consensus Assessment of Reviewers: Inter and Intra Rater Agreement

The two reviewers, a Cardiologist and an Emergency physician, both independently reviewed all 137 cases for concordance with guidelines. Their initial assessments agreed for 131 of the 137, giving an inter-rater adjusted Kappa statistic for the two reviewers of 0.89 (95% CI 0.81 - 0.97). For those six cases where the reviewers initially disagreed, they were re-convened together to review all six cases and reach a consensus decision. In all six cases, consensus was readily achieved.

The intra-rater agreement was estimated by having each reviewer re-assess 15 randomly selected patients they had previously assessed, without knowing their previous decision. For both reviewers, the second assessment agreed with the first in all 15 cases, resulting in an intra-rater adjusted Kappa for both reviewers of 0.93 (95% CI 0.74 - 1.0).^ψ

5.2.1 Overall concordance with clinical guidelines

Concordance between the actual clinical decisions and the “gold standard” assessment is presented in table 7.

Table 7. Concordance with consensus assessment

		Consensus Assessment		Total
		Should be Thrombolysed	Should not be Thrombolysed	
Clinical Decision	Thrombolysis YES	25	6	31
	Thrombolysis NO	3	103	106

Of the 31 thrombolysed patients, in 25 there was concordance between the clinical decision and the guidelines, as assessed by the two reviewers. Of the 106 patients not thrombolysed, in 103 there was concordance between the clinical decision and the guidelines. These results give an adjusted Kappa statistic of 0.85 (95% CI 0.76 - 0.94) for concordance between the clinical decisions and the guidelines.

^ψ Even with “perfect” agreement (e.g. 15 out of 15), the adjusted Kappa statistic does not equal 1.0 since a pseudocount of 1 is added to the agreement table and divided equally among all cells.(see ref 46 and appendix B).

5.2.2 Percent Concordance by Thrombolysis Status

In addition to looking at overall concordance, concordance was analysed in the two separate groups, those who received thrombolysis and those who did not. By doing so, however, Kappa statistics could no longer be calculated, only percent concordance. These percentages do not account for chance agreement, but do allow for comparison with previous studies that have assessed “appropriate” thrombolysis based on percent concordance.

Overall, there was agreement in 128 of 137 patients, giving a percent concordance of 93.4% (95% CI 87.9 - 97.0). Among the 31 thrombolysed patients, 25 were concordant with the guidelines, giving a concordance rate of 80.6% (95% CI 62.5 - 92.5). Among the 106 non-thrombolysed patients, 103 were concordant, giving a rate of 97.2% (95% CI 91.9 - 99.4).

5.2.3 Analysis of Concordance by Final Diagnosis

Table 8 presents the distribution of final diagnoses after patients are stratified by pattern of concordance between clinical decisions and the consensus assessments. Of the 25 subjects where clinical decision to thrombolyse was in accord with the guidelines, 22 had a final diagnosis of acute MI, one had a final diagnosis of unstable angina, while two had other cardiac diagnoses (one pericarditis, one arrhythmia).

Table 8. Concordance pattern by final diagnosis

Concordance pattern*		Final Diagnosis					Total
Clinical Decision	Consensus AssessmentΦ	Acute MI	Unstable Angina	CP-NYD	Other Cardiac	Non Cardiac	
Thrombolysis given	Meets Guidelines	22	1	0	2	0	25
	Does not meet Guidelines	4	2	0	0	0	6
Thrombolysis not given	Meets Guidelines	0	2	0	1	0	3
	Does not meet Guidelines	19	65	14	4	1	103
Total		45	70	14	7	1	137

*see Table 7

 Φ Consensus assessment of the two reviewers.

Of the six subjects who were thrombolysed but who did not meet the criteria for thrombolysis, two had unstable angina, while four had a final diagnosis of acute MI (these four acute MI patients had the following peak CK and CKMB levels: 285/22, 902/110, 1370/94, 290/23). Among the three subjects who were not thrombolysed but who nonetheless were judged to meet the criteria for thrombolysis, none had a final diagnosis of acute MI (two had unstable angina and one had a diagnosis of old MI).

Finally, of the 103 subjects who were not thrombolysed and did not meet the criteria for thrombolysis, 19 had an acute MI, 65 unstable angina, 14 chest pain not yet diagnosed, 4 other cardiac diagnoses, and 1 non-cardiac diagnosis.

5.2.4 Physician-Specific Concordance Rates: Hierarchical Modeling

The 137 subjects for which concordance was determined were then stratified according to the treating Emergency physician. The individual concordance rates were determined for each physician (four physicians who treated less than two patients each in the sample were excluded).

The individual physician concordance rates cannot simply be pooled to express the average physician performance, since to do so would be to assume that all physicians' concordance rates are identical, and that observed differences are due to random fluctuation only. In fact, the observed differences are in part due to random fluctuations, but are also due to true differences in physician-specific concordance rates. The hierarchical model avoids this assumption, and instead models *the variation in individual physician concordance rates*, by estimating the distribution of these rates in a population of physicians. The results are presented in Table 9.

