THE EPIDEMIOLOGY OF ACUTE MYOCARDIAL INFARCTION AND THE ROLE OF THROMBOLYSIS

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ABSTRACT

This thesis examines the epidemiology of acute myocardial infarction (AMI). In particular, the following three areas were investigated in detail:

1. A compilation and examination of national data suggests an important decline in the morbidity and mortality of AMI in the Canadian population. Information from a Quebec provincial hospital database confirmed that a substantial proportion of the falling mortality rates is due to improved cardiology care with lower hospital case fatality rates.

2. A clinical registry of 1357 patients treated with thrombolysis (432 with tissue plasminogen activator (t-PA) and 925 with streptokinase (SK))in 40 Quebec hospitals has been created and extensively analyzed to provide insights into the patient and hospital variables that influence the delay to receiving thrombolytic therapy. The median delay before presentation to hospital was 98 minutes and was longer for women, diabetics and the elderly. The total median in-hospital delay was 59 minutes with the medical decision component taking a median of 12 minutes. Women, the elderly and patients with previous MI also had increased in-hospital delays to thrombolysis. Delays were more prolonged in community hospitals, low volume hospitals and if a cardiologist took the decision for thrombolysis.

3. There remains controversy as to any superiority between the different thrombolytic regimes. Little is known about how medical practitioners have interpreted this conflicting information and the factors important to their decision making process. Hierarchical logistic modeling of this same clinical database has permitted the identification of patient, physician and hospital characteristics associated with the choice of thrombolytic agent.

Independent patient characteristics associated with an increased probability of receiving t-PA were the presence of an anterior infarction, a previous myocardial infarction, a cardiologist decision maker and low blood pressure. The probability of receiving t-PA was decreased for elderly patients and those receiving treatment beyond six hours after the start of symptoms. Gender, diabetes, other past medical history and previous medications were not independently associated with the choice of therapy.

Patients treated in urban and tertiary centers received t-PA more frequently than those in rural and non-tertiary centers. As the hospital caseload increased, there was a decreasing chance of older patients and those arriving after six hours receiving t-PA. All hospitals gave t-PA more frequently to patients with prior and anterior myocardial infarction but this was most pronounced in urban centers.

These practice patterns are compared with the information provided by evidence-based medicine. The results presented in this thesis may be useful in the development of a public health policy for the use of thrombolysis in AMI and in understanding physician prescribing patterns.

ABRÉGÉ

Cette thèse examine l'épidémiologie de l'infarctus aigu du myocarde. En particulier les trois sujets ci-dessous sont étudiés en détail.

1. Un examen des données nationales suggère un déclin important dans la morbidité et la mortalité de l'infarctus du myocarde dans la population canadienne. Une banque de donnée provinciale du Québec nous a permis de confimer qu'une grande proportion de ce déclin de mortalité est secondaire à une amélioration dans les soins cardiologiques avec une diminution des taux de léthalité hospitalière.

2. Un registre clinique de 1,357 patients traités avec la thrombolyse (432 avec l'activateur plasminogène tissulaire (t-PA) et 925 avec Streptokinase (SK)) dans 40 hôpitaux québécois a été creé et une analyse systématique de ces données nous a permis de mieux comprendre les facteurs qui peuvent influencer les délais d'administration de la thrombolyse. Le délai médian avant la présentation des patients à l'hôpital était de 98 minutes et était prolongé pour les femmes, les diabétiques et les personnes agées. Les délais intra-hospitaliers totaux médians étaient de 59 minutes et les décisions médicales prenaient un médian de 12 minutes. Ces délais étaient aussi plus longs pour les femmes, les personnes agées et les patients avec des antécédents d'infarctus du myocarde. Les délais étaient plus prononcés dans les hôpitaux communautaires, les hôpitaux de bas débits et lorsqu'un cardiologue prenait la décision thérapeutique.

3. Une controverse persiste quand à la supériorité d'un agent thrombolytique par rapport à l'autre. Nous ne savons pas comment les cliniciens interprètent ces données parfois contradictoires et les facteurs qui sont importants dans leur processus de sélection d'un agent thrombolytique. Des modèles logistiques hierarchiques de ce même régistre clinique ont permis l'identification des caractéristiques des patients, des médecins et des hôpitaux associées avec le choix d'un agent thrombolytique particulier.

Les caractéristiques indépendantes des patients associées avec une probabilité accrue de recevoir t-PA étaient la présence d'un infarctus à la paroi antérieure, des antécédents d'infarctus, une décision prise par un cardiologue et une diminution de la pression artérielle. La probabilité de recevoir le t-PA était diminuée pour les patients agés ainsi que pour ceux qui ont reçu un traitement au-delà de 6 heures après le début des symptômes. Le sexe, la diabète, les antécédents médicaux et les autres médicaments n'étaient pas associés avec le choix thérapeutique.

Les patients traités dans les centres urbains et tertiaires ont reçu t-PA plus fréquemment que ceux qui ont reçu leurs traitements dans les centres non-urbains et non-tertiaires. Plus le débit hospitalier était élevé moins qu'il y avait une chance que les patients agés ou ceux arrivant après 6 heures avaient de recevoir de t-PA. Tous les hôpitaux ont donnés du t-PA plus souvent aux patients avec un histoire d'ancien infarctus ou avec un infarctus à la paroi antérieure cette tendance était plus prononcée dans les centres urbains.

Ces pratiques médicales sont comparées avec les connaissances du "evidence based medicine". Les résultats presentées dans cette thèse peuvent être utiles pour le développement d'une politique publique pour l'utilisation des thrombolytiques et comprendre le comportement des médecins dans leur sélection d'un agent.

ACKNOWLEDGMENT

I have always liked to count. I am therefore most appreciative of the time and effort that Lawrence Joseph, my thesis supervisor, has devoted to helping me learn to count properly. His availability, keen insights and extraordinary teaching skills have been a constant source of inspiration and made this an outstanding educational experience.

Renaldo Battista, as a member of my thesis committee, has also importantly assisted in my educational development and completion of this project. My understanding of the importance of technology assessment has arisen from his teaching and by his support, as president of le Conseil d'évaluation des technologies de la santé (CETS), of my activities in this burgeoning field. While working as a consultant to the CETS, I was moreover able to have ready access to provincial epidemiological data. I am indebted to Jean Marie Lance, Executive Director CETS, and Marie Josée Blais, research associate CETS, for their help.

I was also privileged to have been associated with le Conseil consultatif de pharmacologie (CCP) and its president, Jacques LeLorier. The occasion to participate in the CCP's working group on the treatment of acute myocardial infarction, presided by Yves Morin, afforded an excellent opportunity for the development and exchange of many ideas regarding thrombolysis.

Without the leadership of Pierre Théroux, the project of a provincial registry of patients with acute coronary syndromes would not have been possible and consequently, the data source for much of this thesis would not have been available. As a world authority of thrombosis in cardiology, Pierre has assured that my epidemiological muses remain grounded in clinical pertinence.

Lastly, I gratefully acknowledge the contribution of Lynda Taylor for her continuing support to the completion of this thesis.

STATEMENT OF ORIGINALITY

I conceptualized the goals and performed the work contained in this thesis during my time as a doctoral student in the Department of Epidemiology and Biostatistics. This work initially involved a literature review followed by the procuring and analysis of federal and provincial epidemiological data. I also participated integrally in the collection of the patient data from the clinical registry. I was uniquely responsible for the analysis of this data. I have written the computer programs for the Bayesian analyses in this thesis. The indispensable help of Lawrence Joseph in assuring the integrity of these programs is acknowledged.

This thesis has allowed an improved perception of the epidemiology and treatment of acute myocardial infarction in Canada and Quebec. The Bayesian approach used herein to analyze both previously published data and newly acquired data has permitted improved insights into the value and utilization of thrombolysis in the treatment of myocardial infarction. This thesis is the first attempt to analyze the practice patterns involved in the selection and administration of thrombolytics. The use of sophisticated hierarchical modeling enables a simultaneous assessment of the important patient, physician and hospital characteristics involved in this process.

Parts of this thesis have been previously published [1-7] but in all cases, I have conceptualized the issues, analyzed the data and been the first author.

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CHAPTER 1 INTRODUCTION

Cardiovascular disease, and in particular acute myocardial infarction (AMI) remains the leading cause of death in western societies, including Canada. It is therefore crucial to accurately describe recent trends in the mortality and morbidity caused by myocardial infarction. Many clinical advances have been made over the last generation and it is equally important to assess their impact at the population level.

While major clinical innovations began more than 25 years ago with the introduction of coronary care units, many new therapeutic and diagnostic modalities have been introduced in the last 15 years. Recent medical advancements have included the selective use of thrombolysis, aspirin, beta blockers and angiotensin converting enzyme (ACE) inhibitors and their utility in decreasing morbidity and mortality has been shown in well designed randomized clinical trials [8-10]. Among these interventions, thrombolysis has had the largest impact. An analysis of death rates in Ontario hospitals suggests that the therapeutic improvements witnessed in clinical trials are being realized in routine clinical practice [11].

Simultaneously, etiological factors in ischemic heart disease have been more clearly elucidated. The successful manipulation of these cardiac risks, in particular, smoking cessation, control of high blood pressure and dyslipidemia have reduced the incidence of acute myocardial infarction and cardiovascular

mortality [12-15]. In addition, improved access to acute cardiac care and public health measures encouraging the rapid reporting of suspected cardiac symptoms may have favorably influenced mortality rates.

Marked variations in cardiovascular resource utilization have been observed between various countries [16-18] and small area variations within a regional health care district have also been demonstrated [19-21]. These local variations were once viewed simplistically as proof of sub-optimal physician practice patterns. It was reasoned that if two rates of resource utilization vary significantly, one must be clearly inappropriately high or low. It is now appreciated that many variables beyond sub-optimal physician performance influence practice variations. Disease prevalence and severity, an incomplete knowledge base, local practice advocates, the availability of medical resources, and the interaction between the physician and the health care system may be important parameters in small area analysis. For example, the practice variations between Quebec physicians in their choice of thrombolytics for the treatment of AMI and the determinants of this selection process are unknown.

Safety and efficacy are now only two of the dimensions that clinicians must consider in deciding to apply a new technology. Clinicians must assess the applicability of the technological advances to their own practice. Also, technological progress is often associated with high price tags which may influence availability and decision making. While the credo of individual physicians is to provide optimum care to their patient, irrespective of cost,

practice patterns are clearly being affected by fiscal considerations. Over the last 15 years, this evaluative process of a new technology taking into account safety, efficacy, effectiveness, cost and ethics has become increasingly formalized with sound methodological underpinnings and has seen the international creation of technology assessment groups. On the local level, provincial guidelines based on these criteria have been developed to assist clinicians in the use of thrombolytics for the treatment of AMI [22]. However, to date there has been no systematic evaluation of thrombolytic therapy in Quebec.

With the abundance of new clinical information in cardiovascular medicine, arise several questions and controversies. For example, has the progress observed in clinical trials been translated to the population level? Have the major improvements in outcomes come from primary or secondary strategies? Is one thrombolytic agent superior to another? Also, if several similar trials are performed simultaneously, when has enough data been accumulated to evaluate the utility of a new treatment? Finally, how do clinicians interpret and integrate this vast new knowledge into their practice and what measures may assist them in this endeavor?

This thesis attempts to provide answers to these questions. Specifically, the goals of the thesis are as follows:

1. to describe the national and provincial epidemiological trends of AMI;

2. to review the literature of the clinical improvements in the treatment of AMI, concentrating in particular on coronary thrombolysis;

3. to present and interpret through a Bayesian paradigm the state of knowledge about thrombolysis;

4. to demonstrate how, regardless of the thrombolytic agent selected, the efficacy of the intervention might be further improved;

5. to describe and analyze how medical doctors are choosing between the different thrombolytic agents as a function of patient, physician and hospital characteristics;

This thesis will begin with a description of the sources of information and the methods used for data collection and analysis (Chapter Two). Next is a chapter reviewing the literature on clinical advances in the treatment of AMI. Chapter Four interprets the scientific literature from a Bayesian perspective. One of the main advantages of a Bayesian analysis is that its basic principles mirror those of scientific learning and questions of direct interest to clinicians and policy makers can be addressed en route to making informed choices.

Chapter Five presents Canadian and provincial epidemiological data for AMI which will illustrate the magnitude of the public health problem caused by cardiovascular disease, and the progress to date. The next two chapters examine the dominant therapy in the treatment of AMI, namely thrombolysis. Chapter Six

documents the patient, physician and hospital characteristics associated with delays in the administration of this potentially life saving therapy. Chapter Seven explains how Quebec physicians have interpreted the literature and are choosing between the thrombolytic agents. Specific patient characteristics are obviously important but geographic and institutional factors are also shown to assume importance. Bayesian hierarchical analysis is employed as it is the best means to fully treat the complexity of the problem. The concluding chapter attempts to incorporate the findings from the earlier chapters into a coherent public health policy for the use of thrombolysis in the treatment of AMI.

CHAPTER 2 METHODS AND DATA

This thesis has employed a variety of epidemiological and statistical methods and has utilized data from several sources. First, a systematic electronic literature review was conducted and the methods for this are presented in Section 2.1. Sections 2.2 and 2.3 discuss the cardiovascular epidemiological data that has come from Federal and Provincial statistical data sources, respectively. The information about the treatment of individual patients has been taken from a province wide clinical registry of patients admitted with acute ischemic events and sponsored by the Fonds de la recherche en santé du Québec (FRSQ). The design and data collection methods for this registry are presented in Section 2.4. Finally, a wide variety of statistical methods were required to appropriately analyze and interpret both the existing clinical literature and the local Quebec data. These methods are reviewed in Section 2.5.

2.1) LITERATURE REVIEW

The literature review has been performed largely with the electronic online search facility provided by The McGill Library Service. Key references have been identified using the terms "acute myocardial infarction", "thrombolysis", "angiotensin converting enzyme inhibitors", "practice guidelines", and "small area analysis". These references have been supplemented by cross checking

bibliographies from these articles and from activities carried out in my cardiology practice, including systematic weekly review of the New England Journal of Medicine, The Lancet, JAMA and a monthly review of the Journal of the American College of Cardiology for the last four years.

While it is recognized that good epidemiological and clinical research using non-experimental methodologies may under the right conditions, for example if there is a very large effect size, provide powerful evidence in favor of a risk or benefit, the gold standard for comparative studies is the randomized clinical trial (RCT). Consequently, in assessing the clinical advantages of thrombolysis and the particular agents, the literature review has concentrated exclusively on RCTs. Well designed RCTs have a respected position in scientific research for their ability to deliver unbiased insights into the "truth", although one must always be aware of issues such as blinding and entry criteria when assessing internal and external validity. Fortunately, there are adequate trials in cardiology to permit an analysis of the comparative benefits of thrombolytic agents. Similarly the assessment of the advantages of ACE inhibitors following AMI is based solely on the results of RCTs.

The results of this clinical literature review are presented in detail in Chapter 3. The utility of a Bayesian paradigm in interpreting this information is discussed in Chapter 4.

2.2) Data from Statistics Canada

To gain insight into the magnitude of the burden of cardiovascular illness in Canada and to document temporal changes, national mortality and hospital separation data were obtained from Statistics Canada via the annual reports of vital statistics (catalogue 84-206 (1976 & 1981), catalogue 84-203 (1986) and catalogue 84-209 (1991)). For each time period, sex specific death rates by five year intervals are reported for both acute myocardial infarction (International Classification of Disease (ICD) codes 410) and all ischemic heart disease deaths (ICD codes 410-414). The crude death rate is simply the total number of deaths divided by the population at risk. Death and hospital separation rates were adjusted to the 1971 Canadian population by the direct standardization method [23]. A weighted average of the age specific length of stay rates (available from the hospital separation data) was performed to obtain the aggregate average duration of stay. The results from this analysis are given in Chapter 5.

2.3) The Quebec administrative database (MED-ECHO)

To study the role of improved hospital care in explaining the changing cardiovascular mortality rates, the provincial hospitalization database was

examined. This database, referred to as MED-ECHO, collects information on all hospitalizations in acute care institutions within the province of Quebec. A pilot phase began in 1976 and the system has been fully operational since 1980. For each hospitalization, a discharge summary form (AH-101P) is completed by a local medical archivist. The data is collected by fiscal year, April 1st to March 31st, and does not include services provided in the emergency room or in out-patient clinics. The same patient may have multiple hospitalizations and data entries in the same year.

The MED-ECHO database respects patient confidentiality by providing anonymous records which were examined for this thesis. If individually identified records are required a formal request must be made to "La commission de l'accès à l'information du Québec". Each year there are about 1,000,000 entries into the MED-ECHO data bank. Each entry includes patient age, sex, principal diagnosis and the possibility of up to 15 secondary diagnoses. In addition, cardiac procedures such as coronary artery bypass surgery and percutaneous transluminal coronary angioplasty are recorded.

The anonymous MED-ECHO database has been interrogated for the years 1985-86 until 1995-96 to identify each record involving a principal diagnosis of AMI, again based on ICD code 410. The patient status at discharge is registered so that in-hospital mortality (case fatality) rates can be measured. Since age and sex are recorded, direct standardization was performed to the 1985-86 Quebec population distribution [23].

Following the suggestion of Naylor[11], the number of alive discharges in less than 4 days was recorded for the period 1986-88 and may be an estimate of potential misclassification. This represented only a very small percentage of the total (<2%) and further the evolution of practice patterns, particularly primary angioplasty accompanied by very early discharge prevents this technique from being used to measure misclassification in recent years. The analyses herein rely on all records so as not to introduce any unknown biases.

The validity of this database had not been previously investigated for cardiology diagnoses and procedures. However, the validity of primary diagnoses for cardiovascular diseases for other provincial hospital databases have been previously verified [24]. Further, as will be shown later, for 1995-96 the mortality for AMI as measured from the FRSQ clinical registry was very similar to that calculated from MED-ECHO. I have also verified the accuracy of the data bank to record the total number of cardiac procedures and found a good correlation with that obtained by direct hospital survey [25].

In conclusion, this data provides useful information about recent trends in hospital mortality following admission with a diagnosis of AMI. It is therefore possible to ascertain if the therapeutic advances in the treatment of AMI described in the literature review are being realized at a population level. The results of this analysis are also presented in Chapter 5.

this thesis. Specifically, this data has been used to identify delays to the administration of thrombolysis and to examine the medical decision making process surrounding the choice of a particular agent.

The founding president of The Acute Ischemic Syndrome Group was Dr. Pierre Théroux of the Montreal Heart Institute. The executive is comprised of Quebec cardiologists who have a particular interest in these syndromes, including this author (see Appendix 1), and has representatives from the four Quebec medical faculties. This group has the following three goals:

1) to establish a network of hospitals (both university and community) interested in participating in clinical research on acute coronary syndromes;

2) to evaluate the current practice of acute care cardiology across the Province of Québec;

3) to provide feedback to participating hospitals thereby contributing to their local ongoing quality control improvement programs.

The first goal has been well attained, as witnessed by the number of Quebec centers now participating in multi-center clinical trials of acute coronary syndromes. Several of these trials were initiated, organized and executed by local cardiologists [26,27]. To assess the second objective, it was decided to form a prospective registry of all patients admitted with a diagnosis of acute coronary syndromes.

Given that thrombolysis importantly decreases mortality in AMI, the executive decided to concentrate initially on procuring information on the use of this treatment modality. It was felt that this emphasis could produce substantial benefits in the quality of care. Furthermore, in these difficult economic times it was anticipated that an observational study on how clinicians select and administer the two currently available thrombolytic agents would be clinically useful. This could also provide some information about the impact of the provincial guidelines published for the treatment of AMI [22].

As has been demonstrated by successful large scale clinical trials [28,29], it was considered important to limit the data acquisition form to a single page (see Appendix II). All hospitals caring for patients with acute myocardial infarction were approached to participate in the registry. A list of the participating hospitals, the principal investigators, the coordinators and the number of patients enrolled is included in Appendix III. Each hospital contributed patients for 12 consecutive months and enrollment ran from January 1995 to May 1996.

Forty-four (52%) of eighty-five Quebec acute care hospitals approached initially agreed to participate in this voluntary registry. Four hospitals contributing a total of only 20 patients were excluded from the final analysis as it was felt that these limited cases may not be representative of these hospitals' practice patterns. Participating hospitals were representative of the spectrum of health care institutions in the province of Quebec.

The province of Quebec is divided geographically into 18 different health regions (regions socio-sanitaires (RSS)) (see Figure 2.1). The registry had hospital participation from 14 of the 18 regions. Two of the four remaining regions are scarcely populated (.3% of the total population). The number of patients per 100,000 from each region is shown in Table 2.1. The hospitals represented a cross section of urban (n=15), rural (n=25), tertiary (n=9) and community (n=31) institutions. Hospitals from the urban areas of Montreal and Quebec City contributed 37.5% of the patients. Among the 40 participating hospitals 17 (42%) had some university affiliation but only 9 (22.5%) are considered tertiary centers.

Each patient admitted to a participating hospital with a presumptive diagnosis of an acute ischemic syndrome was prospectively entered into the registry. On admission, this involved the completion of a one page questionnaire (see Appendix II) containing patient demographic and clinical data including the risk profile, electrocardiographic (ECG) data and information on the administration of thrombolytic agents as well as any complications. This data also included the time of symptom onset, hospital arrival, the diagnostic ECG, the medical decision to proceed with thrombolysis and the start of therapy. The time of arrival refers to patient registration before any diagnostic testing or medical consultation. It was therefore possible to clearly separate the delay in receiving thrombolysis into pre-hospital and in-hospital components. The

in-hospital component could be further subdivided into data accumulation (ECG), medical decision and drug preparation phases.

At hospital discharge, a systematic chart review was performed to establish the resources used and final diagnosis. Specially trained and designated nurse coordinators collected the data at each center. Local approval was obtained to collect this anonymous data in compliance with local ethics guidelines.

The data were then sent to the coordinating center, the Research Center of the Montreal Heart Institute and, after manual and computer validation for consistency, entered into the database with the program software verifying their consistency. The data was originally entered as SPSS files and these files were subsequently electronically transferred to my PC (Pentium 200 MHz microprocessor, 64 meg RAM) upon which all analyses were performed. Notwithstanding the initial steps at the time of data entry to ensure the consistency of the data, occasional errors and omissions were found and, when necessary, verification by individual centers was requested. For example, age was missing in some records but could be determined from birth date. Also gender was missing from 64 patients receiving thrombolysis but was eventually supplied in all but 4 cases. New variables were created from the existing data as needed (e.g. the total in-hospital delay before thrombolysis was obtained by subtracting the date and time of administration from the date and time of arrival).

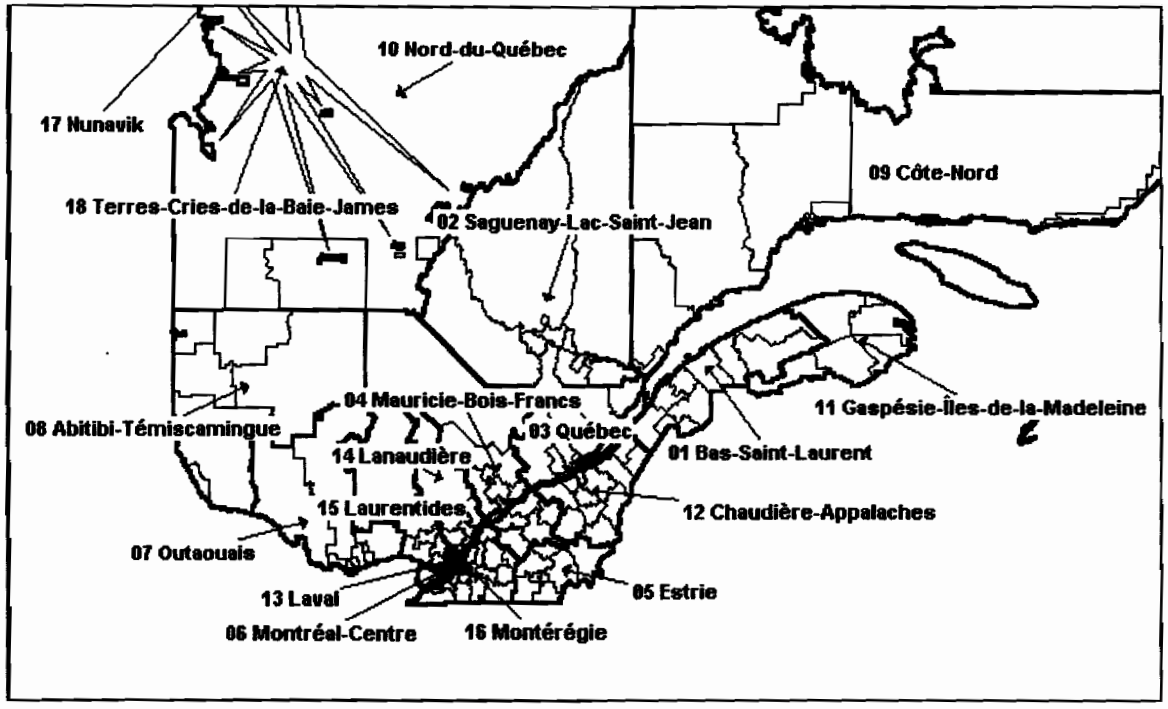


Figure 2.1 Map of the Province of Quebec and its 18 different health regions

Region	Population	No. of cases	No. cases /100,000
01: Bas St-Laurent	205137	307	150
02:Saguenay/Lac St-Jean	286159	932	326
03:Québec	615844	1885	306
04:Mauricie-Bois-Francs	466203	-	-
05:Estrie	268413	156	58
06:Montréal-Centre	1775871	3106	175
07:Outaouais	283782	154	54
08:Abitibi-Témiscamingue	151978	67	44
09:Côte-Nord	103224	34	33
10:Nord-du-Québec	20284	20	99
11:Gaspésie-Iles-de-la-Madeleine	105968	-	-
12:Chaudière-Appalaches	367953	1044	284
13:Laval	314398	306	97
14:Lanaudière	335476	535	159
15:Laurentides	381069	214	56
16:Montérégie	1198187	137	11
17:Kativik	14700	-	-
18:Terres-Cries-de-la-Baie-James	8333	-	-

Table 2.1 Population of the 18 health districts with the cases in the FRSQ clinical registry.

The baseline demographic and clinical variables for the entire cohort, including those receiving thrombolysis for AMI are presented in Chapter 5. For patients receiving thrombolysis, the registry was designed to permit a detailed examination of the different components of delay to treatment. Chapter 6 presents the analysis of the components of delay in administering thrombolysis, where in-hospital (door-to-needle) delays have been separated into the time 1) to obtain the diagnostic ECG, 2) to make the medical decision and 3) to prepare the drug. These time distributions were heavily skewed and consequently medians and interquartile ranges (IQR) are reported. A univariate analysis between the different components of thrombolytic time delays and patient /hospital characteristics was performed using non-parametric statistical tests (Wilcoxon rank-sum test). Statistically significant variables ($p<0.10$) from this univariate analysis were included in a multivariate logistic regression model (based on time greater or less than the median in-hospital delay) to determine the independent predictors of treatment delay.

It has also been possible to examine patient and hospital characteristics associated with treatment delays. The information on the overall performance has been sent to each individual center along with their own results for comparison. It is hoped that such information may serve as a stimulus to modify the practice patterns of any local areas with poor achievement thereby fulfilling the third goal of the Acute Ischemia Syndrome Group.

This registry permits an examination of how patient, physician and hospital characteristics influence the choice of thrombolytic agent. To my knowledge, no other study has examined this process of medical decision making. Given the high costs of treating myocardial infarction and its complications, it is important to understand how physicians choose their thrombolytic agent. This will become even more important as the new agents presently being studied eventually arrive in the marketplace.

The potential interaction between patient, physician and hospital characteristics implies that a multi-level model for these parameters will be required to fully investigate these dependencies. To this end there are substantial advantages to treating all quantities as random variables, since then probability statements may be made directly about quantities of interest. As will be discussed in the next section, an appropriate statistical analysis for this complex problem is Bayesian random effects hierarchical modeling.

The main limitation of this registry is that due to limited funding the data forms as prepared by local investigators were not externally validated. One might have attempted to validate the completeness of the registry by comparing the results with those obtained from the MED-ECHO, although even this would have been imperfect since both the administrative database and registry contain anonymous records. Moreover, no financial resources were available for validation. Indeed the participation of all contributing physicians was without any financial reimbursement. However, the coordinators were experienced

cardiovascular research or clinical nurses who received pre-registry training. There is no reason to suspect any systematic bias in the data collection, although it is not possible to definitively affirm that all consecutive patients were recorded. The following section describes the statistical methodology and techniques employed for the analysis of this data.

2.5) STATISTICAL METHODS

This section presents the statistical methods used for the analysis of the clinical registry data. In particular, these methods have been used to address the clinical question of " which patient gets which thrombolytic agent ?" This question therefore revolves around the issue of practice pattern variations. Beginning with a discussion of the limitations of the standard frequentist approach, I summarize the methods used in the past to evaluate regional variations (Section 2.5.1). Next, the theoretical advantages of a Bayesian perspective will be discussed (Section 2.5.2). Finally, the theory behind simple Bayesian calculations, empirical Bayes and full Bayesian hierarchical random effects modeling will be presented (Section 2.5.3).

2.5.1 Non-Bayesian Techniques

Classical (frequentist) analysis is the most prevalent statistical paradigm used, leading to the ubiquitous p values and confidence intervals. P values from research trials may be viewed as analogs of false-positive (1-specificity) diagnostic tests. If neither the disease nor the treatment is malignant, we may well accept test specificity of 95% ($p = 0.05$). However for example, before accepting a limb amputation for osteosarcoma, we would rightly demand a false-positive value much less than .05. Generally, we are more interested in knowing what is the probability of disease given the test result (analogous to predictive value), or following a clinical trial, what is the probability that a new treatment is superior, and this cannot be supplied from classical statistical considerations alone. Clinicians routinely interpret diagnostic test results in the "clinical context," that is, by considering the background rate of the disease in a given population. In a similar manner, the interpretation of clinical trials should be considered in the light of preexisting knowledge [30].

In the classical approach, model parameters such as population means are fixed (nonrandom) quantities and probability distributions are considered only for test statistics (such as the t statistic in a t test). The randomness of test statistics arises because frequentists must consider not only the observed data in a given experiment, but also other data that might have occurred had the experiment been repeated. Each of these hypothetical repetitions leads to a different value of the

test statistic, and the collection of these form a distribution. It is this distribution that is used to calculate p values and confidence intervals.

Rather than directly addressing desired clinical questions, such as "Which treatment is superior?" or "What is the probability of a clinically meaningful treatment difference?", classical analysis usually examines the null hypothesis of no difference between the competing strategies. P values denote the probability that a statistic as extreme as or more extreme than the observed test statistic would occur on hypothetical repeated trials if the null hypothesis is exactly true. This raises two problems. First, it seems counterintuitive to base statistical inferences on events more extreme than those observed, since these events did not actually occur [31]. Second, one almost never believes that the null hypothesis of exact equivalence is true, and it is consequently usually more relevant to test for a range of equivalence. Such a test is very rarely carried out in practice. P values do not measure the true quantity of interest, namely, the probability that the null or alternative hypothesis is true. This contributes to the confusion between the information p values provide and the information that is more naturally desired. Therefore, it is not surprising that p values are often misinterpreted as the probability that the null hypothesis is true or that 1-p represents the probability that the alternative hypothesis is true. Classical statistical analysis does not directly or indirectly provide these probabilities.

Another inherent limitation of p values derives from their dependence on sample size. Basically, any difference, no matter how small, can reach statistical

significance if the sample size is large enough. For example, an observed difference of only one tenth of a standard deviation will become statistically significant at the .05 level if each group in the trial includes at least 768 subjects and will be nonsignificant otherwise. On the other hand, it is well known that the low power accompanying small trials may lead to p values greater than.05 even when clinically meaningful effects are observed in the trial [32].

All of these limitations of p values have prompted an increased use of confidence intervals. Many clinicians do not appreciate that a 95% confidence interval only means that with unlimited repeated experiments, 95% of all the confidence interval limits derived using similar procedures in different studies would contain the true parameter. While this may provide some comfort in the long run, little can be said about the likelihood that, for example, a given treatment is superior or that the true value of the parameter under current study lies in any particular interval.

The above considerations are not only of theoretical interest, but also of great practical importance. For example, in considering regional variations in medical practice rates, emphasis has often been on significance testing of the null hypothesis of no variation between areas. This approach is relatively sterile for two reasons. First no one reasonably expects there to be absolutely stable, unvarying rates across different areas. Therefore one knows that there is virtually no chance of the null hypothesis being true even before one collects any data. Secondly, one is much more interested in attempting to measure and explain why

the variations exist rather than merely documenting their presence in a simple "yes" or "no" dichotomy. A brief review of the measures of geographic variations follows.

One well characterized distribution which has been used for statistical inference about regional variations is the chi-square. In essence, this distribution can be used to form a global test of homogeneity (i.e., a test of the null hypothesis of prefect equality of rates in all regions). As the number of areas and or the sample sizes within each area increases, however, it would intuitively be surprising if the null hypothesis of no variation were not eventually rejected. The usefulness of this approach is therefore clearly limited, since failure to reject the null hypothesis is more likely to indicate a lack of power than pointing to exact equality of rates in all regions.

Another of the earlier measures of variations involved the ratio of the rate in the highest area to the rate of the lowest area, a ratio identified as the extremal quotient. While this ratio may give large values apparently proving sensational discordance between medical practitioners in different regions, close examination of this statistic shows several undesirable properties. For example, the ratio becomes increasingly unstable with small rates and eventually becomes undefined if the minimal rate is zero. This may happen frequently if the population at risk is small or if the event rate is low. Further there is no known closed form sampling distribution for this ratio and inferences can only be done by computer simulation, although this is not much of a drawback now. Finally, employing this ratio leads

to ignoring and consequently wasting all information between the two extreme areas.

Simulation studies have shown that large values of the extremal quotient may occur by chance alone [33,34]. In particular, the extremal quotient becomes more unstable, with larger 95% confidence intervals, for low event rates, uneven population distributions, small populations or if an individual may be counted more than once in the numerator. As an example, a simulation of surgical rates across 39 counties in Washington State showed that under the null hypothesis of a constant rate of 100/100,000, an extremal quotient of 11 is likely to occur by chance alone [33].

Thus, while the extremal quotient is easy to calculate, it is a poor tool for statistical inference about systematic regional variations and provides no opportunity to understand why any differences may be occurring. There seems little reason to further consider this summary statistic in analyzing geographic variations.

Another measure of variability is the coefficient of variation, which is defined as the standard deviation (std) of the rates between regions divided by the mean rate across regions

$$CV = \frac{std}{mean}$$

Once again there is no closed form distribution of this summary statistic and simulations are required to formulate inferences. The CV suffers from the same limitations as the extremal quotient and is especially erratic in situations of low event rates, small populations and does not assist in explaining the causes of any observed variations.

Variations in the rates of regional resource utilization vary due to sampling (random) error and systematic area-dependent factors. McPherson et. al.[35]were the first to develop the concept of a systematic component of variation (SCV) separate from random variability and to apply it in a study of surgical rates between different countries. Using a Poisson model for rare events, and assuming a multiplicative model to account for systematic variation between regions, leads to the following mathematical expression:

$$SCV = (1/k)\{\sum_{i=1}^{k}((O_i - E_i)/E_i)^2 - \sum_{i-1}^{k}(1/E_i)\}$$

where k is the number of regions under investigation, and O_i and E_i are the numbers of observed and expected events in the i^{th} region under the null hypothesis of no systematic variations. Since the random component of the observed variation is calculated under a Poisson model distribution, this approach can adjust for unequal regional variances due to different population denominators[35].

The SCV, by considering both systematic and random variation, is an important improvement over other summary statistics but nevertheless has several shortcomings. Verification of the validity of SCV has been questioned in a more recent study of Medicare hospitalization rates in the elderly [36] which suggested that it over-estimated the median amount of systematic variation by 55% when compared to an empirical Bayes approach (described in detail below) that also adjusts for the effect of random variation. Inferences form the SCV statistic are again obtained only by computer simulation.

While more satisfactory frequentist methods have been developed such as random effects models, due to the theoretical and especially the practical shortcomings of the frequentist approach in general, this thesis relies heavily on a Bayesian approach to data analysis. For example, as will be shown in Chapter 7, one can easily address questions such as "what is the probability that a hospital in Quebec will favor giving t-PA to younger patients?" which are difficult to formulate using frequentist methods that do not permit probability distributions to be placed on parameters in a model. The Bayesian approach is introduced in the next section.

2.5.2 General Bayesian Techniques

A Bayesian statistical analysis is designed to represent a learning process whereby new information is integrated with our previous knowledge. The first step in any Bayesian analysis is to quantify our previous knowledge by obtaining a prior distribution over all model parameters. The prior distribution summarizes the pre-experimental beliefs about the parameter values. This can be accomplished by using past data, if available, by drawing on expert knowledge, or by a combination of both. This step is nontrivial and can take considerable time and effort. Furthermore, most prior distributions are not unique; clinicians are free to summarize their beliefs into their own prior distribution. Because Bayesian methods can incorporate personal clinical opinions, they are often labeled as "subjective." The experimental data are then used to update the prior distribution to a posterior distribution using Bayes' theorem. This is done through the likelihood function, which provides the probability of obtaining the observed data as a function of the unknown model parameter. This is analogous to using a likelihood ratio (sensitivity/(1-specificity)) to update background probabilities after observing results from a diagnostic test. The posterior distribution represents the post-experimental beliefs about the parameter values, given the new data and the previously stated prior distribution. In a clinical trial, for example, the two main quantities of interest, namely, the probability that a given treatment is superior and the probability of a clinically meaningful effect, are both directly available from the posterior distribution. Unlike the standard approach, no

references to data sets other than those observed are required, since all of the information contained in the data is summarized by the likelihood function.

No single prior distribution is likely to be sufficient to represent the diversity of clinical opinions that exists before an experiment is carried out. In a clinical trial, for example, this diversity is usually a prerequisite for ethical randomization. Therefore, trial results should usually be reported starting from a range of prior distributions [37]. The corresponding set of posterior distributions then summarizes the range of post-experimental beliefs. If this latter set of distributions includes only a sufficiently narrow range of possible effects, conclusions could be drawn with which most clinicians should agree regardless of their initial opinions. Otherwise, the debate continues and further research is indicated.

As an example of a Bayesian calculation, consider a clinical trial of two treatment options. Mathematically, Bayes theorem can be expressed as

$$p(\theta \mid x) = l(x|\theta)\, p(\theta) / \int l(x|\theta)\, p(\theta)\, d\theta \qquad (2.1)$$

where $l(x|\theta)$ is the likelihood function of the data x given the parameter θ, $p(\theta)$ is the prior probability, $\int l(x|\theta)\, p(\theta)\, d\theta$ is a normalizing constant and $p(\theta \mid x)$ is the posterior (final) probability distribution. Thus the posterior distribution is proportional to the likelihood function times the prior probability. The parameters of interest in a clinical trial comparing two treatments for a dichotomous outcome

are the probabilities of success in each group. Let the probability of success in treatment group i by denoted by θ_i where i =1,2. The newly acquired data for treatment i involves n_i patients with x_i successes such that x_i follows a binomial distribution,

$$B(x_i \mid n_i, \theta_i) \propto \theta_i^{x_i}(1-\theta_i)^{n_i - x_i}$$

This is the contribution to the likelihood function of subjects under treatment i. For convenience, prior information about θ_i can be expressed from the conjugate family of Beta distributions, $\theta_i \sim$ Beta (α,β) such that

$$p(\theta) \propto \theta^{\alpha}{}_i (1-\theta_i)^{\beta}$$

A family of distributions is termed a conjugate family for a particular likelihood function if the prior and posterior densities are both members of that family. It will be shown shortly that the beta family of distributions is conjugate for binomial likelihoods. If the prior mean, $E(\theta)$ and the variance of $p(\theta)$, $var\ (\theta)$ were exactly known both α and β could be calculated from manipulation (solving two equations in two unknowns) of the following equations

$$E(\theta) = \frac{\alpha}{\alpha+\beta}$$

$$var\ (\theta) = \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$$

Typically, the exact mean and standard deviation of the difference in probabilities of success of the two treatments is unknown. Historical data from j previous trials may be available and estimates of α and β may be made from the x_i successes from the n_i sample sizes. Prior distributions may then be formed using the historical data, although other ways to construct prior distributions are of course also possible, and are not necessarily restricted to conjugate families.

This analysis requires that both the new experiment and the historical experiments all have exactly the same probability of success. If this assumption is not true, the analysis can be appropriately modified. One simple, although arbitrary method of correcting for differences between the current and historical data is to increase the uncertainty in the historical data. The variance may be increased by decreasing α and β while holding α / β constant. Alternatively, one could elect to count only partially the historical data. More sophisticated model corrections are also possible.

If the prior density for the i th treatment group takes the form of a beta (α_i, β_i) distribution, then from equation (2.1) it can be easily shown[38] that the posterior distribution is also a beta density. This is because

$$p(\theta_i \mid x_i, \alpha_i, \beta_i) \propto \theta_i^{x_i}(1-\theta_i)^{n_i - x_i} * \theta^{\alpha_i}{}_i (1-\theta_i)^{\beta_i}$$

$$= \theta_i^{\alpha_i + x_i}(1-\theta_i)^{n_i - x_i + \beta_i} \qquad (2.2)$$

so that both the prior and posterior densities are of the form of beta densities.

Since the data from the two groups in a clinical trial are usually assumed to arise independently, the joint posterior density of $\theta = (\theta_1, \theta_2)$ is the product of the two marginal posterior densities,

$$p(\theta \mid \alpha_i, \beta_i) = \prod_{i=1}^{2} p(\theta_i \mid \alpha_i, \beta_i)$$

The joint posterior distribution of the success rate then becomes proportional to

$$p(\theta_1, \theta_2 \mid x_1, x_2, \alpha_1, \alpha_2, \beta_1, \beta_2)$$

$$\propto \theta_1^{\alpha_1 + x_1} (1-\theta_1)^{n_1 - x_1 + \beta_1} * \theta_2^{\alpha_2 + x_2} (1-\theta_2)^{n_2 - x_2 + \beta_2} \qquad (2.3)$$

Interest focuses on the difference in mortality $\varepsilon = \theta_1 - \theta_2$, which by the Central Limit Theorem can be approximated, for sufficiently large sample sizes, by a normal distribution with

$$mean = \frac{\alpha_1 + x_1}{n_1 + \alpha_1 + \beta_1} - \frac{\alpha_2 + x_2}{n_2 + \alpha_2 + \beta_2} \qquad (2.4)$$

$$variance = \frac{(\alpha_1 + x_1)(n_1 + \alpha_1 + \beta_1)}{(n_1 + \alpha_1 + \beta_1)^2 (n_1 + \alpha_1 + \beta_1 + 1)} + \frac{(\alpha_2 + x_2)(n_2 + \alpha_2 + \beta_2)}{(n_2 + \alpha_2 + \beta_2)^2 (n_2 + \alpha_2 + \beta_2 + 1)} \qquad (2.5)$$

This normal distribution directly represents the posterior probability distribution for the difference in mortality rates given the number of deaths (x_1, x_2) out of (n_1, n_2) subjects with the prior information represented by the beta distribution parameters (α_1, α_2, β_1, β_2).

I will return to these techniques with direct clinical applications in Chapter Four where existing data from the medical literature has been analyzed to more fully appreciate the role of different thrombolytic agents and the utility of ACE inhibitors in the treatment of AMI. More sophisticated Bayesian models may be developed to address more complex clinical issues, such as establishing the patient, physician and hospital determinants of the choice of thrombolytic agent. These models are presented in the following section and will be applied to data from the FRSQ registry in Chapter 7.

2.5.3 BAYESIAN HIERARCHICAL MODELS

In addition to the imperfections of the summary statistics for regional variations discussed in section 2.5.1, they can only be used for significance testing and don't address the more interesting issue of estimation. When estimating three or more means from normal populations it is advantageous in terms of minimizing total mean square error to use a form of shrinkage estimator or empirical Bayes techniques rather than the simple set of averages of the different populations.

While averages have the desirable statistical property of being unbiased maximum likelihood estimators, it has been shown that these estimators can be improved in terms of overall mean squared error by considering not only individual averages but also the data from the other samples [39]. This apparent paradox actually reflects an effect similar to regression to the mean [40,41], and often involves a tradeoff between individual estimator accuracy and total mean square error.

The empirical Bayes estimator is a compromise between the two possible outcomes of an analysis of variance (ANOVA) [36,40]. In ANOVA, if the null hypothesis (H_O) is true and there is no systematic variation between areas, then the best estimate for each *i th* area is the global mean, $\overline{X}$. If the null hypothesis is rejected and it is concluded that the alternative hypothesis (H_A) of areas having different rates is true, the best estimator becomes the individual averages, $\overline{X}_i$. Empirical Bayes techniques give some weight to the global mean and some to the specific area average when estimating the mean in each area. The amount of "shrinkage" toward the global mean depends on how much support in the data there is for the two competing hypotheses. Practically, this involves shrinking individual rates toward the overall mean by a function inversely proportional to the certainty that the true means are different. The degree of shrinkage will depend on the within and between area variation and how far a particular $\overline{X}_i$ is from the global mean, $\overline{X}$.

Simple empirical Bayes analyses obtain the prior distribution from the data in the current experiment and assume that this is the perfectly correct prior with

no uncertainty. In this way empirical Bayesian methods are not Bayesian "in spirit", since one does not attempt to combine past and present knowledge. In addition, a simple empirical Bayes approach may underestimate the posterior variances thereby providing a false sense of precision, although more complex procedures have been developed to adjust for this[42]. Empirical Bayes analyses may still be useful as an approximation to a complete hierarchical Bayesian analysis, and further it has been shown that these methods typically have good frequentist properties [42] .

In the FRSQ clinical registry there is most probably considerable heterogeneity among centers not only in terms of patient populations but also in terms of physician practice patterns. Thus, an inter and intra-center analysis can be a rich source of information regarding practice patterns. Simple incorporation of hospital center into a logistic model is often problematic conceptually since this assumes that all centers behave identically on all other parameters. Hierarchical modeling attempts to model hospital heterogeneity. The specific random effects hierarchical model developed to analyse the FRSQ data for the choice of thrombolytic agent is now presented.

Conceptually, the participating hospitals may be imagined to be like a random sample from a super population of all possible hospitals where patients with myocardial infarction may be treated with thrombolysis. A separate logistic regression equation is created for each hospital. The ensemble of coefficients for each patient regression parameter from each hospital are used to estimate the

distribution of the parameter across hospitals. If this distribution covers only a very narrow range of values, then the effect of that variable is similar across hospitals (as is assumed by standard logistic regression). Larger ranges imply that the effects differ from hospital to hospital. In the latter situation, it can be useful to try to explain the observed effect differences through a linear regression model using hospital characteristics as explanatory variables, including location, university affiliation and volume of activity. At this level of the model, the unit of analysis has become the hospital rather than the patient. The hospital volume of activity was treated as a continuous variable. For stability of the estimates, we grouped the lowest volume centers (<10 cases) together. Therefore, for the hierarchical modeling 26 hospitals (25 hospitals together with one "hospital" that was a composite of the 15 small volume institutions) were considered. A detailed description of the model for the choice of thrombolytic agent follows. A comprehensive discussion of Bayesian hierarchical modeling for the analysis of practice patterns has been previously published [21].

The hierarchical model can be described by four stages: At the first stage, a separate logistic regression model is fit within patients at each hospital. The within hospital model was

$$\text{logit}(p_{ij}) = \beta_{0i} + \beta_{1i} * \text{age}_{ij} + \beta_{2i} * \text{old\_mi}_{ij} + \beta_{3i} * \text{site}_{ij} + \beta_{4i} * \text{time}_{ij} + \beta_{5i} * \text{bp}_{ij} + \beta_{6i} * \text{md}_{ij} + \beta_{7i} * \text{gender}_{ij}$$

where p_{ij} represents the probability that the j th subject at the i th hospital was administered t-PA, logit $(p_{ij}) = \log\left(\frac{p_{ij}}{1 - p_{ij}}\right)$, and β_{0i} , $\beta_{1i}, \ldots, \beta_{7i}$ represents the intercept and the vector of hospital specific regression coefficients for hospital i , for the patient characteristics age (> or < 65), old MI (yes/no), anterior ECG site (yes/no), presentation within six hours of symptom onset (yes/no), blood pressure (> or < 120 systolic), cardiologist decision maker (yes/no) and gender, respectively. While the dichotomization of continuous variables, such as age and blood pressure, invariably leads to some loss of information, it was felt that the proposed divisions were clinically significant and would facilitate interpretation of the findings. As will be discussed in Chapter 7 where the results of this analysis are presented, the initial selection of patient variables in this model was determined by the presence of significant differences between the thrombolytic groups following an univariate analysis of the individual separate characteristics.

At the second stage, the between hospital variation about the intercept and each regression coefficient is modeled by a normal distribution so that

$$\beta_{ki} \sim \text{Normal}\ (\mu_{ki}, \sigma_k^2)$$

where β_{ki} represents the k th logistic regression parameter (k=0,1,2...,7) in the i th hospital, which is assumed to follow a normal distribution with mean μ_{ki} and variance σ_k^2 . Therefore we recognize that the regression coefficients may vary from centre to centre according to σ_k^2. If $\sigma_k^2 = 0$, then all β_{ki} 's are the equal across hospitals and our model reduces to a standard (non-hierarchical) logistic

regression. Conversely, larger values of σ_k^2 indicate larger between hospital variations for the effects of parameter k. As will be seen in Chapter 7, the data contained evidence of variation between hospitals and so $\sigma_k^2 > 0$ and this stage provided a more realistic model than simple logistic regression.

At the third stage, the between hospital variation in each regression coefficient are explained by regressing the μ_{ki}'s on hospital specific characteristics, so that

$$\mu_{ki} = \alpha_k + \gamma_{1i} * \text{volume}_i + \gamma_{2i} * \text{location}_i + \gamma_{3i} * \text{status}_i$$

where μ_{ki} is the mean of the k th patient regression coefficient γ_{ki} from the i different hospitals, γ_{1i} , γ_{2i} , γ_{3i} are the regression coefficients for the i th hospital characteristics volume of activity, location (urban/rural) and status (tertiary vs. non tertiary), respectively. The choice of hospital variables to include in the linear models for each patient parameter across the different hospitals was determined by approximate Bayes Factors, as calculated by the Bayesian Information Criterion [43].

Finally at the fourth stage, prior distributions are set for σ_k^2 and the above set of third stage regression parameters . The prior distributions represent what is known a priori (before the data was analyzed) about the parameter values. We used non-informative prior distributions (all values in the feasible range have approximately equal probabilities) which contributed only negligible information,

so that our final inferences are based almost exclusively on the information contained in the data.

The computational strategy for complex hierarchical models will now be described. Virtually every realistic problem in medicine requires the estimation of more than one unknown or unobservable quantity. Although in any given problem there are usually several parameters of interest, the formation of realistic models often also involves some nuisance parameters about which there is little substantive interest in making inferences. One simple example of a nuisance parameter would be the scale of the random errors in a measurement problem in the case where a mean measurement is the primary outcome of interest . The parameters of interest and the nuisance parameters may be represented as two vectors θ and ϕ respectively. For a given set of data, y, we are most interested in analytical or numerical methods to obtain solutions for the posterior distribution $p(\theta \mid y)$.

For simple models, the marginal posterior density of θ, $p(\theta \mid y)$ can be determined analytically given the hyperparameters ϕ and the fixed data y while more complex models will require a numerical solution. The marginal posterior distribution of $p(\theta \mid y)$ will lead to an estimate of θ by integrating the joint posterior distribution over ϕ :

$$p(\theta \mid y) = \int p(\theta, \phi \mid y) d\phi$$

There are many situations where the above integral is extremely difficult to perform either by analytical or numerical methods, and/or $p(\theta, \phi \mid y)$ is difficult to obtain usually because of problems with the denominator of Bayes Thereom. Here Markov chain Monte Carlo methods, for example the Gibbs sampler[38] can provide an alternative solution. These methods do not give an exact formula for the posterior density but rather provide a random sample from the desired density. If the size of the random sample is large, the desired quantities can be approximated by functions of the random iterates. The basic idea is to exploit the relationship between joint, conditional and marginal densities to thereby simplify the problem by breaking down one hard step into several easier steps.

Consider first for simplicity the bivariate case. The joint distribution of the two parameters θ_1, θ_2 is equal to the product of the conditional and the marginal densities as shown mathematically below

$$f(\theta_1, \theta_2) = f(\theta_1 \mid \theta_2) * f(\theta_2)$$

The value $f(\theta_1)$ can be determined by averaging the joint distribution over all values of θ_2

$$f(\theta_1) = \int f(\theta_1, \theta_2)\, d\theta_2$$

$$= \int f(\theta_1 \mid \theta_2) f(\theta_2)\, d\theta_2$$

A two stage iterative process can therefore be derived where a value θ^*_2 is drawn from $f(\theta_2|\theta_1)$ and then θ^*_1 is drawn from $f(\theta_1|\theta^*_2)$. This process is repeated M times to obtain samples from the two marginal distributions. The sampling is always performed from the conditional distributions which are assumed simpler than the target marginal distributions and which are often available from the likelihood times the prior formulation in the numerator of Bayes Theorem. A similar multi-stage process may be applied to higher dimensional problems, where again one samples from each conditional distribution in turn.

In Chapter 7, an exact analytic solution for the complex hierarchical model regarding the choice of thrombolytic agent is impossible. Inferences were therefore carried out using the Gibbs sampler, wherein random samples from the marginal distribution of each parameter of interest are generated by intensive computer calculations. I used samples of size 10,000 for each parameter which provide a high degree of accuracy in the final estimates. After ensuring convergence, empirical summary statistics can be formed and used to make inferences about the true values of the quantities of interest. This computational work has been performed using BUGS (**B**ayesian inference **U**sing **G**ibbs **S**ampling) software [44]. A listing of the BUGS program used for the hierarchical modeling is given in Appendix IV.

CHAPTER 3 LITERATURE REVIEW OF TREATMENT OF ACUTE MYOCARDIAL INFARCTION

3.1) THROMBOLYSIS

The role of thrombus in AMI was first observed in 1912 by Herrick [45]. The prevailing pathophysiological model for AMI now involves the rupture of a pre-existing atherosclerotic plaque with superimposed platelet deposition leading to thrombus formation and subsequent coronary occlusion. Typically if this occlusion persists for more than approximately 30 minutes, some degree of myocardial necrosis results. Tissue necrosis proceeds in a wave fashion and is probably not completed for at least six hours. The extent of necrosis seems to be primarily determined by the duration of the occlusion and also the existence of a collateral coronary circulation. Based on this understanding many trials have examined the role of thrombolytic, or more accurately fibrinolytic, therapy in AMI.

Thrombolytic agents are plasminogen activators which convert plasminogen, a proenzyme, to plasmin, an enzyme capable of cleaving fibrin and producing clot lysis. Streptokinase, an enzyme derived from beta-hemolytic streptococcal culture, is the oldest identified plasminogen activator and was the first commercially available thrombolytic agent. Streptokinase binds to circulating plasminogen and the resulting complex then undergoes a conformational change converting complexed plasminogen to plasmin which initiates fibrinolysis.

Streptokinase not only acts on clots but also on circulating fibrinogen, giving rise to systemic fibrinogenolysis. Tissue plasminogen activator (t-PA) is a direct plasminogen activator which is produced endogenously by endothelial cells. Commercial production is available by means of recombinant DNA technology. This agent produces less systematic fibrinolysis than streptokinase since it converts plasminogen to plasmin more efficiently in the presence of clot-bound fibrin.