Table 9. Physician-specific concordance rates* and hierarchical model results

ED physician	MD1	MD2	MD3	MD4	MD5	MD6	MD7	MD8	MD9
Number of patients treated	20	6	24	13	12	4	24	12	18
Number of concordant decisions	19	5	22	12	11	4	23	12	16
% Concordance	95.0	83.3	91.7	92.3	91.7	100	95.8	100	88.9
95% CI	75.1-99.9	35.9-99.6	73.0-99.0	64.0-99.8	61.5-99.8	39.8-100	78.9-99.9	73.5-100	65.3-98.6
Hierarchical Model Results	Mean Median SD 95% CI				0.913 0.919 0.0425 0.813 - 0.976				

*Four MDs who treated only one patient each in the sample were excluded. An additional patient for whom treating physician was not known was also excluded.

The hierarchical model estimated by the ED physician concordance rates in our study has a mean of 91.3%, with standard deviation of 4.25%. The median is 91.9%, meaning that 50% of all Emergency physicians similar to those in the study would be expected to have concordance rates higher than this, and 50% lower. The 95% confidence interval is 81.3% to 97.6%, which means that 95% of all Emergency physicians similar to those in the study would be expected to have true rates in this range.

5.2.5 Documentation of Contra-Indications and Concordance

When determining whether a patient with presumed acute myocardial infarction should receive thrombolysis or not, one of the important elements to consider is the presence of absolute or relative contra-indications (see appendix A).

In the data abstracted from the patients' charts, attempts were made to include information about such contra-indications so that the two reviewers would be able to fully judge whether the patient met the criteria for thrombolysis. However, because of the retrospective nature of our data collection, we could only provide to reviewers that information which was documented by the Emergency physicians in the charts. Therefore, if the ED physician did not document the contra-indication to be present, we assumed it was absent.

The overall documentation of contra-indications was poor. Of the 42 patients thrombolysed in the ED, only 19, or 45.2%, had *any* documentation of contra-indications. Not only does this present a potential medico-legal problem, but, in addition, it has a potential impact on our estimate of the true concordance rate, since if a patient's contra-indication to thrombolysis is not documented, he may be judged by the reviewer to be a candidate for thrombolysis when in fact he is not. This could result in an inflated estimated concordance rate.

5.3 Secondary Analyses

5.3.0 ED Thrombolysis Complication Rates

In order to assess the safety of ED thrombolysis, complication rates in the 24 hour period following thrombolysis were determined (table 10). The first 24 hours following thrombolysis was chosen since complications occurring after this period were unlikely to be due to the thrombolysis itself. All 42 patients thrombolysed in the ED were included.

The following complications were assessed: hemorrhagic CVA, arrhythmias, allergic reactions, hypotension, cardiac arrest and non-CVA bleeding complications. With the exception of CVA, complications were defined to have occurred if they were severe enough to have required a medical intervention (e.g. medication, IV fluids, pressure dressing etc.). In contrast, for CVA, any amount of intra-cranial bleeding was sufficient.

Table 10. Complication rates for patients thrombolysed in the ED (n=42)

Complication	Number	%	95% CI
CVA (hemorrhagic)	1	2.4	0.05 - 12.6
Arrhythmia	5	11.9	4.0 - 25.6
Hypotension	4	9.5	2.7 - 22.6
Cardiac arrest	1	2.4	0.05 - 12.6
Bleed (non-CVA)	2	4.8	0.6 - 16.2
Allergic reaction	1	2.4	0.05 - 12.6

These complication rates were then compared with published complication rates from large thrombolysis trials.

Hemorrhagic CVA

The rate of hemorrhagic CVAs in large trials has generally been reported to be between 0.3-1%,^{6,7,9} depending on the thrombolytic agent used. In our series of 42 patients, hemorrhagic CVAs occurred at a rate of 2.4% (95% CI 0.05-12.6%). However, this represents only one CVA, and, given these small numbers, the point estimate is unstable and it is probably more useful to look at the confidence interval. The confidence interval is wide, but nonetheless includes the previously reported rates of CVA resulting from thrombolysis.

Non-CVA bleeding

Two of the 42 patients suffered bleeding severe enough to warrant intervention (one required dental packing from bleeding dental extraction site, the other discontinuation of heparin therapy for severe bruising). However, this complication is more difficult to compare with published rates, because of non-standard definitions of bleeding severity.

The 1993 Canadian Consensus guidelines, when reviewing bleeding complications, defined severe bleeding as "fatal bleeding, intra-cranial bleeding, bleeding which produces permanent morbidity, retroperitoneal bleeding, bleeding requiring operative intervention and bleeding requiring blood transfusion".⁹

Neither of the two patients with bleeding complications met this definition; only the aforementioned patient with a hemorrhagic CVA does. Therefore, according to this definition, the rate of "severe bleeding" in our series is the same as the CVA rate, 1 in 42 or 2.4% (95% CI 0.05-12.6%). The rates of severe bleeding in published trials have varied from 0.3 - 5% in large trials, or as high as 10% in smaller trials^{7,9}.

The GUSTO trial reports rates of “moderate bleeding” of between 5.1 – 5.8%, depending on trial arm⁷, though they do not define “moderate”. If we consider the two patients with bleeding complications to have represented “moderate bleeding”, then the rate in our series is 4.8% (95% CI 0.6-16.2). Therefore, the rate of bleeding in this series of 42 patients thrombolysed in the ED seems similar to previously reported rates.

Allergic reactions

Allergic reactions occur more commonly with streptokinase than TPA. Minor reactions (fever, rash) occur more frequently than do major reactions (anaphylaxis). The Canadian consensus guidelines report that minor allergic reactions occur at a rate of 0.7-3.5%⁹, while GUSTO reported minor reactions between 1.6-5.8% of the time⁷. Severe anaphylaxis is reported between 0.1-0.7% of the time^{7,9}.

One of 42 patients in this series suffered a minor allergic reaction, and there were no anaphylactic reactions. The rate of minor allergic reactions, 2.4% (95% CI 0.05 - 12.6) once again is within the range of previously reported rates of allergic reactions.

Hypotension

Hypotension in the setting of acute MI may be the result of the infarction itself or a result of treatments such as thrombolysis. In GISSI-2, severe hypotension was reported to occur in 2 – 4.4% of patients.⁵¹ Hypotension has been documented to occur between 10.1-13.3% in GUSTO,⁷ and 7.1-11.8% in ISIS-3.⁵² Again, lack of standard definitions make direct comparisons difficult, but, in this series of 42 patients, 4 suffered hypotension, giving a rate of 9.4% (95% CI 2.7 - 22.6), which is in line with previously reported rates.

Arrhythmias and cardiac arrest

Arrhythmias or cardiac arrest can also be the result of the underlying myocardial infarction or a result of thrombolysis-induced reperfusion arrhythmias. Ventricular fibrillation, the most malignant arrhythmia, has been reported to occur at a rate of 6.0-9.5% in GUSTO,⁷ and 6.5-6.8% in GISSI-2.⁵¹ “Cardiac arrest or ventricular fibrillation” was reported to occur in 9.6-9.8% of patients in ISIS-3.⁵²

In this series of 42 patients, *all arrhythmias* requiring intervention were counted as an arrhythmia. Five of 42 patients suffered an arrhythmia (three bradycardias, one ventricular tachycardia, and one not defined), giving a “all arrhythmia” rate of 11.9% (95% CI 4.0-25.6). If, as in the thrombolytic trials, we consider only the malignant arrhythmias, then the one patient who had a cardiac arrest and the one ventricular tachycardia give a “cardiac arrest or ventricular arrhythmia” rate 2 of 42 patients, or 4.8% (95% CI 0.6-16.2%).

5.3.1 Time to Thrombolysis

As previously pointed out, time to thrombolysis is a crucial determinant of mortality reduction with thrombolysis in acute MI, and the potential for lower time to thrombolysis is one of the main rationales for promoting thrombolysis in the ED.

In the 42 patients thrombolysed in the ED, the median time from arrival in the ED to thrombolysis was 44 minutes, while the 25th, 75th and 90th percentile times were 21, 96 and 117 minutes respectively. The range was from 5 minutes to 669 minutes (this extreme time to thrombolysis was due to a patient's initial refusal of thrombolysis, then later consenting to it after family pressure). Fifteen of 42 patients (35.7%) had times to thrombolysis in excess of the recommended 60 minutes.^{9,10}

5.3.2 Use of Acetylsalicylic Acid (ASA) with Acute Coronary Syndromes

The Canadian consensus guidelines recommend the use of ASA acutely once having made a presumptive diagnosis of acute MI.^{9,10} In addition, ASA is generally recommended for patients with unstable angina.⁵³ In both cases, contra-indications must be considered.

We analysed ASA use for all patients in the study, not only those included in the concordance analysis (see Table 3). Among all 179 patients, 136 had a final diagnosis of unstable angina or acute MI (see Table 6). One hundred of these 136 patients received ASA in the ED, and another 23 had either documented contra-indications or documented daily ASA use, giving an overall appropriate ASA use rate of 90.4% (95% CI 84.2 - 94.8). Among only the 42 patients who were thrombolysed in the ED, 39 received ASA in the ED, giving an appropriate ASA use rate among thrombolysed patients of 92.9% (95% CI 80.6 - 98.5).

5.3.3 Analysis of Independent Predictors of Thrombolysis

The decision of whether or not to thrombolyse a patient with suspected acute MI should be based on the criteria laid out in the guidelines. Other clinical factors such as age and sex of the patient *should not* play a role in the decision to administer or withhold thrombolytics. A recent study of thrombolysis in acute MI in Europe demonstrated sex and age biases. Among patients without contra-indications, older patients were significantly less likely to receive thrombolysis, as were women.⁵⁴ Similar biases have been found in studies of other cardiovascular procedures.⁵⁵

A logistic regression analysis was carried out to determine if such biases existed in our study, that is, whether there were *other independent predictors of thrombolysis after controlling for eligibility for thrombolysis, based on the guidelines.*

The logistic regression was carried out on all 137 patients with **thrombolysis** (*yes or no*) as the dependent variable. The main independent variable controlled for **eligibility for thrombolysis** (i.e. should have been thrombolysed according to the guidelines, or should not have been thrombolysed according to the guidelines) based on the consensus assessment of the two reviewers.