The first studies of thrombolytic therapy in AMI were performed 30 years ago [46] but it is only in the past 10 to 12 years that the conclusive results from large scale randomized clinical trials comparing active treatment and placebo have become available. The first large mega-trial involved a network of 176 coronary care units throughout Italy and randomly assigned 12,000 patients with suspected AMI to either intravenous streptokinase or conventional therapy within 12 hours after the onset of symptoms [8]. The results were published in 1986 and reported a highly significant 18% reduction in the in-hospital mortality from 13% to 10.7%. The second International Study of Infarct Survival (ISIS-2) trial followed and randomly assigned a total of 17 181 patients with AMI to treatment with streptokinase or ASA, both agents in combination or neither at 417 hospitals in Europe, New Zealand, Australia, the United States and Canada. At 35 days follow-up the rate of vascular mortality was 23% lower among the patients given streptokinase alone, 21% lower among those given ASA alone and 39% lower

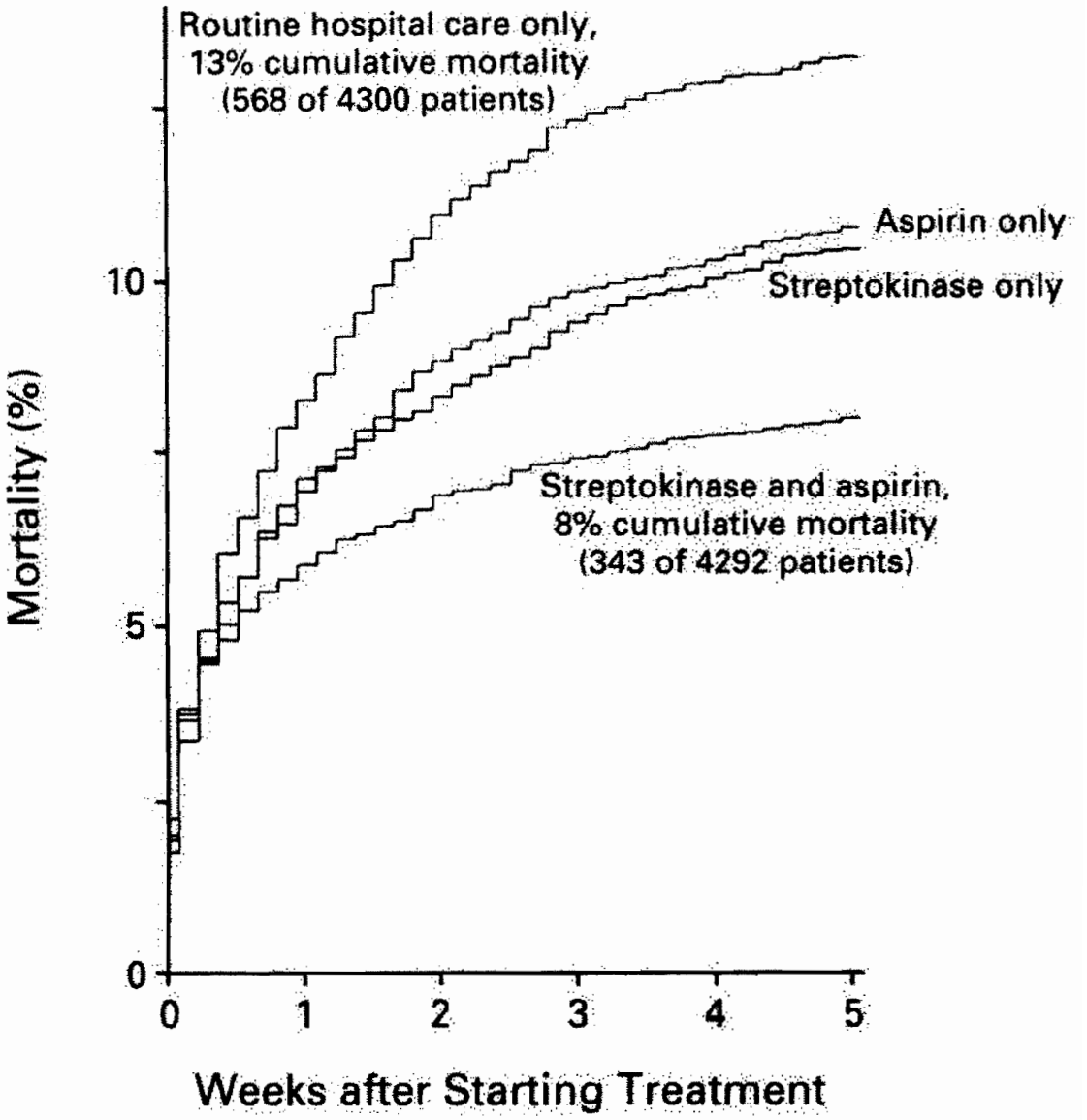


Figure 3.1. Cumulative Mortality from Vascular Causes up to Day 35 in the ISIS-2 Trial. A total of 17,187 patients were randomly assigned within 24 hours after the onset of suspected acute myocardial infarction to one of four regimens: placebo infusion and placebo tablets (i.e., routine hospital care); placebo infusion and 162.5 mg of aspirin daily for one month (aspirin only); an infusion of 1.5 million units of streptokinase over a one-hour period and placebo tablets (streptokinase only); or both streptokinase and aspirin. Reproduced from ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2:349-60

among those given both compared to patients given neither (see Figure 3.1). Following this 1988 publication, thrombolytic therapy began to be widely used.

The Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial was the first large scale mortality trial to compare t-PA and placebo in patients with AMI [47]. At 1 month, mortality was reduced from 9.8% to 7.2%, giving a 26% relative risk reduction (95% CI 11% to 39%, p = 0.0011), similar to the results with streptokinase.

These trials have been large enough to individually demonstrate a substantial overall mortality advantage with thrombolysis. Moreover, an overview of the nine largest randomized trials (each with at least 1,000 patients) has unequivocally proven that this benefit is present in a wide spectrum of patient subgroups [48]. The Fibrinolytic Therapy Trialists (FTT) overview, involving a total of over 58,000 patients, has shown reduced mortality in patients presenting with either ST segment elevation on the electrocardiogram (ECG) or bundle branch block up to at least 12 hours following symptom onset when treated with thrombolysis. The proportional benefit of thrombolysis is similar for all sites of infarction and although the absolute benefit is greatest among the higher risk anterior infarctions there is good evidence of benefit in lower risk inferior infarctions. The FTT overview has demonstrated the benefits in patients at high risk of death but for whom the individual trials had given

inconclusive proof of benefit. For example, the elderly, patients with prior MI and those with hypotension were all shown to have improved survival with therapy. There was no benefit to treating patients presenting with ST depression (14 excess deaths /1000 treated (SD 11)) or a normal ECG (7 excess deaths /1000 treated (SD 7)). Patients with a normal ECG have a very low mortality of 2.3% which is augmented with thrombolysis due to the increased stroke rate. The mortality rate of patients with ST depression is high, about 15%, and the lack of demonstrated benefit with thrombolytics may be due to the relatively small number of patients studied (3500). However another recent study [49] also demonstrated a lack of clinical benefit with thrombolysis for patients with ST depression and perhaps a difference in the underlying pathophysiology may explain this lack of response.

While there is an obvious mortality benefit at 35 days and beyond with thrombolysis, the FTT overview has suggested an early hazard of increased death in the first 24 hours of 2 deaths per 1000 patients treated. This early hazard is in part due to a higher stroke rate but cardiac causes including reperfusion arrhythmias and cardiac rupture are not excluded.

One of the most dramatic findings from the FTT overview is the clear association of reduced mortality with earlier intervention (see Figure 3.2). Thrombolytic therapy reduces mortality among those receiving treatment within six hours of symptom onset by about 30 lives per 1000 patients treated and

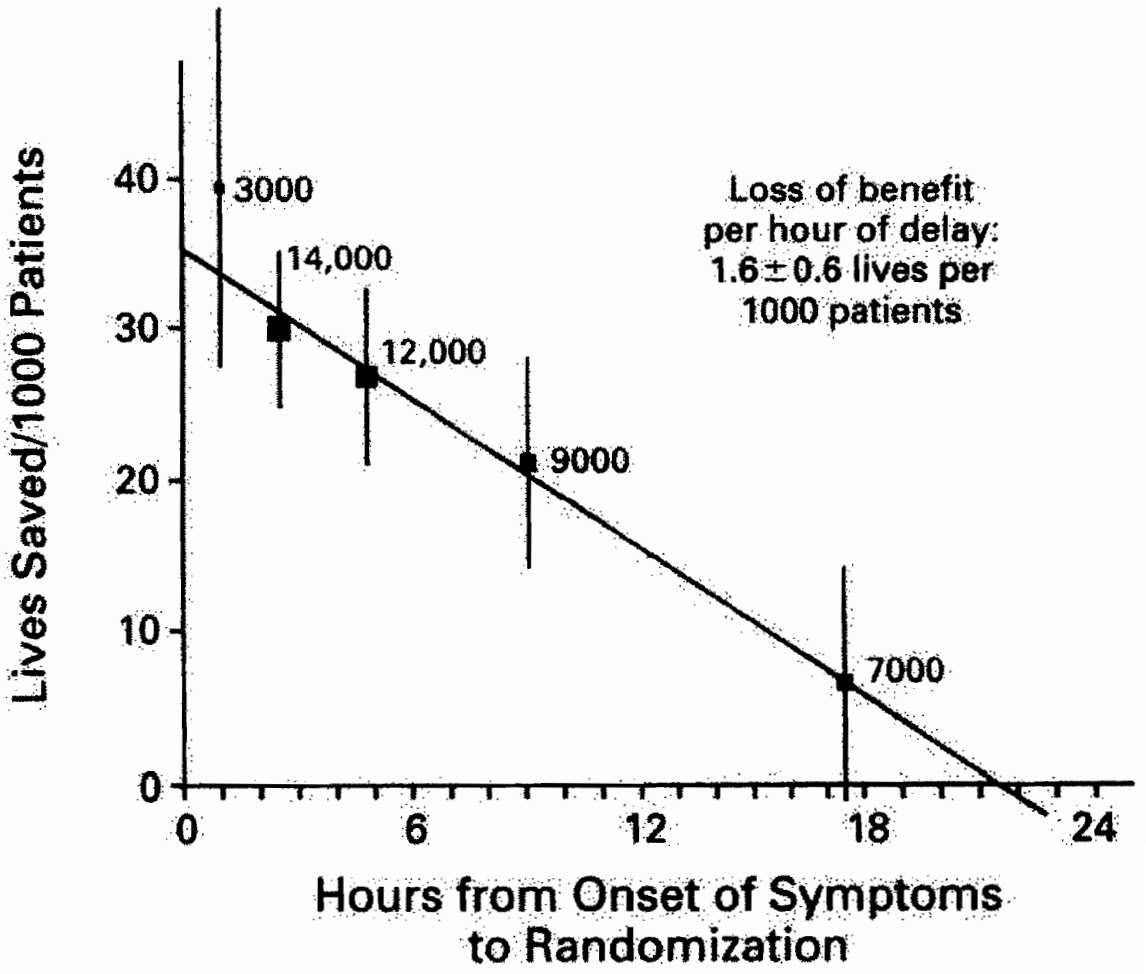


Figure 3.2. Absolute number of lives saved at one month per 1000 patients treated with fibrinolytic therapy, plotted against the time from the onset of symptoms to randomization among 45,000 patients (the numbers on the regression line refer to the number of patients analyzed) with ST-segment elevation or bundle-branch block. The area of each black square and the extent to which it influences the line drawn through the five points are approximately proportional to the number of patients in the category on which it is based (with these numbers shown in the figure) Reproduced from Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet 1994;343:311-22.

declines to approximately 20 lives per 1000 patients treated for those treated within 6 to 12 hours. There is a suggestion that therapy may still be useful beyond 12 hours although the margin of benefit is small. Overall, there is a decrease of 1.6 deaths (SD 0.6) per 1000 patients treated for each hour of earlier treatment. As discussed by the authors, inaccuracies in time estimation may have diluted the true additional hourly benefit which may be closer to 3 lives saved per 1000 patients treated.

Another thrombolytic overview also included smaller randomized trials (>greater than 100 patients) which resulted in a greater proportion of early treated patients and therefore more precision in measuring the effect size in those treated in less than 2 hours [50]. These authors have employed a non-linear model and determined that the benefits of thrombolysis in the first hour and second hours were 65 (SD 14) and 37 (SD 9) lives saved per 1000 patients treated, respectively when compared to placebo. Supporting this larger effect is the biggest trial of pre-hospital versus in-hospital thrombolysis which reported an additional 15 (SD 8) patients alive at 30 days per 1000 patients as a result of one hour earlier treatment[51]. While this result was not statistically significant, it does support the notion that earlier treatment is better and the possibility of a 'golden hour' following symptom onset [50].

There is a benefit of thrombolysis when administered beyond six hours after symptoms even though most animal and human data suggest that necrosis is

complete by this time. Various theories have attempted to explain this phenomena including the difficulty in exactly determining the time of coronary occlusion, the effect of collaterals and the possibility of stuttering infarction with temporary occlusion followed by brief periods of spontaneous lysis.

3.2) THE CHOICE OF THROMBOLYTIC AGENT

Having proven the efficacy of thrombolysis, it was natural that the next generation of clinical trials should attempt to ascertain if there were any substantial clinical advantages among the different agents. The two main commercial agents are streptokinase (SK) and tissue plasminogen activator (t-PA). SK produces a generalized lytic state while t-PA is reputed to be more specific for clot bound fibrin. The typical regime of 1.5 million units of SK administered over one hour takes a median of about 90 minutes to open the occluded arteries. T-PA has a faster action opening a greater percentage at 90 minutes but by 180 minutes patency rates are identical [52]. Moreover, the more intense thrombolytic regimes with t-PA are also associated with an increased stroke rate and the question of whether any small cardiac benefits exceed the neurological risks could only be answered by further large scale trials, coupled with careful cost-benefit analyses.

Three randomized clinical trials have directly compared SK with t-PA in AMI patients. The GISSI-2 (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) trial [8]compared t-PA (alteplase) and SK both with and without subcutaneous heparin beginning 12 hours after the start of therapy. The 35-day total mortality and nonfatal stroke data are summarized in Table 3.1. The ISIS-3 (Third International Study of Infarct Survival) trial [28]compared t-PA (duteplase) and SK both with and without subcutaneous heparin in a similar factorial design but began heparin 4 hours after the start of therapy. The 35-day mortality and morbidity data for this trial are also shown in Table 3.1.

The next comparative trial was GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator in Occluded Arteries) [53] which randomized 41 021 patients to four different thrombolytic strategies involving two SK arms, one with intravenous and the other with subcutaneous administration of heparin, t-PA, or a combination of the two for the treatment of acute myocardial infarction. This multi-center trial recruited patients from the United States (17,796), Canada (2,898 of whom 50 were randomized by myself) and 13 other countries. Compared with the combined SK branches, the strategy of "front-loaded" or "accelerated" t-PA showed a statistically significant lowered mortality (6.3% vs. 7.3%, respectively; p=.001) and combined end point of 30-day mortality or disabling stroke (6.9% vs. 7.8%, respectively; p<.006) . The interpretation of a

Trial	Agent	No. patients	Death	Stroke	Stroke or death
GISSI-2	SK	10396	958 (9.2)	98 (0.9)	1014 (9.8)
	t-PA	10372	993 (9.6)	136 (1.3)	1067 (10.3)
ISIS-3	SK	13780	1455 (10.6)	141 (1.0)	1530 (11.1)
	t-PA	13746	1418 (10.3)	188 (1.4)	1513 (11.0)
GUSTO-1	SK (sc hep)	9841	712 (7.3)	117 (1.2)	783 (8.0)
	SK (iv hep)	10410	763 (7.4)	144 (1.4)	853 (8.2)
	t-PA	10396	653 (6.3)	161 (1.6)	746 (7.2)
	t-PA + SK	10374	723 (7.0)	170 (1.6)	817 (7.9)

Table 3.1 Mortality, stroke and combined endpoint for three mega-trials comparing SK to t-PA. Percentages in brackets. Hep = heparine.

p value of .001 is that if the two agents had exactly equivalent mortality rates, then data as extreme as or more extreme than the observed mortality rates would occur once in every 1000 hypothetical repeated trials.

This well-executed clinical trial possesses many of the desirable attributes of a well-done study. The sample size was very large and was designed to have at least 80% power to detect a 15% reduction in mortality or an absolute mortality difference of 1% between experimental groups. This value has been (completely arbitrarily) defined by the GUSTO-I investigators as the clinically important difference between the two agents. In this thesis, we will continue to accept a 1% decrease as a clinically meaningful difference. Potential confounding and bias were minimized by the randomization process. Most clinicians would accept the frequentist analysis (p=0.001) of this study as being conclusive (or almost conclusive) proof of the superiority of t-PA, that is, the mortality rate for t-PA was less than that for SK. The next chapter will discuss the issue of whether this is an adequate summary of the available evidence.

GUSTO [53] was an Herculean effort that was generally very well executed, but this fact does not exempt it from a careful and meticulous examination, particularly since myocardial infarction is a common occurrence and there are substantial cost differences between thrombolytic agents. Important issues to consider in the interpretation of GUSTO, and all medical research, are internal and external consistency, the differentiation between statistical and clinical significance and integration of new and old knowledge into the clinical context.

The clinical context includes the socio-economic context in which we live and practice. Economic analyses that incorporate patient utilities and health care expenditures may be required to further investigate the cost of any incremental benefit.

A trial lacking internal consistency is a trial with bias. Randomization is an important mechanism to minimize bias and certainly the GUSTO trial, with its central co-ordinating centre is exemplary in this regard. Some controversy has arisen from the unblinded GUSTO protocol although the investigators have countered this criticism by pointing out that not all other thrombolytic trials have been blinded, that mortality trials do not need blinding since death is a "hard outcome" and finally that advanced mathematical modelling (multivariate logistic regression) may account for any unbalancing introduced by the openness of the trial[54,55].

However, blinding remains a key necessity even in a randomized controlled trial with hard outcomes, as unblinded randomized trials have been associated with exaggerated treatment effects [56]. The most important reason for blinding is to avoid intentional and unintentional bias in assessing outcomes across different treatment arms. But in this case, a death is a death, so how can unblinding really matter?

Despite better outcomes with accelerated t-PA (increased early reperfusion rates and less mortality), this strategy was associated with 1% more early

revascularizations, an unbalancing beyond what is expected by the play of chance. While reductions in mortality by appropriately employed revascularizations in stable angina may take a long time to be realized [57] this is not necessarily the case in the setting of acute ischemic syndromes. North American physicians are increasingly performing routine early post infarctus angiography and revascularization [16] with the widespread, albeit unsupported belief [58,59], that such interventions may reduce morbidity and mortality.

The GUSTO investigators [54] included a revascularization term in their logistic model and maintain this did not negate the "significant" mortality advantage for t-PA. So all is again well, or is it? First of all, while the difference between the two agents may still be statistically significant, we are not told what is the adjusted difference. With a sample size of 41,000, a mortality difference that had shrunk from 1% to perhaps 0.2% or 0.3% (two or three lives saved /1000 treated) could remain statistically significant. Furthermore, we are not told the exact logistic model employed and different models may have produced different results. Moreover, mathematical modelling (including logistic regression) can only adjust for confounding variables that are measured and included in the model. The difference in revascularization rates may not represent simple confounding (risk factor control) but also unmeasured and unmeasurable bias in the selection of future treatments, which is of special concern in an unblinded trial.

In this light, the recent publication [60] of variations in patient management and outcomes between patients in the US and other countries is interesting. After controlling for baseline characteristics, overall prognosis was statistically improved in patients randomized in the US. Randomization in the US may be a marker for increased revascularizations as these procedures were three times more common in US patients. Further, there was a non statistically significant trend for an interaction term between treatment arm/country ($p=0.07$) and this reached statistical significance for the case of t-PA versus combination therapy ($p=0.02$). These authors conclude, as I did in an earlier publication [1], that "... the results suggest that differences in routine patient management may have affected survival, although to a limited extent".

While such post hoc subgroup analyses must be viewed very cautiously, the large sample size, the prospective planning and consistency with previous European thrombolytic trials do suggest that part of the 30 day mortality advantage attributed to accelerated t-PA may be the result of an interaction with the significantly different health care system in the US. This data is, of course, open to differing interpretations. The absence of statistically significant interaction terms between other treatment branches and country may be due to an underpowered study for these effects. On the other hand, it is also possible that any positive sub group findings are simply the result of the increased type I error from multiple comparisons.

The 30 day mortality in the 17,796 patients randomized outside the US was 6.9% and 7.4% for the t-PA and SK with SQ heparin groups, respectively. Total and fatal strokes were more frequent with t-PA (1.59% vs. 1.14%, total and .9% vs. 0.5% fatal). The combined death or nonfatal stroke rate of non-US patients was lower in the t-PA group but by only 0.4% or 4/1000 patients treated. Thus, while the trend for decreased survival is still present in non-US patients receiving accelerated t-PA, the difference is smaller.

Knowledge advances incrementally and it is the rare experiment which is performed in an absence of prior knowledge. GISSI-2 and ISIS-3 have compared SK to t-PA in over 48,000 patients and found no mortality differences, although both had an excess of strokes in the t-PA arm. Objections have been raised about the comparability of these trials with GUSTO due to protocol differences. While these objections have merit, does this mean all this prior information must be discarded? There is certainly no consensus on this issue.

The external consistency of GUSTO has been examined from a clinical cardiologist perspective by Sleight [61] who concludes that the GUSTO treatment effect is disproportionately large compared to what is expected from the literature. Dr. Sleight points out that angiographic studies reveal that t-PA increases artery perfusion at 90 minutes but that there is a rapid catch-up phenomenon by SK. The advantage in reperfusion time over SK is 45-60 minutes and according to the correlation presented by the Fibrinolytic Therapy Trialists (see above) this advantage would translate into less than 5 extra lives saved/ 1000 treated for

treatment begun in the first two hours. One hour earlier reperfusions in patients presenting later in the course of their myocardial infarction would be expected to save 2 to 3 extra lives/1000 treated. This opinion is compatible with the data from the GUSTO international patients.

Standard statistical analysis as exemplified by p values and confidence intervals does not attempt to consider our prior knowledge, can not provide a direct answer to the pertinent question "which agent is better, by how much and with what certainty" and does not assist in placing trials in their proper context. These shortcomings may be addressed only by the Bayesian analysis which is presented in the next chapter.

3.3) ADJUNCTIVE THERAPY TO THROMBOLYSIS

Both anticoagulants and antiplatelet agents have been evaluated for use as an adjunct to thrombolytic therapy. Aspirin exerts its antiplatelet effect by inhibition of cyclooxygenase thereby reducing the production of thromboxane A2 a powerful promoter of platelet activation and aggregation. It has been shown to reduce 35-day mortality in AMI by almost as much as streptokinase and when used in combination with streptokinase to almost double the mortality reduction (Figure 3.1). This reduction represents the avoidance of about 25 deaths for each 1000 patients treated with 162.5 mg of enteric aspirin and seems independent of

any delay between symptom onset and treatment [62]. An overview of 133 trials of antiplatelet therapy in 53,000 patients with prior cardiovascular disease has confirmed the beneficial effects of long term therapy [63].

A recent review article has examined the role of adjunctive therapy with intravenous heparin following thrombolysis and concluded that despite increased rates of coronary artery patency, this more intensive anticoagulation has no clinically significant advantages compared to aspirin alone [62]. Following heparin administration, there was no reduction in mortality, reinfarction or total stroke, although major bleeding and hemorrhagic stroke rates were increased. While the routine administration of heparin to a standard regime of t-PA has not been found useful, there are no trials comparing accelerated t-PA with and without heparin. Consequently, there remains a doubt as to the possibility of a synergistic interaction between intravenous heparin and the accelerated administration of t-PA.

3.4) Other therapies for AMI

Several other pharmacological interventions have been evaluated in the management of acute myocardial infarction. Besides thrombolytic therapy and aspirin, beta-blockers and angiotensin converting enzyme (ACE) inhibitors have been proven to reduce mortality and morbidity following AMI. Beta blockers

have been studied in randomized trials of over 20,000 patients following AMI and have demonstrated decreased morbidity (reinfarctions) and improved survival by 20% to 40% [64]. Large scale randomized trials of (ACE) inhibitors have demonstrated a strong and consistent reduction in the long term mortality of high risk patients following AMI [10,65,66 67]. A small benefit was also noted at 35 days for all patients of whom the vast majority were considered to be at low risk [68 69,70]. ACE inhibition has been studied in over 100,000 patients and the need for such extensive proof will be discussed in the next chapter.

Drugs that have as yet not been shown to have a role in the routine management of acute myocardial infarction include Class I antiarrhythmic agents, magnesium and calcium antagonists. Ventricular arrhythmias are frequent following myocardial infarction are may be a harbinger for cardiac death. It seemed a reasonable hypothesis that prophylactic suppression of these arrhythmias would improve outcomes. Unfortunately, this hypothesis has been proven false[71,72]. An overview of mortality data from 138 trials on 98 000 patients [73] has confirmed an increased risk of death with class I agents (51 trials: odds ratio (OR), 1.14; 95% confidence interval (CI), 1.01 to 1.28; p=.03). However as mentioned above, beta-blockers have been shown to significantly reduce mortality (55 trials: OR, 0.81; 95% CI, 0.75 to 0.87; p=.00001) perhaps due to both their anti-ischemic as well as anti-arrhythmic characteristics. Trials with amiodarone (a class III agent) have been promising (eight trials: OR, 0.71; 95% CI, 0.51 to 0.97; p=.03)

while class IV agent (calcium channel blockers) have not (24 trials: OR, 1.04; 95% CI, 0.95 to 1.14; p=.41).

Other trials have shown no significant reduction in mortality with early nitrate [69] or magnesium therapy [68]. An extensive series of studies evaluating various strategies for coronary angiography and prophylactic angioplasty also showed no benefit [49,58].

CHAPTER 4 THE INTERPRETATION OF CLINICAL TRIALS - THE BAYESIAN PARADIGM

4.1) INTRODUCTION

Bayesian analysis, as discussed in Chapter 2, integrates the summation of our past knowledge (via the prior distribution) with the newly acquired data (through the likelihood function) by Bayes theorem to arrive at a newer understanding of the studied phenomena (summarized by the posterior distribution). Bayesian analysis are often criticized for their use of subjective priors, which, if inappropriately chosen, may give a false impression of reduced uncertainty. However, an appropriately chosen range of priors can facilitate debate following the publication of clinical trial results.

Bayesian analyses of randomized clinical trials provide a clearer interpretation not only of the final data than standard statistical analysis that typically provides only a p value or confidence interval from the current trial data with no formal attempt to put the trial into the current clinical context, but also of interim data where it can assist in the sometimes difficult task of deciding whether a trial should continue. This chapter will use two examples from the cardiology literature of new treatments for AMI to show the limitations of standard frequentist analyses, as discussed theoretically in section 2.5.1, and to illustrate the advantages of a Bayesian approach.

4.2) ARE THERE CLINICALLY IMPORTANT DIFFERENCES BETWEEN THROMBOLYTIC AGENTS?

Before any clinical trial results are available, different clinicians will have different opinions regarding the relative benefits of the therapies under study. These opinions will usually range from skepticism to enthusiasm for a new therapy compared with a standard therapy. Regardless of how well it is conducted, a single clinical trial can not generally provide absolutely definitive conclusions. Thus, even after trial results are reported, it is reasonable to expect that a diversity of opinions will persist, although perhaps with some convergence toward the observed trial results. The degree of convergence will depend on the strength of the trial in terms of sample size and scientific rigor in its execution. Therefore, in any medical experiment, clinical researchers must give careful consideration to issues of both design and analysis. Randomized clinical trials are almost universally accepted as the gold standard design for comparative clinical research, since bias and confounding are minimized. Much attention has been directed to the scientific reasoning behind statistical analysis in the medical and statistical literature [30,31,74]. However, while most clinicians are aware of the importance of good experimental designs, few are aware of the full array of statistical methods available. Some of these methods allow for the reporting of a range of conclusions corresponding to the diversity of prior opinions. They can also answer directly questions of interest to clinicians.