The additional independent variables considered in the initial model were **age**, **sex**, presence of **cardiac risk factors** (*no risk factor, one or more risk factors*), previous **cardiac history** (*yes or no*), **day of week** (*week-end vs. weekday*), **day shift** and **night shift** (*two dummy variables coding for day, evening or night*), and **ED physician years of experience** (*less than 10 years, more than 10 years*).

The Spearman correlation matrix for independent variables is presented in Table 11. The only variables with evidence of excessive collinearity are NIGHT SHIFT and DAY SHIFT, which is expected since these are dummy variables which together code for the three 8 hour shifts in a day.

Table 11. Spearman correlation matrix of independent variables

	Eligibility for thrombolysis	Age Category	Sex	Cardiac History	Cardiac Risk Factors	Day of Week	Day Shift	Night Shift	ED-MD Experience
Eligibility for thrombolysis	1	-0.027	-0.024	-0.302	0.032	-0.064	-0.134	0.147	-0.012
Age Category	-0.027	1	0.250	0.214	-0.264	-0.093	-0.063	0.085	0.008
Sex	-0.024	0.250	1	-0.081	-0.112	0.034	-0.021	-0.061	-0.066
Cardiac History	-0.302	0.214	-0.081	1	-0.077	-0.089	-0.019	0.038	0.025
Cardiac Risk Factors	0.032	-0.264	-0.113	-0.077	1	-0.091	0.066	-0.004	-0.044
Day of Week	-0.064	-0.092	0.034	-0.089	-0.091	1	0.034	-0.104	-0.145
Day Shift	-0.134	-0.063	-0.021	-0.019	0.065	0.034	1	-0.428	0.024
Night Shift	0.147	0.085	-0.061	0.038	-0.005	-0.104	-0.428	1	-0.121
ED-MD Experience	-0.012	0.008	-0.066	0.025	-0.044	-0.146	0.024	-0.121	1

Model selection was carried out by entering all independent variables into the initial model, and then a manual step-wise backward elimination was carried out with the least significant variable being removed from each model in turn. Thus, a total of nine models were compared. Model selection was carried out using the Schwarz criterion (SC); the model with the smallest SC was considered best.⁵⁶

As expected, *eligibility for thrombolysis* was a very strong predictor of thrombolysis (crude OR=143.1, 95% CI 33.5 - 611.8), and the model containing only this independent variable was the one with the smallest SC. None of the other independent variables were significant independent predictors of thrombolysis at the $\alpha=0.05$ level in a model containing only *eligibility for thrombolysis*. Only two other independent variables, *sex* and *day of week*, came close to statistical significance, and the models containing only *eligibility for thrombolysis*, *sex* and *day of week* are presented in Table 12.

Table 12. Comparison of selected logistic regression models*

Independent Variables in Model	Adjusted ORs (95% CI)	p Value for Variable	Reference Category for Variable	Schwarz Criteria for Model
eligible for thlysis ^ψ sex day of week	289.81 (44.3-999.0) 4.60 (0.88- 23.90) 0.25 (0.05-1.14)	0.0001 0.069 0.074	does not meet guidelines male weekend day	78.22
eligible for thlysis ^ψ sex	222.9 (39.38-999) 4.22 (0.83-21.40)	0.0001 0.08	does not meet guidelines male	76.68
eligible for thlysis ^ψ	143.1 (33.5-611.8)	0.0001	does not meet guidelines	75.37

*All models have "thrombolysis" as the dependent (outcome) variable

^ψ"thlysis" = thrombolysis

Given the wide confidence intervals, the estimated adjusted odds ratio (OR) for sex remained relatively constant (varying from 5.55 to 4.22) across all models indicating little confounding. The same was true for *day of week* (varying from 0.24 to 0.28).

With the very strong effect of *eligibility for thrombolysis* and the small sample size, it is important to note that other independent variables in the model would have had to have been quite strong predictors to have achieved statistical significance. In other words, our sample had low power to detect such effects. As well, the effect of sex in this regression analysis, though non-significant, suggests that women would be *more likely* to be thrombolysed after controlling for eligibility for thrombolysis (adjusted OR=4.2; 95% CI 0.83 - 21.4). This sex bias, if it exists, would be counter to what has been previously reported,^{54,55} and makes it even more likely to be artefactual.

5.3.4 Survival

Survival was determined among all study patients, not only those for whom concordance was determined. Among all non-thrombolysed acute MI patients, 13.6% died (3 of 22; 95% CI 2.9 - 34.9), compared to 8.6% of thrombolysed acute MI patients (3 of 35; 95% CI 1.8 - 23.1). Among all patients with a final diagnosis of unstable angina, 6.3% died (5 of 79; 95% CI 2.1 - 14.2), while 29% patients with "other cardiac" final diagnoses died (2 of 7; 95% CI 3.7 - 71.0). No patient with a "non-cardiac" or "chest-pain, not yet diagnosed" final diagnosis died.

6 Discussion

6.0 Thrombolysis in the ED and Concordance with Guidelines

The estimate of overall concordance, the adjusted Kappa of 0.85 (95% CI 0.76 - 0.94), suggests highly appropriate use of thrombolytics by the ED physicians in our study, based on a blinded explicit comparison with standard Canadian guidelines. Adjusted Kappa scores above 0.8 represent excellent agreement.^{42,57}

When thrombolytics are not used appropriately, it may represent underuse or overuse. In order for a study to fully assess both, *all patients with acute chest pain of presumed cardiac origin* should be eligible for inclusion, and not, as in previous studies, only thrombolysed patients^{13,20,23} (since underuse cannot be assessed), or only patients with acute MI^{14,21} (since overuse cannot be fully assessed).

In our study of ED thrombolysis, 22 of 45 (48.9%) acute MIs were assessed as meeting the guidelines for thrombolysis, and all of them received thrombolysis. There were no patients with acute MIs who met the thrombolytic criteria who did not receive thrombolysis. Among all non-thrombolysed patients the concordance rate was 97.2% (95% CI 91.9 - 99.4), which is very high and has not previously been reported. This indicates little, if any, underuse of thrombolysis. This is not very surprising given that most patients presenting with chest pain clearly do not meet thrombolytic criteria. Nonetheless, several studies have found evidence of underuse of thrombolysis in acute MI.^{9,12-14,37-39,54} A recent review of 4035 patients with acute MIs in eleven European centers showed that a median of 36% (range 13-52%) were thrombolysed, and they estimated that a further 20% of these patients met the criteria for thrombolysis but did not receive it.

After assessing thrombolytic criteria at presentation including time since onset of pain, ECG criteria, and contra-indications, they estimated the maximum thrombolysis rate to be 55%.⁵⁴ This underlines the fact that basing the definition of “appropriateness” on simply a final diagnosis of acute MI may seriously overestimate appropriateness rates.

Overuse of thrombolytics was also assessed in this study. Among the 31 thrombolysed patients, the percent concordance was 80.6% (95% CI 61.5 - 92.5), which is somewhat lower than previously reported. Previous studies have generally found high rates of “appropriate” thrombolysis. All studies have used percent concordance rather than Kappa statistics. McKendall reported 100% appropriateness among 32 thrombolysed patients, but did not define “appropriate”.²³ Pell reported 93% “appropriate” thrombolysis among 136 thrombolysed patients, but thrombolysis was defined as appropriate simply if the final diagnosis was acute MI.¹⁴ Sharkey reported that 83 of 93 patients (89%) in his series were “appropriately” thrombolysed, though the assessment was based on an unblinded review by a cardiologist with the criteria not defined.²⁰ Finally, Tsuyuki reported 100% “appropriateness” out of 79 thrombolysed acute MIs based again on an unblinded review, and only after excluding patients with “poor prognosis” from the analysis.²¹

Our study definition of appropriateness was explicitly based on standard guidelines, and was the first to use blinded reviewers and to adjust for chance agreement using Kappa statistics. The slightly lower rate we estimated probably reflects our more rigid definition of appropriateness and the effect of blinding reviewers.

A closer look at those patients where the thrombolytic decision was discordant with the consensus assessment is warranted (table 8). Of the six thrombolysed patients who did not meet the guidelines, four had acute MIs. One complication occurred in these six patients; a fatal hemorrhagic CVA in a patient who had an acute MI. Of the three subjects who were judged to meet the guidelines but who were not thrombolysed, none had a final diagnosis of acute MI.

The latter three cases could be seen to suggest that the guidelines as interpreted by the assessors were insufficiently specific in selecting candidates for thrombolysis. However, we believe they more likely demonstrate the difficulty of interpreting thrombolytic criteria when the clinical context is retrospectively recreated from a chart, a process which may not convey all the subtleties appreciable at the bedside.

6.0.1 Physician-Specific Concordance Rates

The hierarchical model describes *the variation in individual physician concordance rates*, by estimating the distribution of these rates in a population of Emergency physicians. All nine physicians who treated more than one patient in the sample had high rates of appropriateness, and the resultant hierarchical model indicates that the estimated mean ED physician concordance rate is 91.3%, with a standard deviation of 4.25%. The median of 91.9% means that 50% of all Emergency physicians similar to those in the study would be expected to have concordance rates above this, and 50% lower. The 95% confidence interval indicates that 95% of all Emergency physicians similar to those in the study would be expected to have true concordance rates in the range of 81.3% to 97.6%.

By estimating the variation in *individual* physician concordance rates, hierarchical models provide information that is complimentary to estimates of overall appropriateness. Reliance on only the adjusted Kappa (and its confidence interval) would give an overall picture of appropriateness, corrected for chance agreement, but would not give as much information about the distribution or range of individual physician appropriateness.

6.1 Complications of ED Thrombolysis

The second objective of this study was to investigate whether ED thrombolysis is as safe as thrombolysis in other critical care areas of the hospital. The rates of all major thrombolytic complications were no higher than those reported previously in large thrombolysis trials. The importance of this finding relates to minimizing time-to-thrombolysis.

Previous studies have reported that one important cause of delay in administering thrombolytic agents involved the transfer of patients from the ED to the ICU or CCU setting where thrombolytic agents were given.^{13-15,19} Demonstrating that ED thrombolysis is safe would remove one more barrier and thus reduce time to thrombolysis. However, the small sample size of our study results in wide confidence intervals and low power to identify differences, therefore further study is warranted to ensure the comparability of complication rates when thrombolysis is initiated in the ED.