The shortcomings of classical statistics may obscure the interpretation of even a well-designed and well-executed trial. Keeping in mind the goal of this thesis to

study the epidemiology of AMI and its treatment, let us re-examine the GUSTO-1 trial described in the previous chapter. This trial is of particular interest since there continues to be controversy over the clinical importance of any treatment differences. In addition, there have been other randomized trials involving large numbers of patients that examined the same question, namely, is tissue-type plasminogen activator (t-PA) superior to streptokinase (SK) in the treatment of acute myocardial infarction [8,28]. The question of therapeutic superiority is of considerable public health importance, since myocardial infarction is a frequent occurrence and t-PA is approximately 8-10 times more expensive than SK. While many critiques of the GUSTO-1 trial have been published [75-77] these have mostly centered on design issues and the interpretation of the clinical relevance of the observed mortality differences. This chapter raises further questions while highlighting some advantages of an alternative (Bayesian) statistical approach.

Bayesian analysis has often been dismissed due to its "subjectivity" and because of computational difficulties. While Bayesian analysis can be computationally complex, computer algorithms, such as the Gibbs sampler discussed in Chapter 2, now exist that make this hurdle more historical than contemporary. As will be seen, Bayesian subjectivity is an asset that can provide an ideal forum for debate, since prior beliefs, including clinical experience, must be formally specified, and one can directly observe how the beliefs are updated in the light of new data. This procedure permits the appreciation of the logic for various a posteriori opinions, which should tend to converge as data accumulate. This process is different from

classical meta-analysis, which suffers from all the problems associated with p values and confidence intervals mentioned in section 2.5.1 and furthermore does not permit the incorporation of prior beliefs [78].

While there is an abundance of prior information comparing these two thrombolytic agents (see Table 3.1), there is little consensus as to which agent is superior. Clinicians may vary in their weighting of the importance of the similarities and differences between the trials. This only enhances the utility of a Bayesian analysis, because individual uncertainty can be explicitly considered by employing a range of prior beliefs [37,79].

These methods and their interpretation are illustrated below. Other studies[31,37,79] provide fuller descriptions of the use of Bayesian analysis in the context of clinical trials. In this thesis, posterior distributions for the difference in survival rates between groups of patients receiving two different thrombolytic regimens following acute myocardial infarction are derived and graphically displayed.

As an example of a Bayesian technique, let us consider a clinical trial of two treatment options. Recall from Chapter 2 that Bayes theorem can be expressed as

$$p(\theta \mid x) = l(x|\theta)\, p(\theta) / \int l(x|\theta)\, p(\theta)\, d\theta \qquad (4.1)$$

where $l(x|\theta)$ is the likelihood function of the data x given the parameter θ, $p(\theta)$ is the prior probability, $\int l(x|\theta)\, p(\theta)\, d\theta$ is a normalizing constant and $p(\theta \mid x)$ is the posterior (final) probability distribution. Thus the posterior distribution is

proportional to the likelihood function times the prior probability. The parameters of interest in the clinical trial example are the probabilities of success (paradoxically referring to the chance of death) with each treatment i, and referred to as θ_i, where i =1,2 for a typical two arm study.

Again recalling from Chapter 2, interest focuses on the mortality difference $\varepsilon = \theta_1 - \theta_2$, which by the Central Limit Theorem can be approximated by, for sufficiently large sample sizes, a normal distribution with

$$mean = \frac{\alpha_1 + x_1}{n_1 + \alpha_1 + \beta_1} - \frac{\alpha_2 + x_2}{n_2 + \alpha_2 + \beta_2} \qquad (4.2)$$

$$variance = \frac{(\alpha_1 + x_1)(n_1 + \alpha_1 + \beta_1)}{(n_1 + \alpha_1 + \beta_1)^2 (n_1 + \alpha_1 + \beta_1 + 1)} + \frac{(\alpha_2 + x_2)(n_2 + \alpha_2 + \beta_2)}{(n_2 + \alpha_2 + \beta_2)^2 (n_2 + \alpha_2 + \beta_2 + 1)} \qquad (4.3)$$

This normal distribution directly represents the posterior probability distribution for the difference in mortality rates between treatment *1* and *2* given the number of deaths (x_1, x_2) out of (n_1, n_2) subjects with the prior information represented by (α_1, α_2 , β_1 , β_2).

For example, consider a clinician who believes the thrombolytic trials are sufficiently similar that the prior distributions should be constructed using all the data from past trials[28,77]. Then considering only mortality and using the data from Table 3.1 (page 65) gives

$\alpha_1 = 993 + 1418 = 2411$

$\alpha_2 = 958 + 1455 = 2413$

$\beta_1 = (10372 - 993) + (13746 - 1418) = 21707$

$\beta_2 = (10396 - 958) + (13780 - 1455) = 21763$

The mean of the prior distribution for the difference is 0.00015 and the standard deviation is 0.0027. Figure 4.1 shows the probability density for the difference in mortality between t-PA and SK as determined from the data of GISSI-2 and ISIS-3. The area under the probability density curve between two given points on the x-axis represents the probability that the difference in mortality will fall between the two points. The difference in mortality rates between t-PA and SK appears along the x-axis (0.01=1% and so forth), and the height of the probability density for this difference is given by the y-axis. The mean of these curves is very close to zero, suggesting little difference between the two agents. Fully accepting the results of these two trials would suggest almost no possibility of t-PA's being clinically superior to SK (a decrease in the mortality rate with t-PA >=1% is represented by the area to the left of -0.01, and this area is essentially zero when using 100% of the prior data). This leads to a very skeptical prior distribution as to the superiority of t-PA.

On the other hand, a clinician who believes that the difference in trial protocols cannot be ignored might elect to only partially consider the earlier results. For example, one could arbitrarily treat the value of each observation in the previous

trials as worth only 50% or even 10% of each observation in the GUSTO-1 data. Prior distributions based on these weights also appear in Figure 4.1. A more extreme position would be that the trials are too dissimilar to be combined and that consequently all previous research should be ignored, thereby assuming that nothing is known about the potential difference in mortality between the two agents (in statistical parlance, this implies a noninformative or uniform prior distribution). Other prior distributions are also possible and are not necessarily derived by a weighting of previous data. Most of these would fall in between the above-mentioned extremes. As the belief in the utility of the prior studies decreases, so increases the possibility that t-PA is a clinically superior agent with widening of the curves and increasing area to the left of -0.01 (see Figure 4.1).

These prior distributions can be updated to posterior distributions with the GUSTO-1 data by means of Bayes theorem. For example, updating the skeptical prior distribution above with the SK and accelerated t-PA data from the GUSTO-1 trial, using equations 4.2 and 4.3 leads to a posterior distribution mean of 0.0013 and a standard deviation of 0.0020. From standard normal tables, the probability that $\varepsilon < 0$ (t-PA is superior to SK) using $z = \frac{0 - 0.0013}{0.0020} = -0.65$ is 26.7% and similarly, the probability that $\varepsilon < -0.01$ (t-PA is superior to SK by at least 1%) is less than 0.0001. This corresponds to the area under the curve for death to the left of 0 and -0.01 respectively in Figure 4.2a.

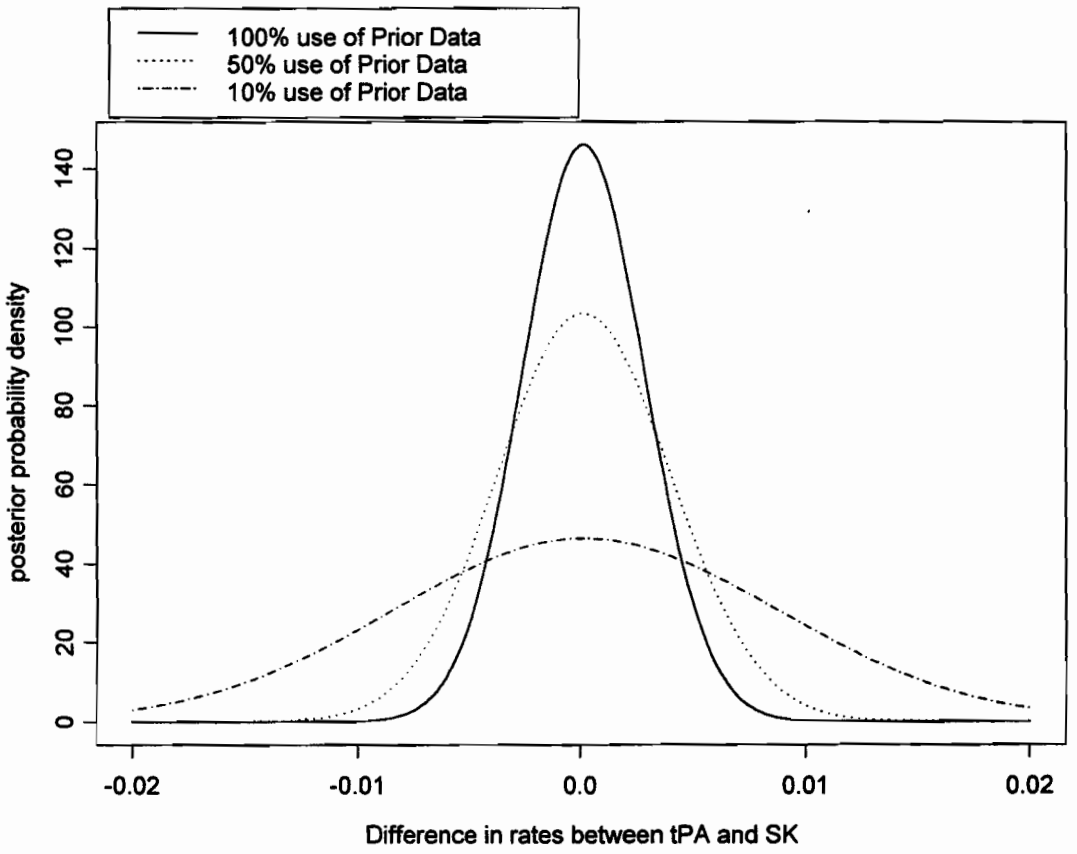


Figure 4.1 Plot of the prior distributions for the difference in mortality rates between tissue-type plasminogen activator (t-PA) and streptokinase (SK) using weights of 100%, 50%, and 10% of the GISSI-2 and ISIS-3 data, representing a range in prior beliefs in the relevance of these trials to the GUSTO-1 trial. The area under the curve between any two points on the x-axis is the posterior probability that the difference in mortality rates lies between those limits. Numbers to the right of zero indicate the superiority of SK, while those to the left of zero indicate the superiority of t-PA.

Figure 4.2a also demonstrates that there are 0.15% more nonfatal strokes with t-PA and that the probability that the rate of nonfatal stroke is greater with t-PA exceeds 99.5% (the area to the left of the curve <.005). A similar interpretation of the combined curve suggests that the probability that t-PA is superior to SK is 13.9% with an almost zero probability of exceeding the clinically significant difference of 1% (area to the left, on the combined curve of 0 and -0.01, respectively).

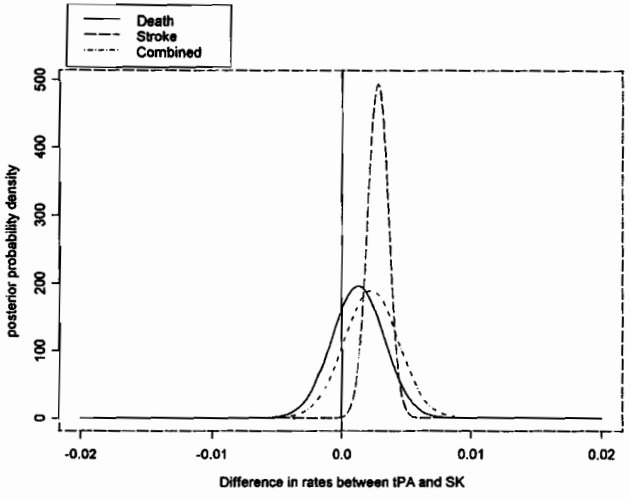
Figure 4.2b considers observations from the previous randomized clinical trials to have 50% the value of each observation in GUSTO-1, a more intermediate prior belief. This figure shows that the probability that t-PA is superior to SK for mortality alone is 52.5% (again referring to the area to the left of 0 for the appropriate curve). Accepting that a difference of 1% mortality is the minimum clinically significant value, the probability that t-PA is clinically superior nevertheless remains negligible. The probability of increased stroke with t-PA remains high at almost 98%.

Figure 4.2c reveals the probability distributions for t-PA superiority when only 10% of the prior information is considered. In this situation, our final conclusions are more strongly dominated by the new (GUSTO-1) data and it is fairly certain that overall mortality (probability of 98.1%) and the combined net clinical benefit (probability of 95.2%) are improved with t-PA . However, the probability of a clinically meaningful decrease in mortality or in the combined stroke/mortality outcome remains low at 7.6% and 4.8%, respectively.

Finally, Figure 4.2d shows the scenario where all prior data from GISSI-2 and ISIS-3 are considered irrelevant and are ignored. In this case, t-PA is virtually certain to have a lower death rate than SK (99.95%), but the probability that t-PA exceeds the defined clinical superiority is only 50.3%. The probability of a net clinical benefit exceeding 1% is only 38%, and the probability of increased stroke with t-PA is 86%. The salient elements of Figures 4.2a through 4.2d are displayed in Table 4.1.

The Bayesian analysis presented herein suggests that restraint in accepting t-PA into routine clinical practice would be appropriate. The same conclusion was reached by Diamond and colleagues [80] who used a Bayesian point null hypothesis test. When one accepts only partial recognition (50%) of previous randomized clinical trials, the probability that t-PA is superior to SK for mortality or net clinical benefit is only 52.5% and 38.1%, respectively. The probability that either mortality or net clinical benefit would exceed clinical importance with the 50% assumption is much less than 1%. Even if one totally ignores all prior studies, the chance that t-PA would exceed the clinical superiority cut point for mortality and net clinical benefit is only 50.3% and 38.0%, respectively.

a) All the thrombolytic data



b) GUSTO-1 + 50% prior data

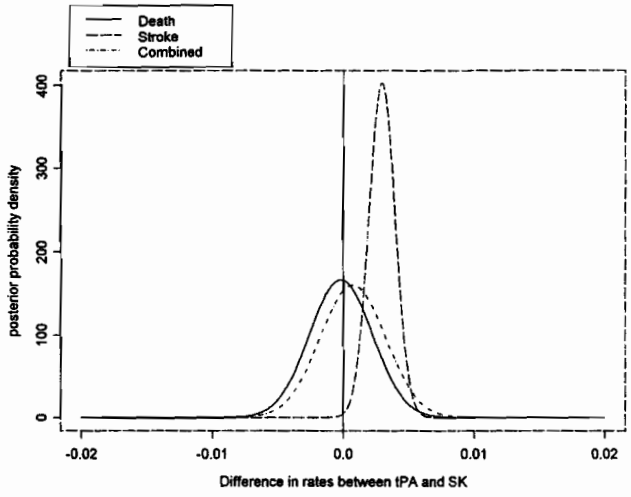
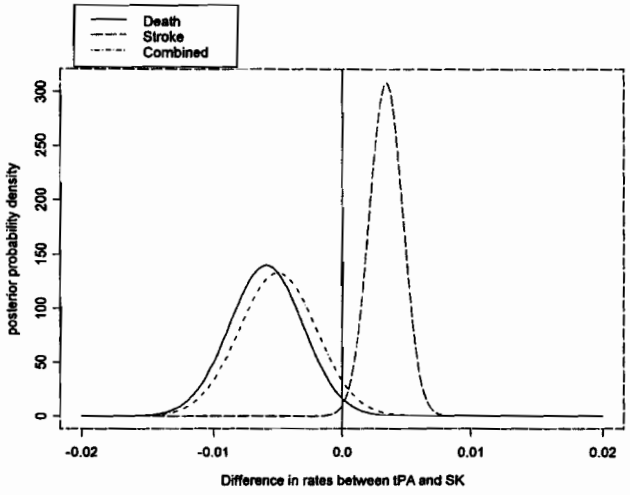


Figure 4.2 a) Plot of the posterior distribution for the difference in mortality, nonfatal stroke, and combined stroke and mortality rates between t-PA and SK using data from the GUSTO-1 trial, with full prior use of data from the GISSI-2 and ISIS-3 trials. b) Plot of the posterior distribution for the difference in mortality, nonfatal stroke, and combined stroke and mortality rates between t-PA and SK, using data from the GUSTO-1 trial, with 50% prior use of data from the GISSI-2 and ISIS-3 trials. The area under the curve between any two points on the x-axis is the posterior probability that the difference in rates lies between those limits. Numbers to the right of zero indicate the superiority of SK, while those to the left of zero indicate the superiority of t-PA

c) GUSTO-1 + 10% prior data



d) GUSTO-1 data alone

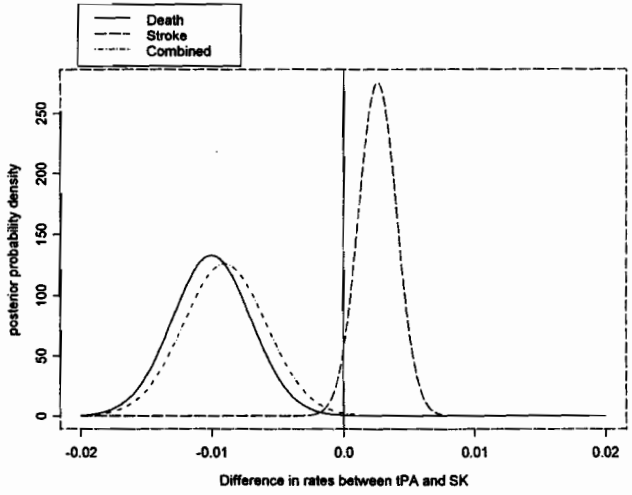


Figure 4.2 c) Plot of the posterior distribution for the difference in mortality, nonfatal stroke, and combined stroke and mortality rates between t-PA and SK using data from the GUSTO-1 trial, with 10% prior use of data from the GISSI-2 and ISIS-3 trials. d)) Plot of the posterior distribution for the difference in mortality, nonfatal stroke, and combined stroke and mortality rates between t-PA and SK, using data from the GUSTO-1 alone. The area under the curve between any two points on the x-axis is the posterior probability that the difference in rates lies between those limits. Numbers to the right of zero indicate the superiority of SK, while those to the left of zero indicate the superiority of t-PA

Varying prior beliefs	Mean difference (lives saved/1000)	P(t-PA > SK) %	P(t-PA > SK by >10/1000)
Mortality alone			
Selected[1] GUSTO-1, all others	-1.3	26.7	0.0
Selected GUSTO-1, 50% others	0.0	52.5	0.0
Selected GUSTO-1, 10% others	5.9	98.1	7.6
Selected GUSTO-1, no other	10.0	99.9	50.3
Mortality and stroke			
Selected GUSTO-1, all others	-2.2	13.9	0.0
Selected GUSTO-1, 50% others	0.7	38.1	0.0
Selected GUSTO-1, 10% others	5.0	95.2	4.8
Selected GUSTO-1, no others	9.0	99.7	38.0

Table 4.1. Probability of t-PA superiority for mortality and the combined mortality/stroke outcome, as a function of prior belief in GISSI-2 and ISIS-3 data after consideration of selected GUSTO-1 data. The last column represents the probability of a clinically significant difference (exceeding 1%). Others = GISSI-2 + ISIS-3.

[1] selected GUSTO-1 data refers to both SK branches and one accelerated t-PA arm

Before leaving this example, there is one last substantive issue to consider. The Bayesian analysis above has followed the GUSTO-1 investigators in ignoring patients in the combined t-PA and SK branch. However this represents an important loss of information (10,374 patients). As has been appropriately emphasized, to reliably interpret clinical trials biases must be minimized and this is obtained by emphasis on the overall trial results as well as a systematic overview of all relevant randomized trials[81]. Excessive emphasis on certain sub-groups and the elimination of valid trials, or branches of trials, may substantially bias the interpretation of the data. This is especially crucial for this debate as any advantages or disadvantages between the two agents are likely to be small and consequently any net differences even smaller. Further, as shown by Collins et. al. [62], it is not totally reasonable to exclude the combined SK+ t-PA arm since these patients received up to 90 mg of t-PA compared to 100 mg in the accelerated t-PA arm. Moreover in the crucial first hour the amount of t-PA received was very similar at 82 and 78 mg in the accelerated arm and combined arms respectively.

Consequently, the Bayesian analysis has been repeated, again accompanied by varying prior beliefs, but this time combining the two t-PA branches and therefore using all the GUSTO-1 data (see Table 4.2). While the inclusion of this extra information strengthens our belief that t-PA leads to improved survival compared to SK (cf. with a 50% prior, the probability of t-PA superiority has increased from 52.5% to 97.7%), it also strengthens our conviction that this difference is most likely much less than a clinically important 1%. In particular, considering all the GUSTO-1

Varying prior beliefs	Mean difference (lives saved/1000)	P(t-PA > SK) %	P(t-PA > SK by >10/1000)
Mortality alone			
All the data	3.1	95.3	0.0
All GUSTO-1, 50% others	4.2	97.7	3.7
All GUSTO-1, 10% others	5.9	99.3	4.8
All GUSTO-1, no others	6.6	99.5	8.7
Mortality and stroke			
All the data	1.8	82.1	0.0
All GUSTO-1, 50% others	3.0	91.2	0.0
All GUSTO-1, 10% others	4.8	97.1	2.1
All GUSTO-1, no others	5.5	98.1	4.6

Table 4.2. Probability of t-PA superiority for mortality and the combined mortality/stroke outcome, as a function of prior belief in GISSI-2 and ISIS-3 data after consideration of **all** the GUSTO-1 data (both SK and both t-PA arms). The last column represents the probability of a clinically significant difference (exceeding 1%).

data, and only this data (as proponents of t-PA have maintained is the only acceptable position[54]) leads to a decrease in the probability of a greater than 1% difference in favor of t-PA from 50.3% to 8.7%. The Bayesian analysis above suggests that considerable uncertainty should remain about the clinical significance of any difference between the thrombolytic agents. This finding is undoubtedly disconcerting to sponsors, physicians, and patients.

The controversy surrounding the interpretation of these trials arises from the heterogeneity in their results, although this is somewhat reduced by the appropriate inclusion of all the GUSTO-1 data. The heterogeneity of the individual trial results is displayed graphically in Figure 4.3. It is convenient to imagine a super-population of thrombolytic trials from which these three particular trials have been selected, and estimate the range of potential results via a simple hierarchical model. I performed this Bayesian hierarchical meta-analysis using commercial software [78] resulting in the beta distribution ($\alpha = 14723$, $\beta = 14756$) plotted in Figure 4.4.

It is also of interest to try to explain the observed variations between the trials through higher level hierarchical modeling, but this is not possible with data from only three trials. This technique, however, will be used in Chapter 7 to analyze my own data concerning the choice of thrombolytic agent by physicians in Quebec hospitals. While the implication of Figure 4.4 is that considerable uncertainty should exist as to any difference between the thrombolytic agents (from a 1% benefit to 1% disadvantage), it seems unlikely that most physicians share this opinion and it is consequently important to try and understand their selection process.

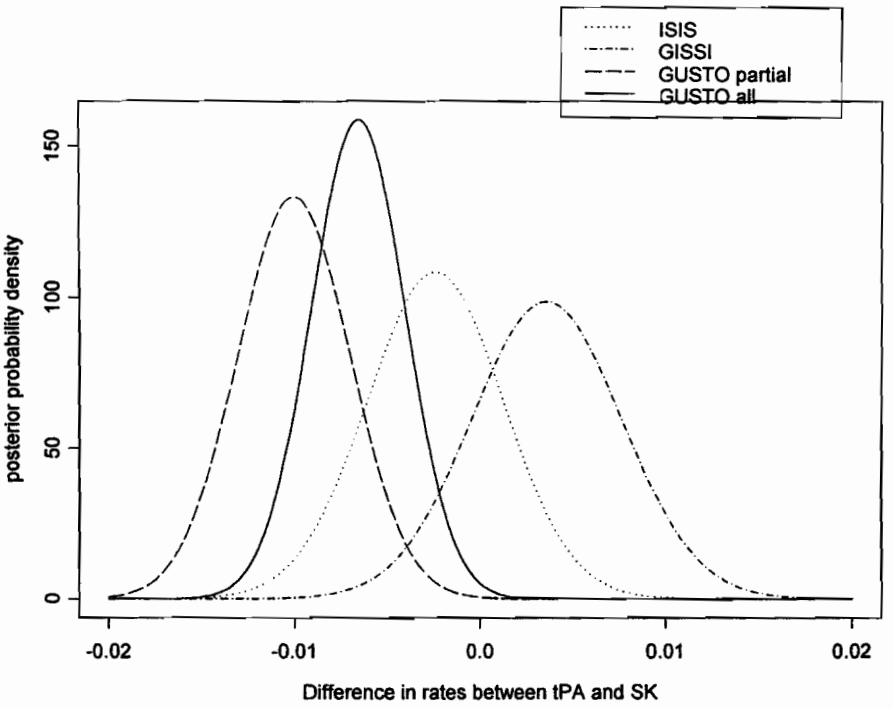


Figure 4.3 Posterior distributions using noninformative prior distributions for the difference in mortality rates between SK and t-PA for the GISSI-2, ISIS-3 and GUSTO-1 (using ½ and all the t-PA data)

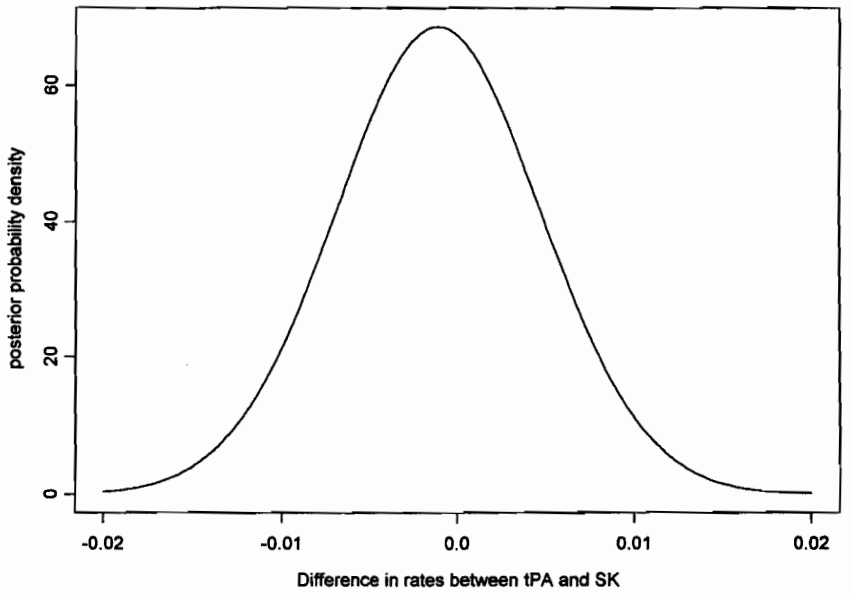


Figure 4.4 Posterior distribution of a hierarchical model from which the thrombolytic trials may be drawn

4.3) When do we know enough ? - ACE inhibitors for high risk AMI patients

To reiterate, Bayesian analysis integrates the summation of our past knowledge (via the prior distribution) with the newly acquired data (through the likelihood function) by Bayes theorem to arrive at a newer understanding of the studied phenomena (summarised by the posterior distribution). Here I will apply this idea to data from another intervention following AMI, namely the set of trials examining the use of ACE inhibitors. Bayesian analysis will not always lead to increased uncertainty about treatment effects, as in the example in section 4.2. Indeed, this section presents an example where a Bayesian analysis will suggest that a clinical trial should have been stopped earlier.

Uncertainty, although not always recognized, is pervasive in clinical medicine and, paradoxically, may be increasing despite advances in our knowledge[82]. Evidence-based medicine is a construct that attempts to formalize our knowledge, but its inability to cover all aspects of patient care has been recognized [83]. Randomised clinical trials have been championed as the best method to advance evidence-based medicine, but they are not always feasible because of, for example, cost and ethical issues. Furthermore, the stringent criteria used to select patients for trials may limit the generalizability of results to routine practice. Consequently, before embarking upon or continuing with a randomized trial it is important to ensure that the proposed research question is still relevant. As the following example illustrates, Bayesian

interim analysis of randomized clinical trials may occasionally provide a clearer interpretation of the data than standard statistical analysis and assist in the sometimes difficult task of deciding whether a trial should continue.

In the 1980s, angiotensin-converting-enzyme (ACE) inhibitors were shown to improve the morbidity and mortality of patients with established congestive heart failure [84]. Consequently trials were planned to test the hypothesis that early administration of these drugs to post-myocardial-infarction patients would improve outcomes. The first results came from the SAVE investigators [10] and showed a 19% reduction in total mortality ($p<0.02$) in post-myocardial-infarction patients with significant left-ventricular dysfunction but no clinical signs of heart failure (see Table 4.3). The AIRE [65] study confirmed a reduction in total mortality (27%, $p<0.002$) in patients with clinical signs of heart failure following myocardial infarction.

The TRACE trial[66], published in December 1995, was of patients with left-ventricular dysfunction after myocardial infarction randomized to trandolapril, another ACE inhibitor, or placebo. This trial, like SAVE and AIRE, randomized only patients with significant left-ventricular dysfunction and confirmed results from other randomized trials [67-70] showing decreased mortality with ACE inhibitors. TRACE randomized patients from May 1, 1990, to July 7, 1992, with a 2 year minimum follow-up, implying that some patients received placebo until July, 1994. The SAVE results, published in September, 1992, are applicable to 40% of TRACE patients with left-ventricular dysfunction without signs of heart failure, and the AIRE results,

TRIAL	CONTROL		TREATMENT		LIVES SAVED	SD
	DEATHS	TOTAL	DEATHS	TOTAL	/1000 TREATED	
SAVE	275	1,116	228	1,115	41.9	4.9
AIRE	222	992	170	1,014	56.1	2.2
TRACE	367	873	304	876	73.4	6
SMILE	111	784	77	772	41.8	3.6
TOTAL	975	3765	779	3777	52.7	1.7

Table 4.3 Trials of ACE inhibitors post myocardial infarction in high risk patients.

published in October, 1993, are directly applicable to the other 60% of the TRACE population. Therefore, the publications of SAVE and AIRE raised ethical questions for the TRACE investigators. Should the TRACE patients be advised of the new results? Is a revised informed consent necessary? Should the TRACE trial be prematurely ended?

The TRACE safety committee received quarterly safety reports, did three interim analyses (the last in August, 1993), and recommended that the trial continue. It is not known if any statistical criteria were employed to assist in the decision to continue the trial or whether patients were advised of the other published trial results. TRACE mortality results at the final interim analysis are not given but may be inferred from a previous publication, giving an overall 1 year mortality of 23%, (12) or about 25% and 21% for placebo and trandolapril, respectively. Whereas a chi squared test of these results ($p=0.03$) may not be statistically significant enough in an interim analysis to cause abandonment of the trial, incorporation of the SAVE and AIRE results with these interim results presents a different picture.

Since the SAVE and AIRE trials had similar entry criteria to TRACE, a Bayesian analysis, which permits the formal inclusion of these previous results, may have been helpful in deciding whether to continue the trial. Letting the results from SAVE and AIRE represent our prior knowledge and updating this knowledge with the interim TRACE results by Bayes theorem (using the simple Bayesian techniques in section 2.5.2), reveals that the best estimate for the

difference in mortality between treatment with ACE inhibitors and placebo is 4.9 lives saved per 100 patients treated. The 95% credible interval (the Bayesian analogue of a confidence interval) for this estimate is from three to seven lives saved per 100 patients treated. Furthermore, this analysis reveals that we are 99.8% certain that the benefit of ACE inhibition is at least two lives saved per 100 treated (see Figure 4.5). Thus, even without terminating the TRACE trial, it seems almost certain that a clinically significant benefit exists with active treatment. Incidentally, a similar Bayesian analysis shows the necessity of continuing the TRACE trial at least until the publication of the AIRE results. An analysis limited to SAVE gives a point estimate of 4.2 lives saves per 100 treated for ACE inhibitors, but the credible interval is still relatively wide and the probability that the benefit exceeds at least 2 lives saved per hundred treated (a reasonable starting point for clinical significance) is only 89%. Further the patient populations from these two trials while very similar are not totally identical and more knowledge was consequently desirable to be certain of the clinical benefit.

A Bayesian analysis combining data from SAVE, AIRE and TRACE seems reasonable as all trials enrolled patients within 3-16 days of a confirmed myocardial infarction resulting in relatively severe left ventricular dysfunction, although the method of determining this dysfunction varied between the trials.

One must obviously be prudent not to prematurely halt a trial and thereby arrive at an inconclusive result but in this case the relative uniformity in patient selection, homogeneity of results and the large treatment effect argue convincingly

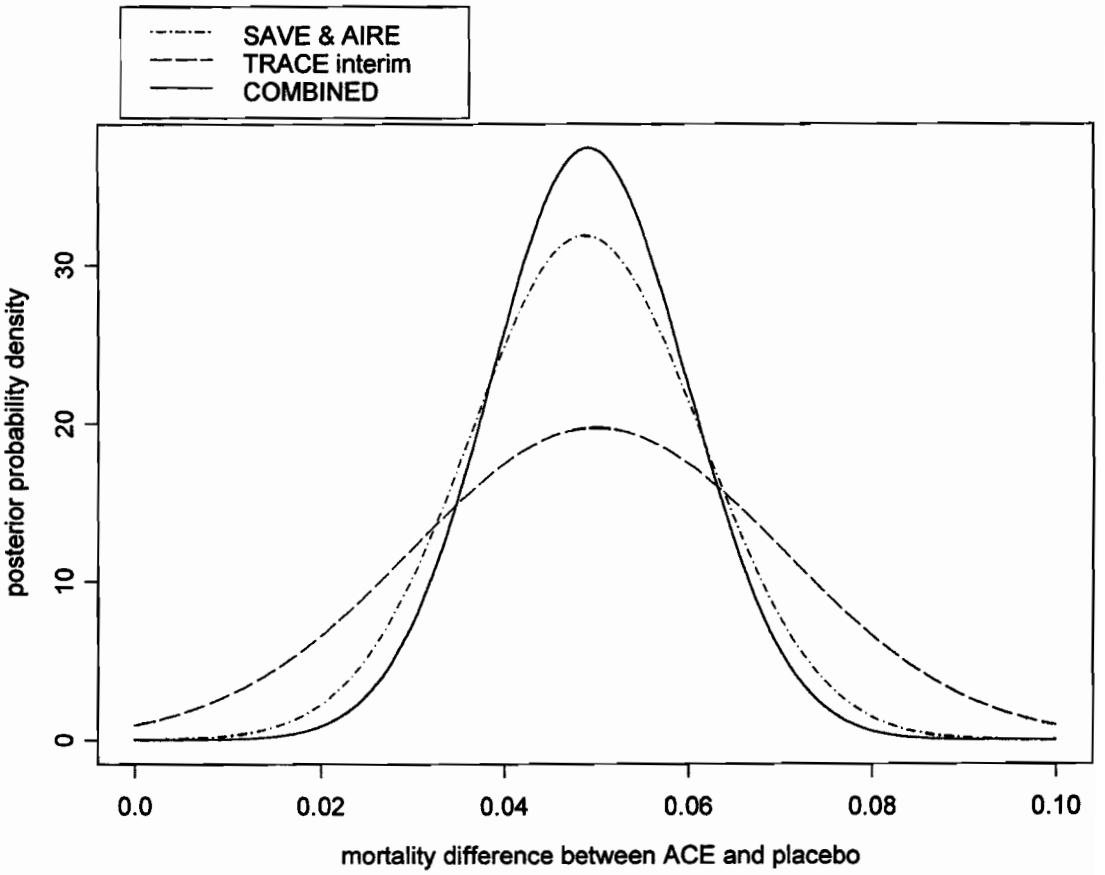


Figure 4.5 Probability density plots of the mortality difference between placebo and ACE inhibitors in post-myocardial-infarction patients representing prior knowledge (SAVE and AIRE), new data (TRACE), and the updated posterior distribution.

in favor of a Bayesian analysis (a similar conclusion would be reached by conventional meta-analysis). Consequently, the TRACE trial could have been halted in October 1993 or possibly earlier and patients receiving placebo offered ACE inhibitors. This is not an isolated example and these observations may also be applicable to another recent trial of ACE inhibition following myocardial infarction [67].

It should be noted that this opinion about the utility of a Bayesian interim analysis is not shared by the TRACE investigators who claim that differing entry criteria and uncertainty as to whether the benefit of ACE inhibition was a class effect justified the continuation of the trial [85]

4.4 ACE INHIBITORS FOR ALL ?

Although the first trials of ACE inhibition following AMI addressed only the patient subgroup with substantial myocardial infarction, there have been numerous trials[68-70,86] that have examined the early (within 12 hours of admission) administration of ACE inhibitors to all patients with AMI and not only the high risk patients discussed previously. These trials are summarized in Table 4.3. Conventional overviews of these trials have stressed the safety of early administration of these agents to virtually all patients with AMI[87] and have encouraged their widespread use in all patients. This recommendation is based on the small p value associated with the

testing of the null hypothesis that there is no difference between treatment and placebo. However, a Bayesian approach based on probability distributions permits the calculation of more useful quantities such as the probability that the treatment effect exceeds a clinically significant level.

Moreover, the clinical hemodynamic status of these patients as measured by the Killip class is available (personal communication, Zhengming Chen, Oxford University) and are also presented in Table 4.3. The probability distributions for patients in Killip class 1 and >1 are displayed in Figure 4.6 and compared with the results from the high risk patients discussed previously. It can be appreciated that the majority of patients presenting with AMI are in Killip class 1 and the best estimate of the 35 day survival benefit of ACE inhibition is 2.9 lives saved per 1000 patients treated (i.e. mortality difference = 0.0028). While it is highly likely that this intervention is safe for this low risk group (probability of benefit = 96%), there is virtually no chance of an effect size as large as 10 lives saved / 1000 treated. Higher risk patients, Killip 2-4, some of whom would have been randomized in the earlier trials of high risk patients have an estimated 35 day survival advantage of 14 lives / 1000 treated. In this case it is certain that the intervention is safe (probability of benefit = 99.6%), with a substantial 77.2% probability that the effect size exceeds 10 lives /1000 treated.

This analysis helps to clarify how to approach patients with AMI. There seems little risk but also a very small benefit in treating low risk (Killip 1) patients with ACE inhibitors. However, there is a substantial short term benefit in treating higher

TRIAL	CONTROL		TREATMENT		LIVES SAVED	SD
	DEATHS	TOTAL	DEATHS	TOTAL	/1000 TREATED	
CONSENSUS	192	3046	219	3044	-8.9	6
ISIS 4	2231	29022	2088	29028	4.9	2.2
CHINESE	645	6820	617	6814	4.0	4.9
GISSI 3	673	9460	597	9435	7.9	3.6
TOTAL	3741	48348	3521	48321	4.5	1.7
KILLIP 1	2340	39926	2224	39895	2.9	1.6
KILLIP >1	1308	8489	1189	8491	14.1	5

Table 4.3 Trials of early administration of ACE inhibitors in low and high risk patients.
N.B. Killip 1 + Killip >1 does not equal the total due to missing values.

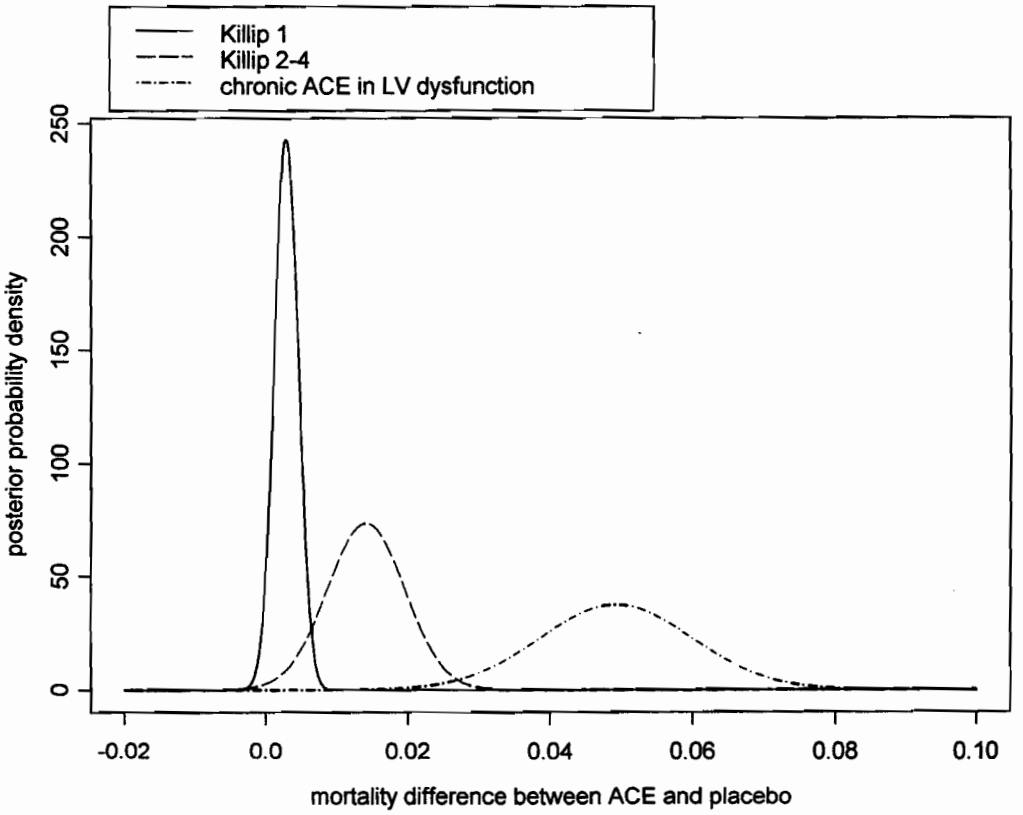


Figure 4.6 Plot of posterior distribution for the mortality difference at 30 days between placebo and ACE inhibitors for all patients (Killip 1 and 2-4) compared with long term mortality results for selected patients with left ventricular dysfunction.

risk patients immediately with these drugs and in continuing the treatment long term. This ACE inhibitor example could be further developed by the use of a random effects model which would more accurately reflect the complexities of this situation with multiple trials. This additional level of sophistication will be employed in Chapter 7 when the question of the selection of thrombolytic agents is presented. First, the next chapter will explore the impact that the clinical advances discussed in this chapter have had at the population level.

CHAPTER 5 EPIDEMIOLOGY OF AMI IN QUEBEC AND CANADA

5.1) INTRODUCTION

This chapter will begin with a description of the national magnitude of the cardiovascular disease burden over time using mortality data for AMI from Statistics Canada. Next, employing the Quebec province wide hospital administrative database, the impact on routine practice of the clinical advances in the treatment of AMI presented in the previous chapter will be assessed by an analysis of in-hospital fatality rate for AMI. Finally, the baseline results of the clinical FRSQ registry involving patients with acute ischemic syndromes, including AMI, in 40 Quebec hospitals will be presented.

A study of acute myocardial infarction in Nova Scotia and Saskatchewan[24] using record linkage found a decreasing incidence, standardized mortality and case fatality rates for the period 1974 to 1985. This chapter extends the observations for acute myocardial infarction and ischemic heart disease to the whole Canadian population for the period 1976 to 1991. The evaluation of national trends in the incidence of and mortality rates from myocardial infarction permits not only an evaluation of our success in implementing new clinical and

epidemiological knowledge, but also may assist in predicting future orientations and needs.

5.2) National Mortality Trends for AMI

The mortality and hospital separation data were obtained from Statistics Canada as discussed in Chapter 2. The total number of deaths due to ischemic heart disease (International Classification of Disease , ICD 9th revision code 410-414) decreased from over 51,000 deaths in 1976 to 44,000 in 1991 (Table 5.1). Deaths from myocardial infarction alone (ICD 9th revision code 410) declined from 31,500 to 23,500 for the same period. There has been a reduction in deaths from ischemic heart disease for both men and women, although the unadjusted rates of decline are much larger for men.

To better appreciate these mortality trends, it is necessary to account for the shifting age distributions in the Canadian population. Death rates were adjusted to the 1971 (census year) Canadian population by the direct standardization method [23]. The age adjusted mortality rates are also reported in Table 5.1 and show a marked decrease in mortality for both men and women over the last 15 years (Figure 5.1). The improvement in mortality rates is greater for men whether examining death from acute myocardial infarction or from all causes

year	men						women					
	410			410-414			410			410-414		
	total number	crude /100,00	adjusted /100,000	total number	crude /100,00	adjusted /100,000	total number	crude /100,00	adjusted /100,000	total number	crude /100,00	adjusted /100,000
1976	20669	180	173	31183	271	262	10959	94	86	20163	174	158
1981	18462	152	138	28875	239	217	10760	87	71	19808	161	130
1986	16289	130	109	27154	217	182	10783	84	61	20307	158	112
1991	13779	103	80	24499	184	143	9844	71	46	19496	142	90
1976-91 % decrease/ yr.	2.7	3.7	5	1.6	2.5	4	0.7	1.8	4	0.2	1.4	3.7
1981-91 % decrease/ yr.	2.9	3.9	5.2	1.6	2.6	4.1	0.9	2	4.2	0.2	1.3	3.6

Table 5.1. Total deaths, crude and age adjusted mortality rates /100,000 population for myocardial infarction (410) and all ischemic heart disease (410-414)

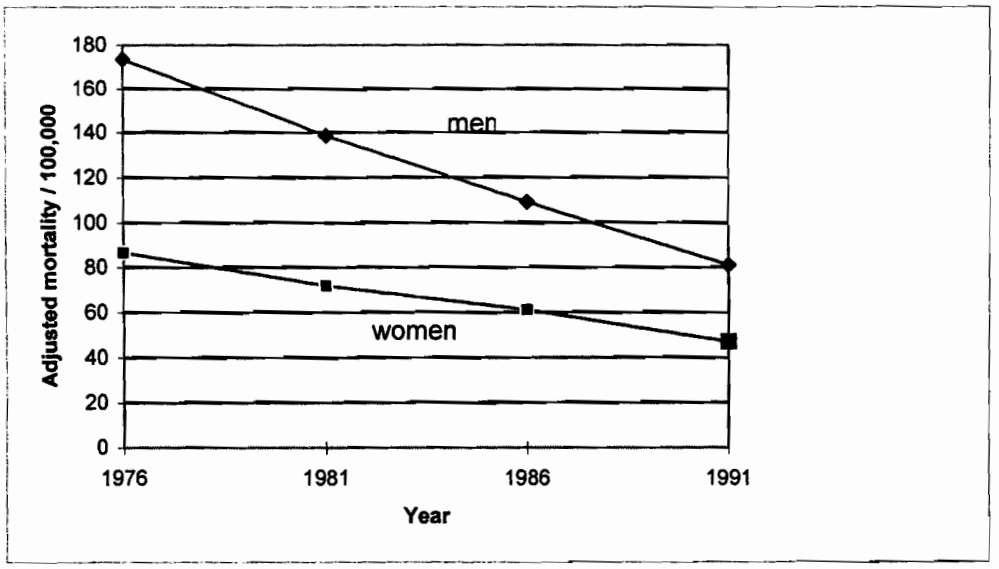


Figure 5.1. Age adjusted mortality rates per 100,000 for acute myocardial infarction (ICD 410) for men and women.

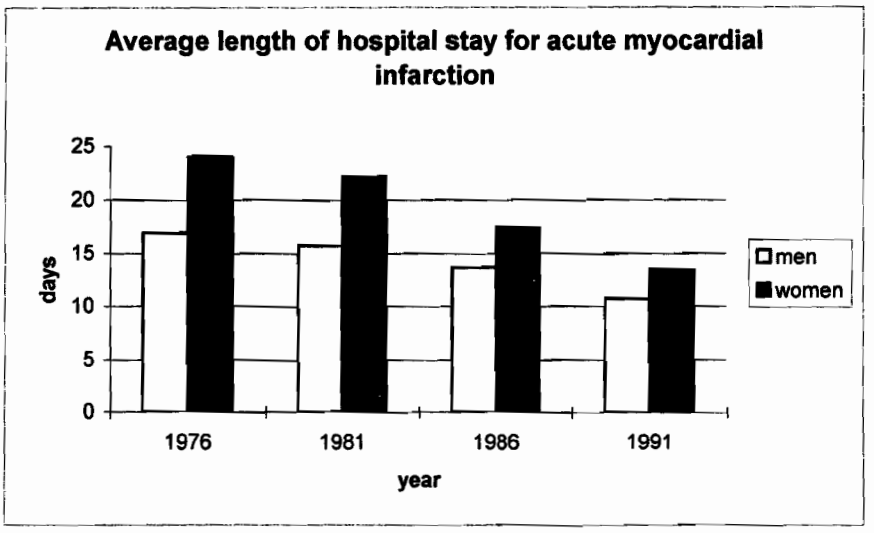


Figure 5.2. The variation over time of the mean hospital stay for men and women with a diagnosis of acute myocardial infarction (age and sex adjusted to the 1991 myocardial infarction population).

	men						women					
		rates /100,000						rates /100,000				
year	number AMI	crude	<45	45-65	>65	age adjusted rate	number AMI	crude	<45	45-65	>65	age adjusted rate
76-77	32504	284	34	757	1520	234	14894	129	6	211	858	109
81-82	33519	278	33	685	1479	221	16238	132	5	192	832	104
85-86	35399	285	36	643	1480	218	18316	144	5	184	852	104
91-92	36472	273	33	565	1419	201	19741	144	6	164	810	98

Table 5.2. Separation rates for acute myocardial infarction according to gender and age

of ischemic heart disease. However these differences are much less pronounced after adjusting for age.

The number of hospital separations (admissions) for acute myocardial infarction increased from about 47,000 in 1976 to 56,000 in 1991 in parallel with the aging Canadian population (Table 5.2). Again standardizing for age to the 1971 Canadian population reveals that hospital separations rates have actually decreased over the 15 year interval. This decrease was present for men and women as well as those above and below age 65, although the dramatic gradient in hospital separation rates with advancing age remains. There is a more than doubling of the hospitalization rates for the elderly compared to those in the age group 45-65. The fall in separation rates over the 15 year study period was more pronounced in the 45-65 group (25%) compared to the elderly (6%).

The duration of the average hospital stay has fallen impressively by almost 40% for both men and women (Figure 5.2). The average length of stay in 1991 was 10.7 and 13.4 days for men and women, respectively, down from 17 and 23 days in 1976.

This population data suggests that important improvements have been realized in cardiovascular care and health promotion in Canada for the period 1976-91 with a major fall in deaths from all causes of ischemic heart disease but principally from a decrease in the number of deaths from myocardial infarction.

Decreasing age adjusted mortality rates for ischemic heart disease are evident for both men and women. The decline in mortality rates is greater in males, although the absolute number of cardiovascular deaths remain greater for men, whether for acute myocardial infarction or all ischemic deaths. The age adjusted mortality declines of 53% and 46% (5% and 4% average annual decrease) for men and women, respectively, with acute myocardial infarction are impressive. This data does not permit any explanation as to why mortality reductions may differ according to gender. A similar decline in age adjusted myocardial infarction mortality rates was observed by the Nova Scotia-Saskatchewan cardiovascular disease epidemiology group [24].

The number of hospitalizations for acute myocardial infarction has increased from over 47,000 in 1976 to over 56,000 in 1991. However, the age adjusted hospital separation rates of myocardial infarction appears to have fallen by about 10-15% for both men and women. The impact of reduced hospital separations is especially evident in the younger age group. While there has probably been no major change in the percentage of myocardial infarctions surviving long enough to require hospitalization, the number of recurrent infarctions has perhaps decreased, and it is therefore impossible to conclude that this decrease in age adjusted separation rates reflects a true reduction in the incidence of acute myocardial infarction. This data alone does not allow the partition of any decrease in hospitalizations for acute myocardial infarction to primary or secondary prevention mechanisms.

Nevertheless, it is interesting to speculate how many lives might be saved by these reductions in hospitalization rates. During the 15 year interval, the age adjusted hospital separation rates for men and women has fallen by about 33 / 100,000 and 11/100,000 respectively. Let us assume that during this period the out of hospital and in hospital mortality for myocardial infarction were 50%[88] and 20%[11] respectively. The 33 less myocardial infarctions per 100,000 men would then potentially save 20 lives (33*0.5 + 33*0.5*0.2). This implies that approximately one sixth of the total 120/100,000 lives saved may be attributed to out of hospital health promotion programs perhaps through a falling incidence. Similar percentage results are hypothesized for women.

The decrease in mortality from acute myocardial infarction may be attributed not only to decreased incidence, but also improved hospital care or reduced disease severity. A recent study from Minnesota [89] has also concluded that improved hospital care had more impact in reducing mortality than prevention, at least for men. The present analysis also suggests that improved hospital care is the primary mechanism for decreased mortality. Major medical improvements in the last 15 years have been the routine use of thrombolytics, aspirin, beta blockers and angiotensin converting enzyme inhibitors. High risk patients are increasingly referred early for invasive evaluation and when appropriate revascularization which is perhaps further contributing to improved survival. The importance of wide access to acute cardiac care and progress in

shortening the delay before patients seek medical care may also be expected to have diminished mortality.

These mortality improvements have been achieved against a background of decreasing length of hospital stay. While the 1991 length of hospital stay for myocardial infarction had decreased by 40% compared to 1976, clinical experience suggests that substantial shortening of hospital stay has continued to occur since 1991.

It has been noted that practice patterns following myocardial infarction differ greatly between Canadian and American physicians [16,17,90]. For example, the threshold for cardiac catheterization post myocardial infarction is very low in the US and over 70% of this patient population now receives this intervention [90]. Canadian physicians are much more selective in the use of invasive procedures and they tend to more closely follow the evidence from randomized clinical trials[49,58]. Despite these practice variations, there have been no mortality differences noted in post hoc subgroup analysis of Canadian and American patients participating in randomized clinical trials. An improved quality of life in American versus Canadian patients following myocardial infarction has been attributed to the higher rates of revascularization [16], but the validity and significance of these claims have been questioned [3].

Against this background, it is interesting to compare the epidemiology of acute myocardial infarction in the US with these Canadian results. A recent

study[91] has reported cardiovascular mortality rates for American men and women age adjusted to the 1940 American population (RF Gillum, personal communication). The rates of hospitalization (per 100,000) for all patients with acute myocardial infarction were similar in the two countries for both those between 45-64 (497 US vs. 363 Canadian) and those over 65 (1270 vs. 1084). The age adjusted mortality rate for American white men and women in 1990 were 145/100,000 and 68/100,000 respectively. By comparison, transforming the 1991 Canadian mortality rates to the same American standard leads to comparable values of 130/100,000 and 58/100,000, respectively. Moreover, the average annual decreases in American cardiovascular mortality for 1980 to 1988 was 3.7% for white males, 3.1% for black males, 2.9% for white females and 2.2% for black females are very similar to, albeit slightly inferior to those of this study (see Table 5.1). Within the limitations of these crude data, this epidemiological view suggests that Canadian practice patterns surrounding the treatment of ischemic heart disease, including the more selective use of invasive cardiac resources, do not lead to poorer outcomes on a population level compared to the American experience. A recent population study comparing elderly Canadian and American post myocardial infarction patients has also confirmed no mortality differences despite much higher rates of invasive cardiac procedures [18].

It is important to realize the limitations of this data. The information that Statistics Canada receives for cause specific deaths comes from the provincial health ministries and its validity may be questioned. During this time period, the

ICD classification system was revised and although the codes for ischemic heart disease were largely unchanged, it is possible that this had a minor effect on the results. This study reports on all total cardiovascular mortality and provides no information on the division of in and out of hospital death rates nor on quality of life.

In conclusion, this national data from 1976 to 1991 suggests that clinical cardiology has achieved important progress in decreasing the morbidity and mortality of ischemic heart disease in the Canadian population. The mortality reductions appear to be due to a decreasing incidence of acute myocardial infarction and improved treatment but further community based studies are required to define their relative importance. This progress has been realized in the presence of shortening hospital stays and is comparable to what has been obtained in the United States. To better appreciate the importance of new treatment advances in this declining mortality we will next examine the Quebec in-hospital case fatality rate of myocardial infarction.