6.2 Time to Thrombolysis

This study confirms what several previous studies have shown, that thrombolysis can be carried out rapidly in the ED. The median time to thrombolysis of 44 minutes compares well with previously reported times, and is well within the recommended time to thrombolysis in the guidelines of under 60 minutes. The inter-quartile range of 21 to 96 minutes also compares well with previous studies (see table 2).^{11,13-16,20,23}

However, 15 of 42 patients had times to thrombolysis in excess of the recommended 60 minutes.^{9,10} These may have represented more difficult cases, or cases where the clinical or ECG criteria changed while in the ED, thus prolonging their times, but nonetheless it indicates that still more improvement may be possible in reducing times to thrombolysis.

6.3 Factors Affecting the Decision to Administer Thrombolysis

Patients presenting to the ED with acute chest pain should ideally all have equal likelihood of being treated in accordance with standard thrombolytic regardless of their age or sex or factors such as when they present or the ED staff physician they are treated by.

The logistic regression analysis was carried out to determine if there were *other factors which were significant predictors of thrombolysis, independent of whether patients met thrombolytic guidelines or not*. No significant independent predictors were found by our logistic regression, which suggests that, quite appropriately, these factors did not influence the decisions to administer thrombolytics. However, the power to detect significant predictors was low given the small sample size, and therefore we cannot exclude the possibility that these effects indeed might be present. Further study using a larger sample size is warranted.

6.4 Study Limitations

All studies based on retrospective review of charts suffer from problems of data availability and reliability. In this study, there were two main problems of this type encountered. The first was that of missing ED ECGs which necessitated the exclusion of patients from the concordance analysis. According to the ED director and Medical Records personnel, there were no systematic reasons for this absence of ECGs.⁴⁴ Careful analysis showed that the missing ECGs did not introduce any bias into our results.

The second problem was that of poor documentation of contra-indications to thrombolysis, which represents a possible bias which could inflate concordance rates. Both of these problems represent potential medico-legal issues, and demonstrate the need for maintaining full and accurate medical records, from both research and patient-care perspectives. As well, they underline that a prospective study with standard data collection would provide some protection against these problems.

Finally, some of the point estimates for mortality were higher than those reported in other large trials.^{9,10,53} Unstable angina patients had a mortality rate of 6.3% (95% CI 2.1 - 14.2), while those with "other cardiac" diagnoses had a mortality rate of 29% (95% CI 3.7 - 71.0). Among acute MI patients, 8.6% (95% CI 1.8 - 23.1) of thrombolysed patients died, compared to 13.6% (95% CI 2.9 - 34.9) of non-thrombolysed patients. These somewhat higher mortality rates for unstable angina and "other cardiac" diagnoses likely represent chance variation due to the small sample sizes, and are not likely to effect the generalizability of the results.

6.5 Conclusion

Emergency physicians are routinely faced with the dilemma of patients presenting with chest pain. Today, physicians must not only accurately determine which of these patients are having acute MIs, they must as well decide which should receive thrombolytic drugs, and act on their decisions as rapidly as possible.

The importance of this study of ED thrombolysis is three-fold. First, these results indicate that a model of thrombolytic use in which ED physicians routinely administer these drugs without prior consultation with consultants can result in safe and highly appropriate use of these drugs, while minimizing time-to-thrombolysis. Second, this study provides a more valid method for assessing appropriateness of thrombolysis than has been used previously. Finally, this method can be used for continuous quality improvement purposes by any institution trying to determine how appropriately these agents are being utilized by their ED physicians or Cardiologists.

Since Emergency departments vary in terms of the physicians who staff them and the availability of consultants, our results are not necessarily generalizable to all hospitals. Nonetheless, the Mount-Sinai Hospital ED is representative of many tertiary care and community hospital EDs. It has approximately 30,000 visits per year, and a staff made up of six full-time and seven part-time physicians (1 FRCP, 12 CCFP-EM). There was no special training in the use of thrombolytics beyond usual "in-service" rounds.⁴⁴

Expanding the use of thrombolytics by Emergency physicians would be expected to reduce unnecessary delays in the administration of thrombolytics, and, therefore, maximize the benefit of these effective new therapies for patients suffering acute myocardial infarctions.

Appendix A. Summary Of 1994 Canadian Consensus Guidelines On Indications For Coronary Thrombolysis

Adapted from: Canadian Consensus Conference on Coronary Thrombolysis-1994
Recommendations. Can J Cardiol. 1994;10;5:517-529
(The guidelines below were almost identical in the 1993 version)

A Contra-indications:

<u>Absolute:</u>	-aortic dissection -acute pericarditis -active bleeding	<u>Relative:</u>	-previous CVA or brain tumour -GI or GU bleeding -recent major surgery, biopsy or puncture on non-compressible vessel -major trauma or CPR -proliferative retinopathy -severe uncontrolled hypertension -bleeding diathesis -liver dysfunction -pregnancy
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B Certainty of diagnosis of evolving acute MI:

Coronary thrombolysis strongly recommended in patients with:

- 1) at least 0,5hr of ischemic cardiac pain
and
- 2) any of the following ECG changes thought to be of acute onset:
 - at least 1mm of ST segment elevation in at least two adjacent limb leads
 - or
 - at least 1 to 2mm of ST segment elevation in at least two adjacent precordial leads
 - or
 - complete bundle branch block

It is recommended that most patients with only ST segment depression or with a normal ECG should not receive thrombolysis.