5.3) PROVINCIAL CASE FATALITY RATES FOR AMI

Ischemic heart disease and acute myocardial infarction (AMI) in particular, remains the leading cause of death for Canadians despite the observed decrease in the population based mortality from AMI demonstrated above. As

discussed in the preceding section, the decreasing mortality probably results from both a falling incidence, due to improved risk factor management and due to improved hospital care[6]. Regarding improved hospital care, by 1986 clinical trials among AMI patients had been published clearly showing the benefits of beta blockers [92,93], and thrombolysis [94]. Slightly later, a large clinical trial unequivocally demonstrated the benefit of aspirin in AMI[9]. More recently, trials of the early introduction of angiotensin converting enzyme inhibitors to AMI patients have shown improved survival[10,68,69]. It is of interest to assess the impact of these clinical trial results on a population level.

A population based analysis of death rates from AMI in Ontario hospitals from 1981 to 1991 has shown encouraging improvements in survival [11]. After age and gender adjustment, there was a 26.9% (99% confidence interval 26.8% to 26.9%) overall relative reduction in in-hospital case fatality rates during this period suggesting that the therapeutic improvements witnessed in clinical trials are being, at least partially, realized in routine clinical practice. The size of the mortality reduction was not as large as might be predicted from the clinical trials possibly due to the selection bias of less ill patients entering clinical trials and the incomplete penetration of proved therapies into routine practice. The present section seeks to determine if this same trend of improving in-hospital survival is present in Quebec, and also assesses the situation over a more recent time period.

The data for this thesis on the number of hospitalizations for AMI and the number of survivors came from the Quebec provincial administrative database,

MEDECHO, as described in Chapter Two. The database has been interrogated for the years 1985-86 until 1995-96 to identify each record involving a principal diagnosis of AMI, as defined by the ICD, 9th edition code 410. The patient status at discharge is registered so that in-hospital mortality rates (case fatality) can be measured. To reduce misclassification errors, hospital survivors of AMI discharged home in less than 4 days were excluded. Since age and sex are recorded, direct standardization (to the 1986 population) was possible [23].

The total number of hospital admissions for AMI increased from 13,534 to 14,332 over the decade 1986 to 1996 (see Table 5.3). However, the crude in-hospital case fatality rate decreased from 18.4% to 12.7% (adjusted rates from 18.4% to 11.5%) representing an absolute decline of 5.7% (adjusted 6.9%) and a relative decline of 31% (adjusted 37%). The absolute decrease in mortality for men and women was 5.2% and 6.4% respectively, while the relative decreases were greater in men than women (34.9% vs. 25.8%). In-hospital mortality rates were much higher for the elderly (> 65) and independent of the two age groups considered were higher for women (see Figure 5.3).

While all age and sex groups experienced falling in-hospital mortality rates, a close examination of the data shows some interesting time trends (see Table 5.4). The average yearly decline in mortality over the whole 10 year period was similar for both men and women under the age of 65. For men, this decline was relatively constant over the first and second half of the decade while for women the fall in mortality was much more pronounced in the second half of the decade (4.1% vs.

10.0%). The decrease in average mortality rates among the elderly was less impressive and differed between elderly men and women at 4.2% vs. 3.0% respectively. For elderly patients, more improvement in survival again occurred in the later half of the decade.

In summary, this study of the Quebec administrative hospitalization database from 1986 to 1996 has shown a decline of in-hospital mortality for AMI from 18.4% to 12.7%. The average yearly decline in mortality has been similar between men and women but reduced among the elderly. An examination of the time trends suggests that the largest improvement in survival for both women and the elderly have occurred in the last five years.

This chapter extends our knowledge about the epidemiology of hospital management of AMI by examining the previously unstudied Quebec population. The major finding is a declining in-hospital mortality rate comparable to that reported in Ontario hospitals from 1981 to 1991 [11]. This study suggests that in-hospital mortality has continued to fall since 1991. The magnitude of the decrease from 1986-96 is slightly larger than that reported in Ontario for the period 1981-91. Although differing populations could theoretically explain these differences, the time trends seen in this data suggest that the continued decline is perhaps most likely due to the extension of previously proven treatment strategies to women and the elderly.

Year	No. hospital admissions for AMI	In-hospital mortality (%)	Adjusted * in-hospital mortality (%)	% Mortality for men (adjusted)	% Mortality for women (adjusted)
95-96	14332	1824(12.7)	11.5	9.7 (8.6)	18.4 (16.9)
94-95	13972	1877 (13.4)	12.3	10.2 (9.1)	19.6 (18.0)
93-94	13947	1954 (14.0)	12.9	10.3 (9.5)	20.9 (19.5)
92-93	13911	1998 (14.3)	13.1	11.0 (10.0)	20.5 (18.7)
91-92	13636	2124 (15.6)	14.5	12.3 (11.4)	21.4 (20.2)
90-91	13141	2156 (16.4)	16.4	12.8 (12.6)	23.3 (23.5)
89-90	13068	2199 (16.8)	17.2	13.0 (13.2)	24.0 (24.6)
88-89	13398	2451 (18.3)	18.3	14.4 (14.3)	25.5 (25.8)
87-88	13774	2559 (18.6)	18.3	14.6 (14.4)	26.0 (25.4)
86-87	13534	2491 (18.4)	18.4	14.9 (14.9)	24.8 (24.8)

* age and sex standardized to the 1986 population

Table 5.3. The number of admissions and in-hospital mortality for men and women in Quebec hospitals from 1986 to 1996.

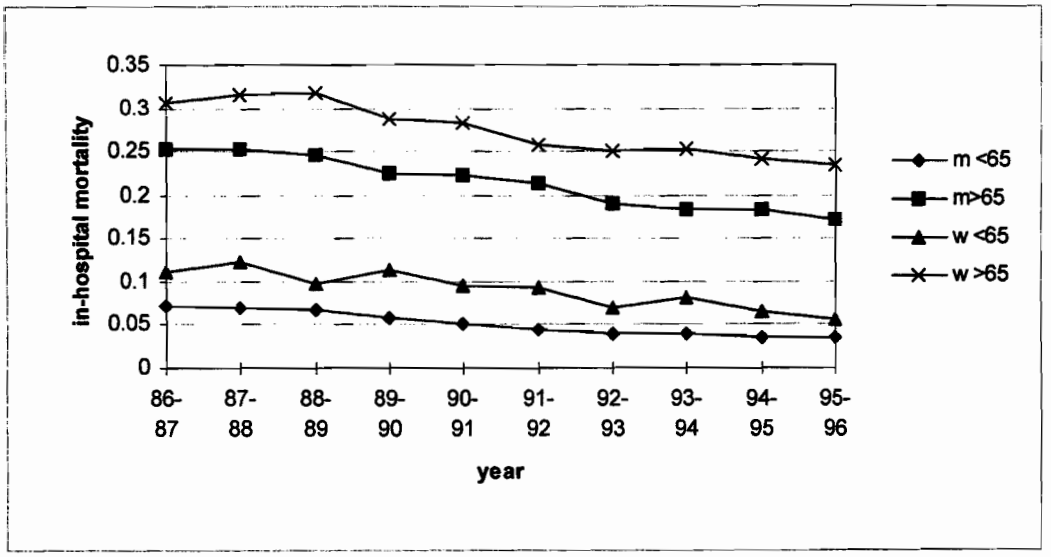


Figure 5.3. Plot of yearly in-hospital mortality rates for different groups of patients according to age and gender for the period 1986-96.

Average yearly mortality decline	men <65	men >65	women <65	women >65
period 86-96	7.60%	4.20%	7.40%	3.00%
period 86-91	8.00%	3.10%	4.10%	2.00%
period 91-96	7.20%	5.10%	10.00%	3.70%

Table 5.4. Summary of the time trends for average yearly percentage decline in-hospital mortality according to age and gender for patients admitted with AMI in Quebec hospitals.

Individual randomized trials of thrombolysis[9] have had the statistical power to demonstrate overall mortality benefits but were not large enough to firmly establish benefits for particular patient subgroups. This may partly explain why previous research in both Europe [95] and the United States [96] has suggested that certain subgroups including the elderly and women may less frequently receive established treatments such as thrombolysis. However, a recent meta-analysis of all the large scale thrombolytic trials has shown a treatment advantage for all patient groups [48]. The present data indirectly suggests that this anomalous situation of preferentially treatment of specific groups is being gradually reversed, at least in Quebec hospitals, and that a wider diffusion of proven therapeutic successes is occurring . However, definite conclusions about the appropriateness of thrombolysis in this cohort would require blinded data extraction from the medical charts to be analyzed by an expert panel using accepted national treatment guidelines.

The major limitation of this study is that the validity of this database has not been previously verified for cardiology diagnoses. However, other Canadian provincial hospital databases have verified the validity of primary cardiovascular diagnoses [24]. In addition, the absolute total mortality for the overlapping years with the Ontario study [11] show similar results (1991 - 17.1% vs. 16.4%, 1989 - 18.9% vs. 18.3%). Further, the mortality for AMI as measured from the FRSQ hospital clinical registry for the period 1995-96 was found to be similar to that calculated from this database (see next section). Finally, the validity of this administrative database in

recording the number of cardiac procedures, such as angioplasties and coronary artery bypass surgeries, has been examined and a good correlation found with that obtained by direct hospital survey [25].

In conclusion, this data provides useful information about recent trends in hospital mortality following admission with a diagnosis of AMI. It appears that a continuing application of proven treatment strategies to a widening patient population is perhaps responsible for a large portion of the ever declining in-hospital mortality. However, in assessing the use of medical therapeutics and practice patterns, this administrative database is clearly insufficient. First of all, the use of pharmaceuticals, like thrombolytics, are not recorded. Furthermore, despite the presence of secondary diagnoses, there is no validated method of calculating disease severity and relevant comorbidity. The further exploration of some of the potential factors responsible for declining in-hospital mortality, such as thrombolysis, requires a detailed clinical database, as described in the following section.

5.4) THE FRSQ ACUTE ISCHEMIC CLINICAL REGISTRY

As discussed in Chapter Two, the FRSQ registry collected clinical data on 8917 patients with acute ischemic syndromes admitted to 40 acute care Quebec hospitals. A final diagnosis of AMI and unstable angina was made in 3741 (42%) and 3341 (37.5%), respectively. Another diagnosis, including but not limited to

stable angina and atypical chest pain, was made in 1605 (18%) and in 230 (2.5%) the final diagnosis was missing (Table 5.5).

Men comprised 63% of the population, women 35% and in 2% gender was missing. The average age of the women was significantly older than for the men (68 (SD 12) vs. 61 (SD 12), $p<0.001$). The time of onset of symptoms was recorded in 2556 (68%) of AMI patients and showed an excess of events between 06:00 and 12:00 (32%, where 25% might have been expected) which is concordant with the well established circadian variation of ischemic heart disease. Not surprisingly, conventional risk factors for acute coronary events were common; previous myocardial infarction 36%, smoking 45%, diabetes 20%, high blood pressure 39% and hypercholesterolemia 33%.

Among the 3741 patients with AMI, 2133 (24%) had a Q wave on their ECG while the remainder had a non-Q wave myocardial infarction for whom there is a consensus that thrombolysis is not indicated[97]. Current criteria for thrombolysis specify that the ECG show significant ST elevation, typically greater than 1 mm. Generally such ECG changes will result in the development of a Q wave a few hours later. However among patients with a final diagnosis of Q wave AMI, 369 (18%) were considered to not have the necessary ECG criteria on admission for thrombolysis. Other reasons reported for not receiving thrombolysis included the following, where a patient may have more than one justification: delayed presentation (312, 15%), advanced age (76, 4%), intention to perform primary angioplasty (44, 2%) and other non-specified reasons (132, 6%).

	AMI n=3741	UA n=3341	Other n=1605
Men / women	70 / 30	63 / 37	55 /45
Age (median +/ IQR)	64	65	64
Systolic BP (median +/ IQR)	140	150	142
Dyslipidemia	33	41	33
Smoking	44	30	30
Diabetes	21	23	21
Previous MI	29	45	40
Previous CABG	9	20	17
Previous CVA	7	7	8
Peripheral vascular disease	12	16	13
Pre-admission ASA	27	56	43
Pre-admission ACE	12	17	17
Pre-admission BB	18	41	27

entries are in percentages: AMI= acute myocardial infarction UA= unstable angina CVA = cerebral vascular accident, ASA = aspirin, ACE = angiotensin converting enzyme, BB = beta blockers, IQR = inter-quartile range, CABG = coronary artery bypass graft

Table 5.5 Patient characteristics of the FRSQ clinical registry according to the final diagnosis

A total of 1357 patients received thrombolysis and the next two chapters will analyze in depth the delay to treatment and the choice of thrombolytic agent employed in this sample. Chapter Six will analyze the various levels of delay to the administration of thrombolysis and seek to establish their determinants. Chapter Seven will explore the patient, physician and hospital characteristics which influenced the choice of thrombolytic agent in this cohort.

CHAPTER SIX THE DELAY TO THROMBOLYSIS

6.1 INTRODUCTION

As reviewed earlier, large clinical trials have definitively shown the value of thrombolysis in acute myocardial infarction (MI) [5,8,9] and that the benefit of this therapy can be maximized with earlier treatment [2,48,50,62].

The penetration of the clinical trial results concerning the benefits of thrombolysis into routine practice has increased with time. In the late 1980's about 20% of American AMI patients received thrombolysis but more recently 35% of European AMI subjects were treated [95]. The majority of untreated patients did not fulfill the necessary criteria but this study suggests that, for unclear reasons, this therapy has not fully permeated clinical practice as some eligible patients remain untreated [95]. Moreover, important delays in the administration of this therapy have been observed. These delays may reduce the efficacy of thrombolysis by increasing not only mortality [98] but also morbidity [99]. In an attempt to rectify this, clinical guidelines have been propagated to assist in the identification of appropriate patients for treatment [97]. These guidelines have also set benchmarks for delays in drug administration of 60 minutes from symptom onset and recently 30 minutes has been advanced as the standard [100].

As described in detail in the Chapters Two and Five, the Quebec Acute Coronary Care Working Group established a prospective registry of all patients admitted with a diagnosis of acute coronary syndromes in order to evaluate the performance of acute care hospitals in the delivery of thrombolysis. Subsequently the individual and global results were supplied to the participating centers and it is hoped that this feedback may help address any local problems identified.

This chapter presents the main findings of this analysis and is the first to describe the detailed components of the delay to thrombolytic treatment in routine practice over a large spectrum of Quebec hospitals. The components of delay are referred to as the 4 D's, and include the time from symptom onset to arrival at the emergency room (Door), the time to obtain a diagnostic ECG (Data), the time for the medical decision (Decision) and finally the time to prepare the thrombolytic (Drug). In addition, the hospital and patient determinants of these delays have been assessed. The data were prospectively collected and reflect recent practice patterns. Finally, by including the full spectrum of patients presenting with acute MI, this registry mirrors the "real world" more comprehensively than the post hoc analyses of clinical trials which are often limited to specific subgroups of patients and which may have superimposed protocol constraints .

6.2 RESULTS

During the period of observation, data were collected from 8917 patients admitted with a suspected acute ischemic syndrome. A final diagnosis of acute myocardial infarction was made in 3741 patients of whom 1357 (36%) received thrombolytic therapy in 40 different hospitals.

The patient characteristics of this thrombolytic cohort are displayed in Table 6.1. Seventy-four percent of patients were men and the average age was 60 years. Streptokinase (SK) was used in 68% of cases and tissue plasminogen activator (t-PA) in the remainder. Slightly more than one fifth of patients had a previous history of myocardial infarction. As expected, the prevalence of the conventional risk factors was high. Dyslipidemia, hypertension and diabetes requiring medical therapy were present in 32.6%, 30.1% and 14.7%, respectively. Current smokers represented 55.4% of the cohort.

Demographic data of age and sex was missing in 1 (0.1%) and 33 (2%) patients, respectively. Information on patient characteristics were missing more frequently and may be calculated as shown in the footnote to Table 6.1. Smoking status was the most commonly missing patient variable (11%). Unfortunately, the different components of the time intervals were missing for 15% of the patients.

The median time from the onset of pain until arrival at the emergency room was 98 minutes (IQR 56-180) (Table 6.1). The median delay to the

Sex (m/f)	978 / 346
Age (years)*	60.2 +/- 12.3
Previous MI (%)	273 (21.3)
Presently smoking (%)	667 (55.4)
Diabetes (%)	188 (14.7)
High blood pressure (%)	389 (30.1)
Dyslipidemia (%)	405 (32.6)
Anterior MI (%)	502 (38)
Agent (SK/t-PA)	925 / 432
Time[+] from symptom onset to ER arrival	98 (56-180)
Time from ER arrival to diagnostic ECG	15 (8-28)
Time from diagnostic ECG to thrombolytic decision	12 (4-27)
Time from thrombolytic decision to drug administration	22 (15-34)
Time in hospital to thrombolysis (total)	59 (41-89)
Time from symptom onset to thrombolysis (total)	172 (115-270)

Table 6.1. Characteristics of the complete thrombolytic cohort (n=1357)[#]

[#] due to missing values each entry may not total to 1357. Sex was missing for 4 patients, age for 1 patient and the number of missing data entries for the other patient characteristics may be calculated as follows:
e.g. missing for previous MI = 1357 - (273/.213) = 75 patients, and so on
* mean +/- standard deviation
[+]all time intervals are minutes expressed as median with interquartile range
MI = myocardial infarction
SK = streptokinase
t-PA = recombinant tissue plasminogen activator
ER = emergency room

administration of thrombolytics was 59 minutes (IQR 41-89) with substantial delays evident at all levels of the process. The time to obtain the diagnostic ECG was 15 minutes (IQR 8-28). Physician decision making including history, physical examination and ECG interpretation required a median of 12 minutes (IQR 4-27) and the preparation of the thrombolytics accounted for 22 minutes (IQR 15-34). The site of thrombolysis (emergency room vs. the coronary care unit) was not systematically recorded.

Table 6.2 shows the effect of hospital specific characteristics on the total hospital delay and its various components. Tertiary centers performed slightly better than community centers at each level of the process, although the only statistically significant difference was in more rapidly obtaining the ECG leading to a 3 minute improvement in overall door-to-needle time ($p<0.05$). If the decision to administer thrombolysis was taken by a cardiologist, the time for a diagnostic ECG, the decision time and the total time were prolonged by 3, 5 and 13 minutes ($p<0.001$), respectively .

Low volume centers were defined a priori as hospitals whose volume was in the lowest quartile of the distribution of patients thrombolysed per center. This cut-off point was 23 patients treated per center per year. Nineteen centers treating a total of 143 patients were thus identified as low volume centers. These centers had marginally slower performance at each stage of the process and the cumulative in-hospital delay was increased by 11 minutes ($p<0.01$).

	Hospital affiliation		Physician status		Volume of activity	
	Tertiary (n=478)	Community (n=879)	ER physician (n=706)	Cardiologist (n=613)	High volume centers (n=1214)	Low volume centers (n=143)
Time to ER	101 (60-180)	95 (55-180)	95 (60-180)	102 (54-180)	100 (59-180)	90 (50-180)
Time for ECG	12 (6-25)	15*** (9-29)	13 (7-23)	16 ***(10-35)	14 (8-27)	15 (7-29)
Decision	11 (3-27)	13 (5-27)	10 (3-23)	15***(6-33)	12 (4-26)	15 (4-38)
Drug	20 (15-31)	23 (15-35)	22 (15-34)	22 (15-35)	22 (15-34)	25 (15-36)
Time in hospital [1]	57 (36-86)	60*(44-90)	53 (40-78)	66*** (45-110)	58 (41-87)	69 **(48-111)
Total time [2]	164 (110-270)	175 (117-270)	158 (110-250)	180*** (125-290)	170 (115-269)	187 (115-339)

Table 6.2. Median delays in minutes with inter-quartile ranges according to hospital specific characteristics.

[1] Time in hospital = Σ time (ECG + decision + drug)
[2] Total time = sum of all above components
n = number of patients eligible in each category. N.B. totals may not add to 1357 patients due to missing data
ER = emergency room
Statistical tests (Wilcoxon 2 sample test) are between comparable groups (e.g. community vs. tertiary hospital, cardiologist vs. ER physician, low vs. high volume centers).
* $p<0.05$
** $p<0.01$
*** $p<0.001$

	Gender		Age		Previous MI	
	men (n=978)	women (n=346)	<=65 (n=835)	>65 (n=521)	no (n=1008)	yes (n=273)
Time to ER	90 (51-172)	120*** (70-210)	83 (50-160)	120*** (65-200)	98 (57-180)	98 (55-192)
Time for ECG	14 (8-28)	15 (8-27)	14 (8-26)	15 (8-30)	15 (8-27)	15 (8-30)
Decision	11 (3-26)	17*** (7-30)	11 (4-25)	15*** (5-32)	12 (4-26)	15* (5-36)
Drug	22 (15-35)	25 (15-35)	22 (15-34)	23 (15-35)	22 (15-33)	22 (15-35)
Time in hospital [1]	57 (40-88)	65*(46-93)	55 (40-85)	65*** (47-93)	57 (40-85)	66*** (46-96)
Total time [2]	160 (110-265)	190*** (135-300)	155 (105-252)	195*** (135-311)	169(113-260)	185* (128-307)

Table 6.3. Median delays in minutes with inter-quartile ranges according to patient specific characteristics.

[1] Time in hospital = Σ time (ECG + decision + drug)
[2] Total time = sum of all above components
n = number of patients eligible in each category. N.B. totals may not add to 1357 patients due to missing data
ER = emergency room
Statistical tests (Wilcoxon 2 sample test) are between comparable groups (e.g. men vs. women, age <65 vs. >65, no vs. previous MI)
* $p<0.05$
** $p<0.01$
*** $p<0.001$

The patient characteristics associated with delayed arrival and longer in-hospital time to treatment are shown in Table 6.3. Women and the elderly presented significantly later after symptom onset. Diabetics also presented later to the emergency room (median time 119 vs. 95 minutes, $p<0.01$) but experienced no additional in-hospital delays (data not shown in Table 6.3). However, medical decision making was prolonged for women, the elderly and previous MI patients with median delays of 6, 4 and 3 minutes ($p<0.05$), prolonging total in-hospital times by 8 ($p<0.05$), 10 ($p<0.001$) and 9 ($p<0.001$) minutes, respectively. Neither the choice of thrombolytic agent nor the infarct location (anterior vs. inferior) influenced any of the delay components.

The above variables were highly correlated. For example, comparing patients under and over 65 demonstrated an increased percentage of women (18.7% vs. 37.8%) and patients with a previous MI (16.0% vs. 29.0%). A multivariate logistic regression model, using backward stepwise elimination, recognized these correlations and revealed only age (odds ratio 1.5, 95% CI 1.3- 1.7) and a thrombolytic decision by a cardiologist (odds ratio 1.8, 95% CI 1.6 - 2.0) as being independently associated with an increased delays (beyond in the upper median of 60 minutes of in-hospital delay).

6.3 DISCUSSION

This chapter has described the delays in the administration of thrombolytics to 1357 patients presenting to a broad sample of Quebec acute care hospitals, including tertiary, community, urban and rural hospitals. Significant delays have been noted at all the various stages of the treatment process (Table 6.1). Hospital and patient characteristics associated with increased delays have been identified.

The major delay in instituting treatment is the reluctance of patients to present promptly to the emergency room when they experience characteristic prolonged cardiac symptoms. Even patients with previous infarctions, who presumably have all received the conventional physician advice to present rapidly if symptoms persist beyond 15-20 minutes, appear to resist punctual consultation. In particular, women and the elderly seem to endure symptoms longer and hesitate more before consultation. The greater delay in seeking treatment noted in diabetics has not been previously highlighted and an appealing pathophysiological hypothesis is that a diabetic sensory neuropathy causing symptom attenuation may be responsible.

Fifty percent of this cohort received thrombolysis within one hour of hospital presentation. This is a significant improvement over the results of Cox et al. [99] who reported that 75% of patients enrolled in Canadian hospitals in the GUSTO-1 trial waited more than one hour before treatment. Since the GUSTO-1 data was collected in 1991-1992, it is unclear how much of this improvement is due to increased awareness of the importance of rapid treatment. The GUSTO data may have also

provided inflated measures of contemporary delays by adding its own intrinsic delay related to enrollment and its research protocol. Nevertheless, less than 25% of our cohort received thrombolysis in the ideal 30 minute period currently recommended[100].

This study has permitted an in-depth analysis of the hospital components of the delay to treatment. The median time between a patient presenting to the emergency room with chest pain and obtaining an ECG is 15 minutes (IQR 8-29). The median of 22 minutes for drug preparation seems inordinately long and efforts should be directed at greatly reducing this interval.

The medical decision making process, which includes an adequate history, a search for possible contraindications to thrombolysis, physical examination and interpretation of the ECG, takes a median of 12 minutes (IQR 4-27) which seems appropriate. While accepting that certain presentations are more difficult to assess, it is disconcerting to observe the statistically significant delays in decision making for women, the elderly and patients with previous myocardial infarctions; each being a high risk group. In the case of women and the elderly this amounts to double jeopardy as these groups also delay in presenting to the emergency room. The total median additional delays between symptom onset and thrombolytic therapy for women and the elderly are 30 and 42 minutes respectively and may partly contribute to the known increased in-hospital mortality for these groups.

Decision making which involves a cardiology consultation increased total in-hospital delays by a median of 13 minutes ($p<0.001$). It would be fallacious to

interpret this p value as the probability of the null hypothesis (no difference between cardiologist and ER physicians) being true or equivalently the probability of making an error in rejecting the null hypothesis[30]. It has been shown previously that cardiologists are more aware of and use more frequently clinically proven, evidence based medical therapies including thrombolysis compared to primary care physicians [101,102] and it appears reasonable to assume that they should also be rapid decision makers. Certainly not all patients eventually receiving thrombolysis present initially with a clear cut indication and the delay associated with a cardiologist decision maker may be a marker for these more complex cases. This view is supported by the significantly prolonged delay to acquire the diagnostic ECG ($p<0.001$), implying that earlier ECGs were perhaps ambiguous. From a Bayesian perspective, these arguments imply a very low prior probability that cardiologists would be poorer performers and the present data is by no means strong enough to contradict this prior belief[2].

It is therefore possible that the additional delay associated with cardiology involvement is appropriate to evaluate more complex cases but this cannot be proven from this data. While the clinical significance of this supplemental delay is uncertain and perhaps well justified for difficult cases, it also sends a warning that local institutions must examine their performance to ensure that specialty consultation does not unnecessarily prolong door-to-needle times for routine cases. Cardiologists are not systematically present in the emergency room, consequently evaluation and therapy can be most efficiently begun by the emergency room physician. Simultaneous cardiology consultation while patient evaluation is underway is one means of

permitting specialty involvement, if required by the complexity of the case without incurring further delays. Other institutional characteristics associated with increased delays are community hospitals and low volume centers.

The limitations of this study should be appreciated. While the data for this registry was entered by trained research nurse coordinators and validated when entered in the data base, financial constraints prevented external validation of the source documents from being performed. Nevertheless, it seems reasonable to assume that the large size of the cohort (nearly 9000 patients) implies that most potential patients were included limiting systematic biases in patient selection. The length of the data acquisition (12 months for each center) makes a large "Hawthorn" effect (improved performance since centers knew they were being monitored) unlikely. As discussed above, patients may present initially with a non-diagnostic ECG requiring serial recordings which may artificially inflate the measured delays between admission and thrombolysis. Although there were no obvious systematic biases in the missing time data, this incompleteness obviously limits the strength of our conclusions.

Finally, this data does not permit any conclusions about the appropriateness of thrombolysis in this cohort. The ideal methodology would require blinded data extraction from the medical charts not only of patients receiving thrombolysis but of all potential candidates. This data should then be analyzed by an expert panel using accepted national treatment guidelines [103]. A study of a random sample of 4035 patients with AMI treated in 11 European countries from 1993 to 1994[95] has

attempted to examine the appropriateness of therapy. While this study did not employ the rigorous methodology described above, they nevertheless performed a systematically chart review and determined that 35% of their cohort received thrombolysis and an additional 20% appeared eligible but were untreated. The remaining patients did not fulfill the accepted clinical criteria. The percentage of AMI patients receiving thrombolysis in the Quebec registry is identical but the appropriateness level is unknown.