C Time post MI onset:

It is strongly recommended that most patients presenting within 12 hours of symptom onset should be given thrombolysis. It is recommended that patients presenting 13 to 24 hours after symptom onset not receive thrombolysis routinely. Some patients in this group may benefit.

D Patient Subgroups

It is strongly recommended that absolute benefits and risks be considered in various patient subgroups, but that in general thrombolytic therapy is appropriate for inferior and anterior MI, first and subsequent MI, and for patients of all age groups including those aged 75 years and older.

Appendix B. The Kappa and adjusted Kappa Statistics

The Kappa Statistic

In assessing agreement for cause in dichotomous outcomes, correcting for chance agreement requires subtracting it from observed agreement. This problem led to the formulation of the Kappa statistic, which tries to separate agreement by chance from that for cause.^{42,57}

Its formulation is as follows:

$$\kappa = \frac{P_o - P_e}{1 - P_e} \quad \text{where } P_o = \text{observed agreement} \\ \text{and } P_e = \text{expected agreement due to chance}$$

The denominator, $1 - P_e$, represents the maximum possible agreement for cause, since it subtracts the expected agreement by chance from 1. Kappa, therefore, represents the fraction of agreement due to cause over the maximum possible agreement for cause. Expected agreement is calculated based on the marginal probabilities in the two-by-two table, as in a chi-square calculation. A typical two by two table for assessing agreement or thrombolysis decisions is presented in Table B1.

Thrombolysis Decision	Gold Std YES	Gold Std NO	
Clinician YES	a	b	r1
Clinician NO	c	d	r2
	c1	c2	n

Table B1. 2x2 table for assessing dichotomous agreement
(a,b,c,d = observed outcome counts; r1,r2 = row totals;
c1,c2 = column totals; n = total count)

Expected agreement due to chance would be estimated as:

$$P_e = \frac{(r1c1)}{n} + \frac{(r2c2)}{n} \div n$$

This measure of expected agreement by chance is calculated using the marginal row and column probabilities in a model in which both agreement for cause and agreement for chance are present (since they are both included in the 2 by 2 table), whereas you only wish to capture agreement for chance. As a result, a portion of agreement for cause is attributed to chance. The expected agreement by chance is thus increased and Kappa is reduced. The higher the observed agreement, the greater the "expected" agreement by chance will be, since an ever greater proportion of agreement for cause will be 'erroneously' attributed to chance.⁴⁶ Table B2 demonstrates this effect.

Scenario 1				Scenario 2			
MD A	Gold Std YES	Gold Std NO		MD B	Gold Std YES	Gold Std NO	
YES	9	22	31	YES	18	2	20
NO	11	38	49	NO	2	58	60
	20	60	80		20	60	80

Table B2. Two hypothetical 2x2 agreement tables, using different observed agreement with an identical gold standard (MD A, MD B = hypothetical clinicians' assessments; "Gold Std" = gold standard assessment)

In scenario 1 (MD A), $P_o = (9+38)/80 = 0.59$ and
 $P_e = (20 \times 31 + 60 \times 49)/80^2 = 0.56$

In scenario 2 (MD B), observed agreement with the gold standard has now increased, such that:

$$P_o = (18+58)/80 = 0.95$$

but expected agreement by chance is seen to increase as well:

$$P_e = (20 \times 20 + 60 \times 60)/80^2 = 0.63$$

This increase in the expected agreement (in this case, from 0.56 to 0.63) as observed agreement increases results in observers who agree more being effectively "penalised", and reduces their Kappa scores.

The adjusted Kappa Statistic

The concept of agreement due to chance has been left somewhat nebulous until now, and seems even more confusing when it changes with observed agreement. As a result of this paradox, Aickin in 1990 described the "adjusted Kappa" statistic, which attempts to avoid this faulty attribution of agreement for cause.⁴⁶

In order to better grasp what is meant by agreement due to chance, Aickin begins by dividing the population of all items to be classified into two sub-groups. In one, the items are hard to classify and any agreement which occurs is due to chance, and in the second, the items are easy to classify and any agreement is due to cause.

He then formulates the adjusted Kappa statistic, α , as:

$$\alpha = \frac{\text{Observed Agreement} - \text{Agreement due to Chance}}{1 - \text{Agreement due to Chance}}$$

$$= \frac{P_o - s}{1 - s}$$

The fundamental difference of the adjusted Kappa statistic is that here, agreement due to chance is calculated as the agreement which occurs only among the sub-group of items that are hard to classify.

The adjusted Kappa in practice

The problem that arises is that we cannot truly know which items are hard to classify and which are easy (and do patients in reality ever fall into such tidy categories?). As a result, we cannot obtain 's' directly, the proportion agreement due to chance. What is needed, is a correction factor to apply to the row and column marginals to try to separate the "hard" to classify items from the "easy" to classify ones. Aickin provides a mathematical model to artificially divide the population, and arrive at an estimate of α and s.

He defines the joint distribution of the items classified by two reviewers, i and j, in the following terms:

$$p(i, j) = [1 - \alpha + \frac{\alpha d(i, j)}{s}] p_r(i) p_c(j) \quad (1)$$

where $d(i, j) = 1$ if the two reviewers agree and 0 otherwise,
 α = agreement for cause,
 s = agreement by chance

An iterative process is used to solve for α . The usual formulations of P_e and Kappa are used in the first iteration as approximations for s and α , and the observed marginals as initial approximations for $p_r(i)$ and $p_c(i)$. The results are then re-entered into the following formulae until convergence occurs around a value of α . Convergence usually occurs in 20 iterations or less around the value of α .⁴⁶

$$\alpha = \frac{\sum d(i, j) p(i, j) - s}{1 - s} \quad \text{where } s = \sum d(i, j) p_r(i) p_c(j).$$

$$p_r(i) = r(i) / [n(1 - \alpha) + \alpha \sum_j d(i, j) p_c(j) / s] \quad \text{where } r(i) = a+b \text{ for row 0} \\ \text{and } c+d \text{ for row 1}$$

$$p_c(i) = c(i) / [n(1 - \alpha) + \alpha \sum_j d(i, j) p_r(j) / s] \quad \text{where } c(i) = a+c \text{ for column 0} \\ \text{and } b+d \text{ for column 1}$$

A pseudocount of 1 is added to the agreement table and divided equally among all cells to guard against non-convergence of the algorithm, which could occur in the presence of zero. The result is a slight adjustment of the point estimate toward 0.5 compared to the point estimate if no pseudocount is added. As the sample size increase, this adjustment approaches zero.⁴⁶

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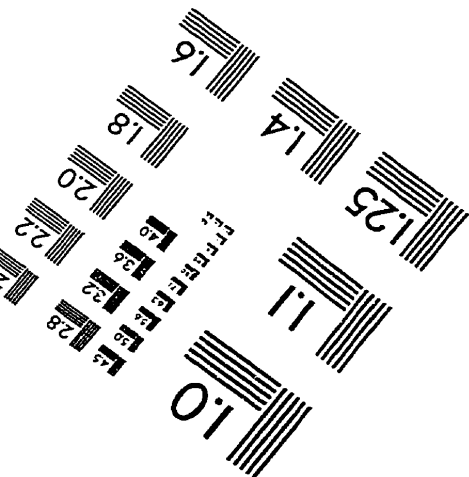
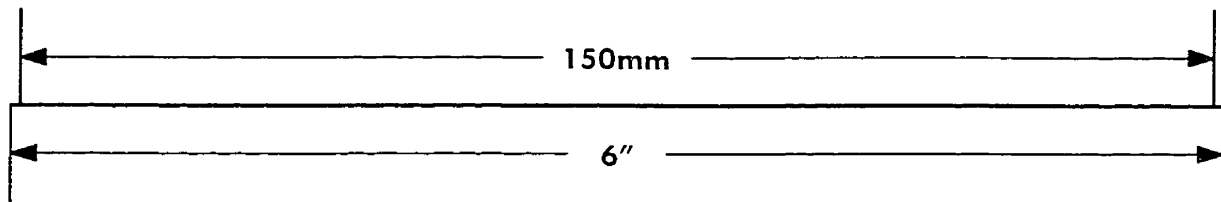
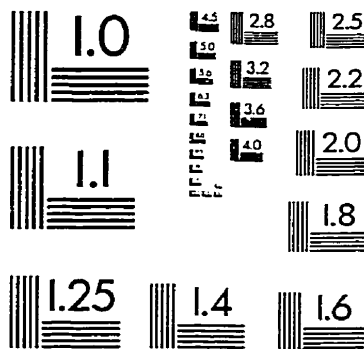
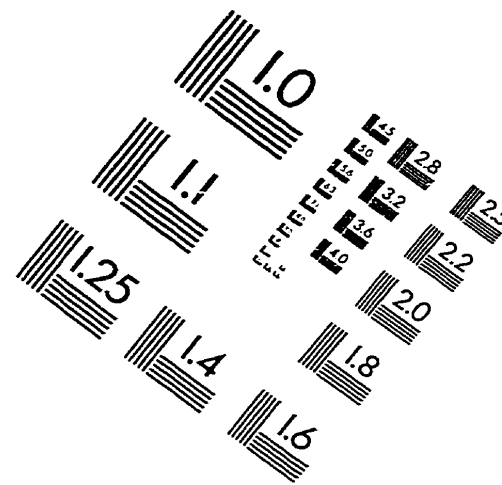
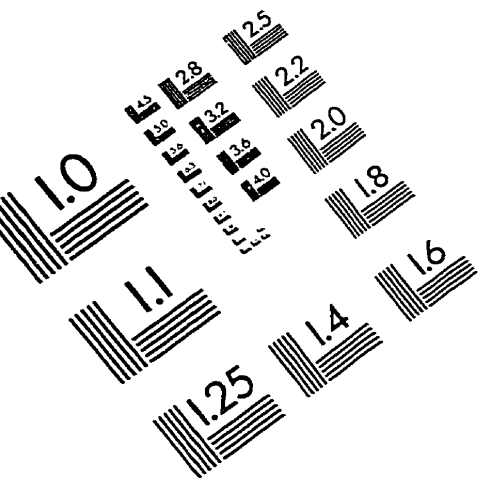
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IMAGE EVALUATION TEST TARGET (QA-3)



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