From a public health perspective, it appears that renewed efforts are required to understand why patients delay presenting to emergency rooms when they are experiencing typical prolonged cardiac symptoms. The importance of cognitive (correctly attributing the ischemic origin of the symptoms) and affective (higher anxiety and comfort in seeking medical care) responses in decreasing the length of delay before seeking medical attention has been recognized [104]. However, the interaction between patient demographic, personality traits, social structures and the health care system is very complex and clearly requires more extensive research.[105]. Our study suggests that these efforts should be particularly directed at women, the elderly, diabetics and former MI patients. Physicians must continue to educate their patients about the importance of promptly seeking medical care for suspected cardiac symptoms but should also be aware of possible barriers potentially limiting the effectiveness of this intervention.

In general, the time for physician decision making appears adequate but efforts must be made to guarantee that all patient groups receive prompt treatment.

However, a large part of the delay in commencing thrombolytic treatment arises from beyond the medical decision making process. To combat these delays, physicians must stress the importance of rapid treatment to all health care professionals and assist in the organization of emergency rooms to facilitate the rapid collection of data and preparation of thrombolytics. Institutions with low volumes may need special attention. Further studies will be required to better understand the mechanisms of the delays identified in this study.

CHAPTER 7 THE CHOICE OF THROMBOLYTIC AGENT

7.1 INTRODUCTION

The aim of this chapter is to describe the patient, physician, and hospital characteristics that determine the choice of thrombolytic agent in the treatment of patients with acute myocardial infarction (MI). Previous studies have concentrated on evaluating the appropriateness of the medical decision to give or withhold thrombolysis, while in Chapter Six I discussed delays to thrombolysis. However, there has been no previous work into understanding the medical decision process involved in choosing a particular thrombolytic agent.

As discussed in detail in Chapter 4, disparate findings from the clinical trials have produced enormous controversy in the medical literature over the choice of the "best" agent [2,5,54,55,61,106]. While this controversy largely settles on how to reconcile the totality of evidence, it is undoubtedly fueled, at least in part, by the large price differences between the two agents. It is unknown how practicing clinicians have interpreted this conflicting clinical information about the relative effectiveness and costs of the different therapeutic agents and integrated it in to their routine practice.

It is well established that physician practice pattern variations exist in cardiovascular medicine at both the international [16-18,60,90] and national levels[19,20,107,108]. Within a given health care system, much of the variation can be explained by patient, physician and hospital characteristics. Among myocardial

infarction patients, specific patient characteristics potentially influencing resource utilization, including the choice of thrombolytic agent, are disease severity and patient demographic factors such as age and sex. Physicians characteristics that may affect resource decisions include specialty training and region of practice [17,19,90,101,102]. Finally, hospital status (university or community), location (urban or rural) and the volume of activity may influence the delivery of cardiovascular care [109,110].

Previous studies have concentrated on identifying patient groups not receiving thrombolytic therapy [95,96] but have incidentally revealed large international variations in the selection of these agents. In Europe, the ratio of SK to t-PA is about 7:1 (personal communication P. Sleight, K. Woods), while in the United States the ratio is 1:3 in favor of t-PA[111]. Canada has a universal health care system similar to most European countries, but also has strong medical ties to the United States and therefore the relative use of these two agents is presumed to fall between these two extremes.

Herein, I report the results from an analysis from the FRSQ clinical registry of patients with acute myocardial infarction, in an attempt to understand the practice patterns surrounding the care of acute coronary syndromes. This registry permitted an examination of how patient, physician and hospital characteristics influence the choice of thrombolytic agent. The multivariate hierarchical random effects model with four levels, as described in Chapter 2 has been employed.

To my knowledge, no other study has examined this process of medical decision making. Given the high costs of treating myocardial infarction and its

complications, it is important to understand how physicians choose their thrombolytic agent. This will become even more important as new agents presently being studied eventually are delivered to the marketplace[112].

7.2 RESULTS

During the period of observation data was collected from 8917 patients admitted with suspected acute ischemic syndromes. A final diagnosis of acute myocardial infarction was made in 3741 patients, of whom 1357 received thrombolytic therapy in 40 different hospitals. SK was given to 925 (68%) patients and t-PA to 432. Complete information for all variables was available for 1165 (86%) patients. A comparison between patients with and without missing values did not reveal any systematic differences in the available data.

The patients were treated in 40 different hospitals composed of urban (n=15) and rural (n=25) institutions. Nine were tertiary care hospitals and eight others had some degree of university affiliation. Urban hospitals contributed 549 (47.1%) of the patients and 391 (33.6%) were hospitalized in tertiary centers. Of patients treated in urban centers, 35.0% (192 patients) received t-PA compared to 29.1% (179 patients) in rural centers (difference =5.9%, 95% CI = 0.3%-11.4%). Patients in tertiary institutions (n=391) received t-PA more commonly than patients in non-tertiary centers (43.0% vs. 26.2%, difference = 16.8%, 95% CI 10.7% - 22.7%). Figure 1 is a

plot of the percentage use of t-PA as a function of the number of cases of thrombolysis for each hospital. There is a very wide variation in the institutional use of t-PA but no obvious association between use of t-PA and volume of activity.

The patient and physician characteristics are displayed in Table 7.1. Overall, 73.9% of the patients were male, with a similar sex distribution in both thrombolytic groups. Compared to SK patients, those administered t-PA were younger, and on average had lower systolic blood pressures on admission, an increased likelihood of a past history of prior myocardial infarction or an anterior infarction, and more frequently had a cardiologist make the therapeutic decision for thrombolysis. Among those receiving SK, diabetes was more common, but known hyperlipidemia and prior treatment with ASA or beta-blockers were less prevalent. Smoking, previous history of hypertension, prior stroke or coronary artery bypass surgery and use of angiotensin converting enzyme inhibitors were approximately equally prevalent among the two groups.

A standard fixed effects logistic regression analysis of the patient characteristics predictive of the selection of a specific thrombolytic agent was first performed (using SAS version 6.1). The results from this analysis were identical, (odds ratios within .1, data not shown) to the results from the fixed effects model using the BUGS software which are now presented and displayed in Table 7.2. The odds of receiving t-PA were decreased for elderly patients (OR 0.67, 95% CI 0.58-0.77) and those receiving treatment beyond six hours after the start of symptoms

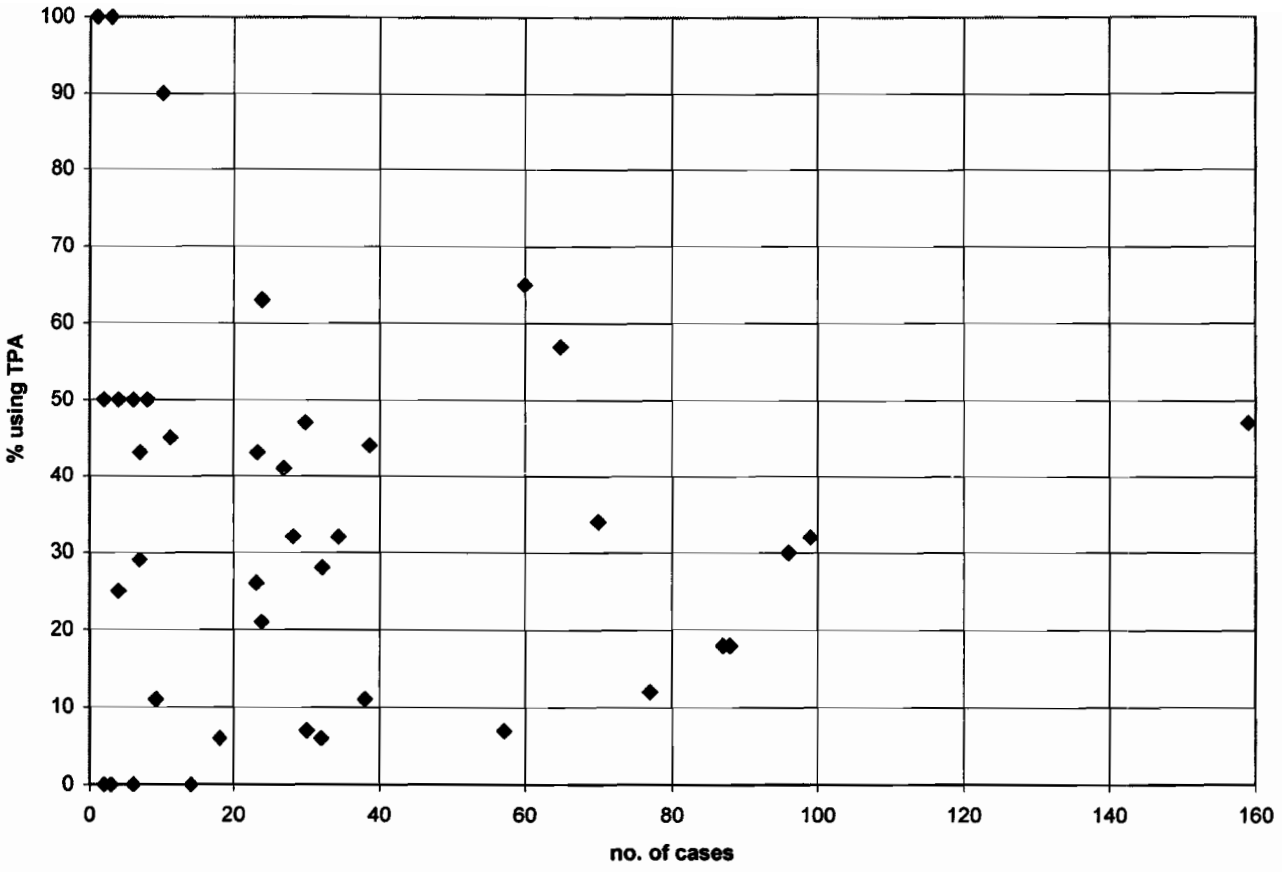


Figure 7.1. Plot of percentage use of t-PA as a function of thrombolytic caseload for each participating hospital.

	SK (n=794)	t-PA (n=371)	Difference SK - t-PA (95% CI)
men/women (%)	73.8/26.2	74.9/25.1	-1.1 (-6, 4)
median age years (IQR)	62 (51-70)	58 (50-68)	4 (2.5, 5.5)
>age 65 (%)	40.2	34.2	6.0 (0.1, 12.0)
median systolic BP on arrival (IQR)	140 (125-160)	135 (110-160)	5.0 (1.0, 9.0)
anterior MI (%)	33.8	50.1	-16.3 (-10.0, -22.5)
previous MI (%)	17.4	29.4	-12.0 (-6.6, -17.6)
cardiologist decision maker (%)	43.8	52.8	-9.0 (-2.7, -15.3)
time from pain to thrombolysis >6hr (%)	16.6	11.1	5.5 (1.1, 9.8)
diabetes (%)	16.2	11.1	5.1 (1.2, 9.8)
previous use of aspirin (%)	19.3	25.9	-6.6 (-1.1, -12.0)
previous use of β blockers (%)	12.7	17.7	-5.0 (-0.3, -9.7)
previous history of hyperlipidemia (%)	28.7	36.8	-8.1 (-2.1, -14.1)
previous history of hypertension (%)	30.5	26.6	3.9 (-1.8, 9.6)
previous history of CABG (%)	3.4	4.5	-1.1 (-3.7, 1.5)
previous history of ACE-I (%)	8.3	9.1	-.8 (-4.5, 2.9)
BP on arrival < 120 mmHg	23.0	34.5	-11.5 (-5.6, -17.3)
tobacco use (%)	56.6	51.2	5.4 (-0.1, 11.7)
previous history of CVA (%)	4.2	3.3	.9 (-1.6, 3.3)

Table 7.1. Characteristics of the thrombolytic cohort with no missing values (n=1165)
IQR = interquartile range
MI = myocardial infarction
SK = streptokinase
t-PA = tissue plasminogen activator
CABG = coronary artery bypass grafts
CVA = cerebral vascular accident
ACE-I = angiotension converting enzyme inhibitors

Variable	no hierarchy (fixed effect model)			simple hierarchy (random effects model)		
	posterior means of the β coefficients	odds ratio (e^{β})	odds ratio 95% CI	posterior means of the β coefficients	odds ratio (e^{β})	odds ratio 95% CI
age >65	-0.403	0.67	.58-.77	-0.614	0.54	0.44-0.67
anterior MI	0.802	2.23	1.95-2.56	1.100	3.00	2.42-3.73
time > 6 hours	-0.563	0.57	.47-.69	-0.587	0.56	0.44-0.71
previous MI	0.814	2.26	1.92-2.65	0.826	2.28	1.82-2.86
low BP (<120 systolic)	0.629	1.88	1.62-2.17	0.741	2.10	1.75-2.51
cardiologist decision maker	0.397	1.49	1.30-1.70	0.595	1.81	1.32-2.49
sex	0.038	1.04	0.89-1.21	-0.019	0.98	0.80-1.20

Table 7.2. Independent predictors of t-PA administration (odds ratios and 95% credible intervals) based on non-hierarchical and simple hierarchical models (n=1165)*

* 95% credible interval (CI) is the Bayesian analogue to confidence intervals. Note that the two types of credible intervals above have different interpretations. In the fixed effects model, the CI reflects uncertainty about each independent parameter value due to within hospital variation. In the random effects model, the 95% CI reflects uncertainty due to both within and between hospital variation.

(OR 0.57, 95% CI 0.47-0.69). On the other hand, the presence of an anterior infarction (OR 2.23, 95% CI 1.95-2.56), a previous myocardial infarction (OR 2.26, 95% CI 1.92-2.65), and a low blood pressure (OR 1.88, 95% CI 1.62-2.17) were independent predictors of receiving t-PA. Finally, the involvement of a cardiologist decision maker (OR 1.49 95% CI 1.30-1.70) was also an independent predictor of receiving t-PA. Gender, diabetes, other past medical history and previous medications were not independently associated with the choice of therapy.

The above model assumes that the impact of each characteristic is identical across all hospitals. A more realistic random effects or hierarchical model would account not only for within but also between hospital variations. Results from this random effects or hierarchical model do not substantially alter the point estimates of the above regression parameters, but the credible intervals (Bayesian analogs of standard confidence intervals) are generally wider since both the between and within hospital variations are now included (see Table 7.2). The width of the credible intervals belonging to the cardiologist decision maker and the ECG site of the infarction increased by the largest amount, signifying the importance of the between hospital variations for these factors.

I next examined the information collected about the participating hospitals, including their volume of activity, geographic location and university status, to see if these characteristics could explain the between hospital variations in the above parameter estimates. Overall, tertiary (university) hospitals systematically had higher

rates of t-PA use. However, tertiary status did not alter the individual patient model coefficients described above.

None of the hospital level variables investigated could explain why patients with low blood pressure on admission had an increased probability of receiving t-PA. The model, however, does predict that as the number of cases of thrombolysis increases in a hospital there are more stringent selection criteria for the administration of t-PA. For example, there is a decreasing chance of older patients and those arriving after six hours receiving t-PA, the odds ratios for receiving t-PA for older patients in low volume hospitals (15 cases/year) was 0.72 (95% CI 0.52-0.98), which decreased to OR = 0.40 (95% CI 0.29-0.54) in high volume institutions (90 cases/year). Patients presenting beyond six hours in low volume hospitals had OR = 0.78 (95% CI 0.53-1.16) compared to OR = 0.44 (95% CI .34-.57) for high volume hospitals. Similarly, the importance of a cardiologist decision maker was attenuated in hospitals with high (OR 1.37, 95% CI 0.86-2.20) versus low caseloads (OR 2.27, 95% CI 1.44-3.58).

The geographic location of the hospitals had an important impact on two patient predictors. While both urban and rural hospitals gave t-PA more frequently to patients with prior myocardial infarction, this was more pronounced for urban compared to rural centers (OR 2.86, 95% CI 2.00-4.08 vs. OR 2.02, 95% CI 1.46-2.80, respectively). The biggest difference in the selection of a thrombolytic agent between urban and rural centers was the importance accorded to the electrocardiographic location of the infarction. An anterior myocardial infarction in a

rural hospital increased the odds of receiving t-PA by 1.66 (95% CI 1.29-2.13), but this was raised to 6.55 (95% CI 5.02-8.56) in urban hospitals.

Supposing that an odds ratio > 1.25 represents a meaningful difference in the selection criteria for a thrombolytic agent, this model predicts that 80% of hospitals would favor giving t-PA to younger patients. Similarly, the percentage of hospitals that would preferentially apply t-PA (odds ratio > 1.25) to anterior infarcts, previous infarcts, patients with low blood pressures and to early presenters is 92%, 83% , 95% and 78% respectively.

7.3 Discussion

The hierarchical analysis presented here has provided insights into the patient, physician and hospitals characteristics determining the choice of thrombolytic agents for patients with myocardial infarction in Quebec hospitals. The independent patient characteristics predicting an increased probability of receiving t-PA include younger age, an anterior myocardial infarction, low presenting blood pressure, a previous myocardial infarction, arrival within six hours of symptom onset and a cardiologist decision maker. It is interesting to compare these decisions with evidence-based results from the medical literature.

A synthesis of the comparative trials of the two main thrombolytics, SK and t-PA suggests no [62] or little difference in mortality between the two agents[2]. However,

one trial [53] did find a mortality difference in favor of t-PA, and the uniqueness of their accelerated protocol and its non-comparability with previous studies has been emphasized. These differences of opinion have undoubtedly contributed to the observed differences in practice patterns. For example, on the international stage, the majority of patients (>85%) in Europe are treated with SK (personal communication P. Sleight and K. Woods) while t-PA is the dominant thrombolytic in the United States (>70%)[111]. The proportion of t-PA utilization may reflect a balance between this conflicting evidence of increased efficacy, societal opinions about escalating medical costs and the importance of cost effective ratios (t-PA is approximately eight times more expensive than SK).

The proportion of use of t-PA in this registry was 31.8%, which is intermediate between American and European rates. This result is not unexpected, since while the universal health care plan in Quebec is similar to most European countries, local practice patterns may be influenced by Canada's geographic proximity to the United States, and by the long standing relationship of collaborative research and post graduate training between these two countries.

While the GUSTO trial had a constant 14% relative reduction of adverse events across patient subgroups, it was the only trial to demonstrate a mortality difference between thrombolytics. Furthermore, the largest absolute gain was for patients with anterior myocardial infarction due to their higher baseline mortality (1.9% absolute reduction in death rate compared to 0.9% for the whole trial). A prior MI is also a significant predictor for increased mortality, so that the absolute

advantage of t-PA should again be maximized within this group. Therefore, current evidence suggests that the most appropriate use of t-PA is for patients with anterior or previous MI and Quebec physicians seem to concur, having adopted such a selective strategy. Finally, the GUSTO trial randomized patients only within six hours of symptom onset and no trial evidence exists to suggest a difference in outcomes between thrombolytic agents when given later. Physicians in our data appreciated this lack of knowledge as seen by the 42% reduction in the probability of receiving t-PA beyond six hours.

Although SK may cause transitory hypotension, which usually responds to a slight reduction in the rate of administration and volume expansion and should not prevent its administration [61], practitioners clearly have a tendency to choose t-PA in this situation. Obviously, hypotension may also be a marker for high risk individuals with extensive myocardial infarctions. Although no published information confirming the superiority of either agent in cases of hypotension exists, this trend was evident across the complete spectrum of hospitals studied.

In GUSTO, the absolute reduction in mortality with t-PA was relatively constant across different age strata (1.1% vs. 1.3% reduction in those under and over 75, respectively) but the accompanying GUSTO economic analysis demonstrated that the treatment of anterior MI with t-PA was much less cost-effective in younger patients [113]. The cost-effectiveness ratios ($/year of life saved) for anterior MI were $125,00, $45,000, $20,000 and $13,000 for patients under 40, between 41-60, between 71-75 and over 75 respectively. Clearly, Quebec physicians were not

influenced by this cost-effective analysis. Elderly patients had a significant 33% reduction in the probability of receiving t-PA (OR 0.67, 95% CI 0.58-0.77). This policy of selectively treating younger patients with t-PA has been recommended by leading authorities[88].

There is no clear explanation for the independent role of a cardiologist decision maker to the increased probability of receiving t-PA. It has been suggested that cardiologists are more aware of and make more frequent use of clinically proven, evidence based medical therapies, including thrombolysis, compared to primary care physicians [101,102]. In this cohort, however, all patients received thrombolysis and the cardiologist remained a significant independent predictor of use of t-PA even after correction for other high risk indicators. Possibly, the cardiologist involvement is a marker for residual unmeasured high risk patient characteristics. Alternatively, cardiologists may tend to less preferentially select patients for treatment with the more expensive agent, perhaps being less confident that SK is clinically equal to t-PA (see Chapter 4). As medical specialists, cardiologists perhaps face diverse pressures to use the most reputed efficacious treatment available, regardless of cost.

There has been considerable debate in the medical literature as to the presence of a gender bias in the treatment of acute myocardial infarction[114,115]. Reassuringly, no evidence of gender bias was found in the selection of thrombolytic agent in our data.

This study also examined the role of different hospital attributes on the choice of thrombolytic agent. In general, as the thrombolytic caseload increases, the hospital practice is to be increasingly more selective in the administration of the more expensive agent to patients perceived as having the most to gain. In this regard, while overall physician practice for this cohort was to preferentially use t-PA for younger patients and those presenting within six hours, these tendencies were more pronounced at high volume institutions. In higher volume hospitals, physicians seemed to behave more homogeneously and consequently the unexplained independent role of a cardiologist decision maker was muted.

Hospital location also apparently influenced physician decision making, as doctors practicing in urban hospitals were much more likely to a treat anterior MI and somewhat more likely to treat previous MI patients with t-PA than their rural colleagues. The explanation for this difference is unknown but many hypotheses could be advanced. The difference could represent different physician beliefs as to the probability of a true efficacy difference between agents, or as to the importance of the cost-effectiveness issues. Possibly rural doctors have listened most closely to regional guidelines which have stressed the importance of rapid administration over the choice of thrombolytic agent [25,97]. One could also speculate that urban physicians have more contact with their US colleagues and drug company sponsored events which may influence their practice patterns.

Several limitations of this study should be mentioned. Unmeasured variables may have resulted in residual confounding of our model estimates. For

example, among patient level characteristics, previous SK exposure was not recorded and among hospital characteristics we did not measure whether hospitals had specific limits on the funds available for thrombolytics. Also, although there were no obvious systematic biases in the missing data, this may still be another source of bias. While the data for this registry was entered by trained research nurse coordinators and validated when entered into the data base, logistic constraints prevented external validation of the source documents from being performed. Finally, this data does not permit any conclusions about the appropriateness of thrombolysis in this cohort, which would require blinded data extraction from the medical charts to be analyzed by an expert panel using accepted national treatment guidelines[103].

CHAPTER 8 PUBLIC HEALTH MEASURES AND CONCLUSIONS

This thesis has applied contemporary biostatistical and epidemiological principles to the substantive topic of acute myocardial infarction. In particular, this thesis has concentrated on the theoretical and practical advantages of Bayesian analysis in both interpreting the results of published clinical trials and in analyzing local data (Chapters Two, Four and Seven). The most apparent advantage of Bayesian analysis is its ability to provide direct answers to pertinent clinical questions and therefore does not suffer from the difficulties of interpreting p values. Bayesian analysis also permits the inclusion of prior information thereby raising the level of debate following the acquisition of new data.

An extensive literature review of the treatment of acute myocardial infarction has been performed (Chapter Three). The epidemiology of acute myocardial infarction at both the national and provincial levels has also been described (Chapter 5) using mortality trends over the last ten years. Local practice patterns in the use of thrombolytic agents for the treatment of AMI have been presented (Chapter 6 and 7). This final chapter will summarize the conclusions that may be drawn from this work. When pertinent, conclusions will be framed within the paradigm of technology evaluation which attempts to reconcile the domains of efficacy, safety, cost and ethics.

8.1 THE EPIDEMIOLOGY OF AMI IN QUEBEC AND CANADA

Using Canadian national data from 1976 to 1991, age adjusted mortality declines for men and women with acute myocardial infarction of 53% and 46%, respectively (5% and 4% average annual decrease) have been demonstrated. These mortality reductions appear to be due to a decreasing incidence of acute myocardial infarction and perhaps most importantly by improved hospital treatment and secondary prevention. Additional community based studies are required to define the relative importance of primary and secondary prevention programs. This progress is comparable to what has been obtained in the United States and has been obtained with a more parsimonious use of resources.

An examination of the Quebec hospitalization data bank has confirmed this experience of improving hospital survival of patients with AMI. Furthermore, these data have demonstrated that this progress has continued unabated from 1991 to 1996. In summary, this study of the Quebec administrative hospitalization database from 1986 to 1996 has shown a decline of in-hospital mortality for AMI from 18.4% to 12.7%. The average yearly decline in mortality has been similar between men and women but reduced among the elderly. An examination of the time trends suggests that the largest improvement in survival for both women and the elderly have occurred in the last five years, perhaps due to the extension of previously proven treatment strategies to these populations.

The first conclusion of this thesis is that national and provincial epidemiological data from 1976 to 1996 demonstrate that clinical cardiology has achieved important progress in decreasing the morbidity and mortality of ischemic heart disease, principally from a decrease in the number of deaths from myocardial infarction. However, the number of people afflicted with ischemic heart disease is increasing with our aging population and continued investment for the development of new therapies to reduce mortality and morbidity will be required.

8.2 WHICH THROMBOLYTIC AGENT SHOULD BE USED IN AMI?

Three states of medical knowledge have been described by Naylor[83] - where we do not know the answer, where we do know the answer and where we think we know the answer but are mistaken. The thrombolytic debate nicely illustrates these three states and the transitions between them. Before the GUSTO trial, we clearly did not know if one agent was superior. After the GUSTO trial, we are virtually sure that total mortality is reduced with t-PA but at the cost of increased strokes. However, we are mistaken if we believe we know, with a high degree of certainty, that this difference in mortality is clinically significant (i.e. at least a 1% difference).

Important issues to consider in the interpretation of thrombolytic trials, as in all medical research, are internal and external consistency, the differentiation

between statistical and clinical significance and integration of new and old knowledge into the clinical context. The clinical context includes among other things the socio-economic context in which we live and practice.

The interpretation of the medical literature concerning the choice of thrombolytic agent is complex and has incited strong polemics. Concerns as to the heterogeneity among the trials results accompanied by economic issues of greatly different costs has undoubtedly been responsible for the lack of consensus as to the choice of agent. Canadian Cardiovascular Society guidelines[97] for the treatment of AMI have explicitly recognised this situation by proposing four acceptable treatment scenarios ranging from a dominant t-PA to a dominant SK position.

Standard statistical analysis is not very helpful in addressing these issues as it does not attempt to consider our prior knowledge, cannot provide a direct answer to the pertinent question "which agent is better, by how much and with what certainty" and does not assist in placing trials in their proper context. A Bayesian analysis, as described and performed in this thesis, can overcome these hurdles to a large degree. A range of prior beliefs stretching from total elimination to complete acceptance of prior data can be considered, realistically reflecting the range of individual beliefs and thereby helping to resolve the dilemma of whether data from different trials should be combined. Given one's initial beliefs, Bayesian statistics assures that one's conclusions, after the collection of new data, is logical and consistent.

Considering the most optimistic scenario for t-PA, where only selected data from the GUSTO trial is considered, Bayesian analysis leads to the conclusion, with 99.7% certainty, that t-PA is associated with lowered mortality but with only 38% certainty that the net clinical benefit is at least 1% superior to treatment with SK. The inclusion of any prior information from previous randomized trials comparing these agents or of both t-PA branches from GUSTO will lead to much lowered probabilities of significant benefit with accelerated t-PA. Including even modest amounts of the previous data leads to a probability of a clinical benefit with t-PA (>1% advantage) over SK of less than 10%. The clarity of a Bayesian presentation of the existing clinical literature may be expected to modify physicians' beliefs as to the superiority of either agent.

In making public policy, issues beyond efficacy become important, for example, safety and cost. Among the four kinds of medical economic analysis available, cost utility analysis is particularly in vogue as it allows assessment not only of the duration of life but also its quality (ignoring for the moment the problem of measurement) [116]. Economic analysis can help in policy decision making but it must be appreciated that this form of analysis is in its infancy, heavily dependent on model assumptions and without universal benchmarks for performance and acceptance. The uncertainties of economic analyses may be forgotten in the presentation of a single summary statistic, e.g. $/quality adjusted life year. Attempts to quantify the uncertainty of cost effective analysis by performing univariate or bivariate sensitivity analysis are somewhat rudimentary,

useful for assessing the influence of individual variables but not for assessing the global uncertainty in cost effective estimates. More complex multivariate assessment of cost-effective studies is essential to fully appreciate the range of uncertainty but this has not been done for the t-PA and SK comparison. Notwithstanding these limitations, it is crucial to examine the costs of thrombolysis.

Assuming the cost of SK and t-PA to be approximately $300 and $2500, respectively, an investment of $30,000 in SK (to treat 100 patients) would save about 3 lives, $10,000/life saved, compared to not giving thrombolysis. Replacing SK by t-PA would require an incremental expenditure of $220,000 to save one additional life, assuming the true mortality difference is 1%. However, my personal best estimate of t-PA superiority is 4.8 lives saved/ 1000 treated (see Table 4.2, considering all GUSTO data and 10% of other data), so that the incremental cost may be more in the range of $450,000, or $45,000 per year of live saved, assuming 10 year survival following AMI. This cost would be even higher if discounting was considered. Obviously, a health intervention should not be eliminated simply because the up-front costs are high, but we must not forget that our resources are indeed limited.

A more extensive comparative cost-utility analysis between SK and accelerated t-PA has been performed by the GUSTO investigators [113]. Assuming the results of GUSTO alone to reflect efficacy differences they determined an average cost effective ratio of $33,000 per year of life saved. While diligently

performed, this study has shown a wide variation in cost-effective ratios for t-PA compared to SK, ranging from $13,500 to over $200,000/QALY, for different clinical scenarios. The variability of these estimates would be even larger if the uncertainty of the mortality differences between the two agents was considered. Due to low mortality rates, these ratios are highest for younger patients with ratios of over $100,000 and $200,000 for patients under 40 with anterior and inferior infarction respectively. This analysis is also driven by the 14 year survival (which may not be reasonable in the elderly) of 4,400 myocardial infarction patients recorded from the Duke Database and as such dependent on local practice patterns. Practice patterns between the US and the rest of the world in the treatment of the post MI patient have been shown to be radically different[60] and it is unclear how reliably this analysis may be applied across international boundaries.

The road from economic analyses to recommendations for the adoption of new technologies is relatively uncharted and clearly many other factors influence decision making. Laupacis et al [117] have attempted, somewhat arbitrarily, to define grades of recommendation from economic studies. Grade A is compelling evidence for adoption and arises when a new technology is more effective and less costly. Similarly, Grade E is compelling evidence for rejection and occurs for less effective and more costly technologies. Grades B-D are defined as strong, moderate and weak evidence for adoption based on improved effectiveness at costs of less than $20,000/QALY, $20,000-100,000 and more

than $100,000 respectively. In their 1992 pre-GUSTO paper, these authors classified t-PA compared to SK as an example of a grade E technology. The improvement in mortality with the accelerated t-PA strategy certainly removes this from a grade E technology, but in these difficult economic times, it remains a expensive technology for routine administration.

The second principal conclusion of this thesis is that SK should be the predominant thrombolytic agent for AMI in Canada. Specific clinical situations may nevertheless support the administration of t-PA, for example in patients with a previous exposure to SK where the possibility of pre-existing antibodies may decrease its efficacy and increase the risk of an allergic reaction. This attitude corresponds to the "SK dominant" position identified by the Canadian Cardiovascular Society [97].

The logic and conclusion favouring restraint in the utilization of t-PA has been published [1,5] and has been attacked as "baffling" [55]. However, subsequently other cardiologists[61], epidemiologists[106] and technology assessment groups in both Canada[118] and the United States[119] have reached a similar conclusion favouring SK.

In assessing the public health impact of choosing a thrombolytic agent, the following seems clear. P values or confidence intervals from conventional statistical analysis are poor tools for formulating public health policy, even when there is a considerable amount of data from the best-designed randomized clinical

trials. This is due to the shortcomings of standard significance tests in addressing clinically relevant questions and to the problems in their interpretation, especially across different sample sizes. Furthermore, classical analysis of clinical trials does not easily permit the synthesis of trial results with the range of clinicians' prior beliefs. This makes it difficult to evaluate the coherence of the conclusions and what clinical impact the trial results should have.

A third conclusion is that Bayesian analyses along the lines presented herein may help to overcome these problems, thereby raising the level of debate following publication of a clinical trial. In formulating policy decisions, results from Bayesian analyses are generally more applicable than those from standard statistical techniques, providing appropriate care is taken to ensure a reasonable range of prior distributions.

Others have come to a similar conclusion [31,37,79,80]. Regarding thrombolysis, the decision of which agent to employ is less important than the issues of rapid and universal administration to all eligible patients and the conclusions of the analysis of Quebec practice patterns are now presented.

8.3 How to improve the process of care with thrombolysis?

This thesis has described the delays in the administration of thrombolytics to 1357 patients presenting to a broad sample of Quebec acute care hospitals,

including tertiary, community, urban and rural hospitals. The mean delay from symptom onset to thrombolysis was 172 minutes with significant delays at all the various stages of the treatment process, including a median delay of 59 minutes from hospital arrival to treatment. Hospital and patient characteristics associated with increased delays have been identified.

Patient reluctance to present promptly to the emergency room when they experience characteristic prolonged cardiac symptoms was the major cause of delay and was particularly evident among women and the elderly. Clearly more extensive research is required to understand the interaction between patient demographic, personality traits, social structures and the health care system that is responsible for delaying hospital consultation.

Regarding the process of hospital care, 50% of this cohort received thrombolysis within one hour of hospital presentation, which is a significant improvement over previous studies. Nevertheless, less than 25% of our cohort received thrombolysis in the ideal 30 minute period currently recommended[100] and this highlights the importance of continued quality control programs. This research has permitted identification of where the hospital delays occur.

As a fourth conclusion, in general, the time for the medical decision making process to administer thrombolysis in Quebec hospitals seems reasonable (median 12 minutes) but there was considerable delay in obtaining a diagnostic ECG and also in drug preparation. This study also identified low volume and

community hospitals as being less proficient in rapidly administering thrombolysis. Clearly, physicians have an essential role not only in decision making but also in assuring that all allied health professionals appreciate the importance of timely interventions for patients with AMI.

This project has also allowed an examination of the medical decision process concerning the choice of the thrombolytic agent and these results are presented in the next section.

8.4 How do Quebec physicians select a thrombolytic drug?

Quebec physicians have adopted a selective policy of reserving the more expensive drug, t-PA, for patients who are either younger, judged to be at high risk (hypotensive, anterior MI and previous MI) or presenting early after symptom onset. This position seems intermediate between the low (European) and high (United States) extremes. While this thesis would suggest that there is little clinical difference between the two thrombolytic agents, there is, nevertheless, good evidence from one mega-trial to support this practice of treating high risk, early presenters with t-PA.

However, there is currently little scientific evidence or justification to support age as a selection criterion for t-PA. Indeed, Quebec physicians seem uninfluenced by analyses which suggest that it is not cost-effective to treat

younger patients with t-PA. To assure that any benefits of the more expensive agent are maximized, measures should be undertaken to publicize the lack of knowledge of any proven advantage for hypotensive patients. Hypotensive patients, of which those in cardiac shock are sub-group, have a very poor prognosis and it is relatively easy to understand the wishful thinking behind the prescription of the more expensive agent. Recent data would suggest that primary angioplasty, when available, should be the preferred treatment for these very high risk patients [120].

There was a systematic higher use of t-PA in tertiary centers and by cardiologists which had not been previously reported. It has also been determined that the medical decision process differs between rural and urban physicians. The reasons for this non-uniformity in practice patterns are unknown but possibly related to different beliefs in the cost-effectiveness data, different exposure to education programs, or by different priorities set in various institutions.

As a final conclusion, the results of this study have provided an improved framework for the evaluation of a medical treatment strategy, namely thrombolysis, extending beyond patients' characteristics, to consider physicians' and hospitals' characteristics. Quebec physicians have adopted a selective role for the more expensive thrombolytic agent which is generally, but not totally supported by evidence based medicine. Institutional and physician characteristics influence the choice of drug.

8.5 FUTURE RESEARCH

Future avenues of research for the treatment for AMI should attempt to determine the reasons that patients delay in seeking medical care. Mechanisms to expedite the process of thrombolysis while continually assuring the quality of care should be investigated. Additional work is also required to understand why physicians in different geographical (urban vs. rural) and institutional (tertiary vs. community) settings behave differently.

The application of statistical hierarchical models, as used in this study, has helped to identify the determinants of current utilization of thrombolytic resources. In the future, these techniques may assist in optimally allocating our limited medical resources.

APPENDIX 1 QUEBEC ACUTE CORONARY CARE WORKING GROUP

The executive of the Quebec Acute Coronary Care Working Group is comprised of Drs. Peter Bogaty, James Brophy, Franz Dauwe, Jean G Diodati, David Fitchett, Richard Gallo, Thao Huyhn, Pierre Laramée, Guy Leclerc, James Nasmith, Michel Nguyen, Normand Racine, Pierre Théroux (Chairman).

APPENDIX 2 FRSQ THROMBOLYTIC QUESTIONNAIRE

ACUTE CORONARY CARE - RÉSEAU F.R.S.Q

TO BE COMPLETED AT ADMISSION

I.D.

Hospital code (R.A.M.Q.) ☐☐☐☐-☐☐☐☐ Patient initials ☐☐ Hospital chart ☐☐☐☐☐☐☐☐
Hospitalized in CCU ☐ other ☐

DEMOGRAPHICS: male ☐ female ☐ Age☐☐ Birth date ☐☐☐☐ Admission date __/__/__

CLINICAL PRESENTATION: (at admission)

Typical acute coronary syndrome: yes ☐ no ☐ if no atypical pain☐, congestive failure ☐, syncope ☐, shock ☐, other ☐
Unusual effort in previous hour: yes ☐ no ☐
Systolic BP ☐☐☐ Way of transportation: Ambulance ☐ car ☐ Duration ____min

ADMISSION ECG: normal ☐, ST depression ☐, ST elevation ☐, LBBB ☐,
if abnormal site:
anterior ☐, inferior ☐

	Hour	Date
onset of pain	_____	__/__
Arrival ER	_____	__/__
ECG admission	_____	__/__
Diagnostic ECG	_____	__/__

THROMBOLYSIS GIVEN ☐; tPA ☐ SK ☐
Time of decision __/__ (hrs)
Starting time __/__
Decision by: Emergency MD ☐ cardiology consultant ☐
Thrombolysis site: ER ☐ CCU ☐
Complication: yes ☐ no ☐
if yes: hemorrhagic stroke ☐
non-hemorrhagic stroke ☐
bleeding with transfusion ☐

THROMBOLYSIS NOT GIVEN ☐
Reasons no ECG criteria ☐
advanced age ☐
too late ☐
non diagnostic ECG ☐
absolute contraindication ☐
relative contraindication ☐
primary PTCA ☐
other(s) _____

TREATMENT BEFORE ADMISSION ASA ☐ Hypolipidemics ☐ ACE inhibitor ☐ Beta blocker ☐

PREVIOUS HISTORY:

Risk factors	yes	no		yes	no
smoking	☐	☐	previous stroke	☐	☐
actual	☐	☐	family history <60	☐	☐
previous	☐	☐	peripheral vascular	☐	☐
diabetes	☐	☐	previous MI	☐	☐
treated HBP	☐	☐	bypass surgery	☐	☐
lipids	☐	☐	PTCA <6 months	☐	☐
			PTCA >6 months	☐	☐
			treated angina	☐	☐

TO BE COMPLETED DURING HOSPITALIZATION

IN HOSPITAL FOLLOW-UP:

Investigation & treatment:
Coronary angiography ☐
Bypass surgery ☐
PTCA ☐

Follow-up:
Hospital discharge __/__/__ (mm.dd.yy)
Transfer __/__/__ (mm.dd.yy)
Hospital _____
Death __/__/__ (mm.dd.yy)

FINAL DIAGNOSTIC: Q wave MI ☐ non Q wave MI ☐ unstable angina ☐ other _____

SIGNATURE: _____

APPENDIX III HOSPITALS, INVESTIGATORS AND NURSE COORDINATORS PARTICIPATING IN THE FRSQ REGISTRY

NAME OF HOSPITAL	INVESTIGATORS	NURSE COORDINATORS	NUMBER (%)
HÔTEL-DIEU DE QUÉBEC	Guy Proulx MD	Michèle Darveau	140 (1.6)
HÔPITAL LAVAL	Peter Bogaty MD	Luce Boyer	799 (9)
CITÉ DE LA SANTÉ	Gebran Boutros MD	Manon Dubé	306 (3.4)
CENTRE HOSP.DE JONQUIÈRES	Réal Brossoit MD	Julie Gravel	354 (4)
CENTRE DE SANTÉ ST-JEAN EUDES	C.Baillargeon MD	Diane Richard	40 (0.4)
HÔTEL-DIEU DE ROBERVAL	André Séguin MD	Arianne Ouellette	22 (0.2)
HÔPITAL DE CHICOUTIMI	Claude Levesque MD	Dominic Brassard	392 (4.4)
CENTRE HOSP. NOTRE-DAME DU LAC	Jean-Marie Deschesnes MD	Léanna landry	48 (0.5)
CENTRE HOSP. DE LACHINE	John Cristie MD	Manon Poulin	167 (1.9)
CENTRE DE SANTÉ PORT-CARTIER	Stéphane Caron MD	Rachel Imbeault	34 (0.4)
HÔPITAL NOTRE-DAME	Pierre Laramée MD	Diane Therien	320 (3.6)
HÔPITAL ENFANT-JÉSUS, QUÉBEC	Paul Talbeau MD	Nicole Bélanger	672 (7.5)
CENTRE HOSP. CHAUVEAU, LORETTVILLE	Camille Cadrin MD	Hélène Simmard	172 (1.9)
CENTRE HOSP. DE MATANE	Pierre LeBlanc MD	Janelle Côté	125 (1.4)
CENTRE HOSP. DES LAURENTIDES	Nicolas Mathieu MD	Louise Tremblay	71 (0.8)
CENTRE HOSP. DU GRAND PORTAGE	Martin Lefebvre MD	Sylvie St-Onge	112 (1.3)
HÔTEL-DIEU DE MONTMAGNY	Yves Grenier MD	Diane Blanchette	164 (1.8)
INSTITUT DE CARDIOLOGIE DE MONTRÉAL	Jocelyn Dupuis MD	Johanne Levesque	695 (7.8)
HÔPITAL SACRÉ-COEUR	James Nasmith MD	Ginette Gaudette	723 (8.1)
CENTRE HOSP. DE LA RÉGION DE L'AMIANTE	Robert Dupuis MD	Lucie Boulé	109 (1.2)
CENTRE HOSP. LAURENTIEN	Jean-Pierre Guimond MD	Martine Laporte	143 (1.6)
HÔPITAL BAIE DES HA HA	C. Dufresnes MD	Sylvie Martin	35 (0.4)
CENTRE HOSP. DE MANIWAKI	André Thérien MD		99 (1.1)
CENTRE HOSP. DE VERDUN	James Brophy MD	Denise Lalonde	394 (4.4)
HÔTEL DIEU DE LÉVIS	François Delage MD	Francine Dumont	771 (8.6)

HÔPITAL NOTRE-DAME DE FATIMA	Mario Lebel MD	Céline Pelletier	22 (0.2)
CENTRE HOSPITALIER DE BUCKINGHAM	Kien Tran MD	Jocelyne Villeuve-Morin	38 (0.4)
HÔPITAL PONTICA COMMUNITY	Athan Karabatsos MD		17 (0.2)
HÔPITAL GENERAL JUIF	Jean Diodati MD	Eileen Shalit	313 (3.5)
CENTRE HOSP. ROUYN-NORANDA	J.Matte MD	Dubé Héroux	47 (0.5)
CENTRE HOSP. DE DOLBEAU	Sylvain Proulx MD	Huguette Noël	129 (1.4)
CENTRE HOSPITALIER DE SHERBROOKE	Richard Harvey MD	Pierrette Chailler	39 (0.4)
CENTRE HOSP. ST-JOSEPH DE LA MALBAIE	Pierre Deshaies MD	Anne Tremblay	16 (0.2)
HÔPITAL ST FRANÇOIS D'ASSISE	Serge Blouin MD	Michèle Belanger	86 (1.0)
HÔPITAL MONTREAL GENERAL	Thao Huynh MD	Monique Besner	494 (5.5)
HÔPITAL LE GARDEUR	Gerry Bédard MD	Chantal Fafard	535 (6.0)
CENTRE HOSP. ST-SAUVEUR, VAL D'OR	Joel Pouliot MD		20 (0.2)
HÔPITAL LA PROVIDENCE DE MAGOG	Mario Wilhelmy MD	idem MD	77 (0.9)
HÔPITAL DE CHIBOUGAMAU	De LaBossière MD	Luc Néron	20 (0.2)
RÉSEAU SANTÉ RICHELIEU YAMASKA	Dominique Grandmont MD	Lucie Beaudreau	137 (1.5)

APPENDIX IV BAYESIAN HIERARCHICAL RANDOM EFFECTS PROGRAM USING BUGS SOFTWARE

```
Welcome to BUGS on 11 th Dec 1997  at 16:17:23
BUGS : Copyright (c) 1992 .. 1995 MRC Biostatistics Unit.
All rights reserved.
Version 0.510 for 32 Bit PC.
For general release : please see documentation for disclaimer.
The support of the Economic and Social Research Council (UK)
is gratefully acknowledged.
Bugs>compile('sk109.bug')
#model E:\registry\new;
model sk109;
const
 #  nj = 1357; #  total number of cases
    n = 1165, # cases with no missing values -low volume hospitals<10 cases combined to
one '99'
    nn = 26; # number of hospitals
#uses optimal model selection from bicreg
#includes a hierarchy on the  hospital characteristics
#intercept based on hospital status tertiary (dichotomous)
#extends the effect of volume (continuous) and urban/rural (dichotomous)
#agent=0,1 sk,tpa
#age65= 0,1 < or > 65
#site =0,1 not anterior, anterior mi
#sex =0,1  male,female
#oldmi = absent, present 0,1
#stat6=< or >6 hours
#md =0,1 ER MD or cardiologist
#bp>120 =1 else=0
#statut is 0,1  tertiary (1) or not (0)
#urban=1 if Montreal or Quebec else =0 instead of region since not #enough data
#volume= number of cases (continous variable)
#N =no. records for each hospital 26 true values then rest have a false #
#nurban nstatut nvolume have valid data only for 26 places corresponding #to hospitals.
#small hospitals (99) are given nregion=0 statut=0 and mean volume

var
N[n],agent[n], p[n], age65[n], sex[n], site[n], nhop[n], stat6[n], oldmi[n],bp[n],urban[n],
md[n],region[n],statut[n],nregion[n],nstatut[n],nurban[n],nvolume[n],
age65.bar, stat6.bar, sex.bar, site.bar, oldmi.bar, md.bar,bp.bar,
tau.intercept,tau.age65,tau.sex,tau.site,tau.oldmi,  tau.stat6, tau.md, tau.bp,
sigma.intercept,sigma.age65,sigma.sex,sigma.site,sigma.oldmi, sigma.stat6,sigma.md,
sigma.bp,
b0.intercept[nn], b0.age65[nn],  b0.site[nn],  b0.oldmi[nn], b0.md[nn],
b0.bp[nn],b0.sex[nn],b0.stat6[nn],
b0.intercept.new,b0.statut.intercept,
b0.age65.new,b0.statut.age65,b0.urban.age65,b0.vol.age65,
b0.site.new,b0.statut.site,b0.urban.site,b0.vol.site,
b0.oldmi.new,b0.statut.oldmi,b0.urban.oldmi,b0.vol.oldmi,
b0.md.new,b0.statut.md,b0.urban.md,b0.vol.md,
b0.bp.new,b0.statut.bp,b0.urban.bp,b0.vol.bp,
b0.sex.new,b0.statut.sex,b0.urban.sex,b0.vol.sex,
b0.stat6.new,b0.statut.stat6,b0.urban.stat6,b0.vol.stat6,
b0.age65.low.pred,b0.stat6.low.pred,b0.sex.low.pred,b0.site.low.pred,
b0.oldmi.low.pred,
b0.md.low.pred,b0.bp.low.pred,
```

```
b0.age65.mid.pred,b0.stat6.mid.pred,b0.sex.mid.pred,b0.site.mid.pred,
b0.oldmi.mid.pred,
b0.md.mid.pred,b0.bp.mid.pred,
b0.age65.high.pred,b0.stat6.high.pred,b0.sex.high.pred,b0.site.high.pred,
b0.oldmi.high.pred,
b0.md.high.pred,b0.bp.high.pred,
b0.age65.xhigh.pred,b0.stat6.xhigh.pred,b0.sex.xhigh.pred,
b0.md.xhigh.pred,b0.bp.xhigh.pred,
age65.low,age65.mid,age65.high,age65.xhigh,
stat6.low,stat6.mid,stat6.high,stat6.xhigh,sex.low,sex.mid,sex.high,
sex.xhigh,site.low,site.mid,
site.high,oldmi.low,oldmi.mid,oldmi.high,
md.low,md.mid,md.high,md.xhigh,bp.low,bp.mid,bp.high,bp.xhigh,
b.intercept[nn], b.age65[nn], b.sex[nn], b.site[nn],b.stat6[nn],b.oldmi[nn],
b.md[nn],b.bp[nn];

data nhop,region,statut,oldmi,agent,sex,site,md,age65,stat6,bp,urban,N,
nregion,nstatut,nurban,
nvolume in "sk109.dat";

#sk109.dat same as 104.dat
#nregion is not used, correlated with nurban, and not enough data points #for regression
#could have been totally eliminated from data set


inits in "sk109.in";

{
  for (i in 1:nn) {

b.intercept[i]~dnorm(b0.intercept[i], tau.intercept);
b.age65[i]~dnorm(b0.age65[i], tau.age65);
b.sex[i]~dnorm(b0.sex[i], tau.sex);
b.site[i]~dnorm(b0.site[i], tau.site);
b.stat6[i]~dnorm(b0.stat6[i], tau.stat6);
b.oldmi[i]~dnorm(b0.oldmi[i], tau.oldmi);
b.md[i]~dnorm(b0.md[i], tau.md);
b.bp[i]~dnorm(b0.bp[i], tau.bp);
b0.intercept[i]<-
b0.intercept.new+b0.statut.intercept*statut[i];
b0.age65[i]<-
b0.age65.new+b0.vol.age65*nvolume[i];
b0.site[i]<-
b0.site.new+b0.urban.site*nurban[i];
b0.oldmi[i]<-
b0.oldmi.new+b0.urban.oldmi*nurban[i];
b0.md[i]<-
b0.md.new+b0.vol.md*nvolume[i];
b0.bp[i]<-
b0.bp.new+b0.vol.bp*nvolume[i];
b0.sex[i]<-
b0.sex.new+b0.vol.sex*nvolume[i];
b0.stat6[i]<-
b0.stat6.new+ b0.vol.stat6*nvolume[i];
```

```
for (j in (1+N[i]) :N[i+1])  {

logit(p[j])<-b.intercept[i] +b.age65[i]*(age65[j]-age65.bar)+b.sex[i]*(sex[j]-sex.bar)
+b.site[i]*(site[j]-site.bar)+b.stat6[i]*(stat6[j]-stat6.bar)+b.oldmi[i]*(oldmi[j]-oldmi.bar)
+b.md[i]*(md[j]-md.bar)+b.bp[i]*(bp[j]-bp.bar);
    agent[j]~dbern(p[j]);
  }
   }

  b0.statut.intercept   ~ dnorm(0,1.0E-1);
  b0.statut.age65~ dnorm(0,1.0E-1);
  b0.urban.age65~ dnorm(0,1.0E-1);
  b0.vol.age65~ dnorm(0,1.0E-1);
  b0.statut.site~ dnorm(0,1.0E-1);
  b0.urban.site~ dnorm(0,1.0E-1);
  b0.vol.site~ dnorm(0,1.0E-1);
  b0.statut.oldmi~ dnorm(0,1.0E-1);
  b0.urban.oldmi~ dnorm(0,1.0E-1);
  b0.vol.oldmi~ dnorm(0,1.0E-1);
  b0.statut.md~ dnorm(0,1.0E-1);
  b0.urban.md~ dnorm(0,1.0E-1);
  b0.vol.md~ dnorm(0,1.0E-1);
  b0.statut.bp~ dnorm(0,1.0E-1);
  b0.urban.bp~ dnorm(0,1.0E-1);
  b0.vol.bp~ dnorm(0,1.0E-1);
  b0.statut.sex~ dnorm(0,1.0E-1);
  b0.urban.sex~ dnorm(0,1.0E-1);
  b0.vol.sex~ dnorm(0,1.0E-1);
  b0.statut.stat6~ dnorm(0,1.0E-1);
  b0.urban.stat6~ dnorm(0,1.0E-1);
  b0.vol.stat6~ dnorm(0,1.0E-1);
  b0.intercept.new~ dnorm(0,1.0E-1);
  b0.age65.new~ dnorm(0,1.0E-1);
  b0.site.new~ dnorm(0,1.0E-1);
  b0.oldmi.new~ dnorm(0,1.0E-1);
  b0.md.new~ dnorm(0,1.0E-1);
  b0.bp.new~ dnorm(0,1.0E-1);
  b0.sex.new~ dnorm(0,1.0E-1);
  b0.stat6.new~ dnorm(0,1.0E-1);
  tau.intercept   ~ dgamma(1.0E-3,1.0E-3);
  tau.age65 ~ dgamma(1.0E-3,1.0E-3);
  tau.stat6 ~ dgamma(1.0E-3,1.0E-3);
  tau.sex ~ dgamma(1.0E-3,1.0E-3);
  tau.site ~ dgamma(1.0E-3,1.0E-3);
  tau.oldmi ~ dgamma(1.0E-3,1.0E-3);
  tau.md~ dgamma(1.0E-3,1.0E-3);
  tau.bp~ dgamma(1.0E-3,1.0E-3);
  sigma.intercept   <- 1/sqrt(tau.intercept);
  sigma.age65 <- 1/sqrt(tau.age65);
  sigma.stat6 <- 1/sqrt(tau.stat6);
  sigma.sex <- 1/sqrt(tau.sex);
  sigma.site <- 1/sqrt(tau.site);
  sigma.oldmi <- 1/sqrt(tau.oldmi);
  sigma.md<- 1/sqrt(tau.md);
  sigma.bp<- 1/sqrt(tau.bp);
```

```
   age65.bar <- mean(age65[]);
   stat6.bar<- mean(stat6[]);
   sex.bar <- mean(sex[]);
   site.bar <- mean(site[]);
   oldmi.bar <- mean(oldmi[]);
   md.bar<-mean(md[]);
   bp.bar<-mean(bp[]);

   #this is for sk107 to re-estimate beta's for hierarchy, low mid high

age65.low<-b0.age65.new+15*b0.vol.age65;
age65.mid<-b0.age65.new+40*b0.vol.age65;
age65.high<-b0.age65.new+65*b0.vol.age65;
age65.xhigh<-b0.age65.new+90*b0.vol.age65;
b0.age65.low.pred~dnorm(age65.low, tau.age65);
b0.age65.mid.pred~dnorm(age65.mid, tau.age65);
b0.age65.high.pred~dnorm(age65.high, tau.age65);
b0.age65.xhigh.pred~dnorm(age65.xhigh, tau.age65);

sex.low<-b0.sex.new+15*b0.vol.sex;
sex.mid<-b0.sex.new+40*b0.vol.sex;
sex.high<-b0.sex.new+65*b0.vol.sex;
sex.xhigh<-b0.sex.new+90*b0.vol.sex;
b0.sex.low.pred~dnorm(sex.low, tau.sex);
b0.sex.mid.pred~dnorm(sex.mid, tau.sex);
b0.sex.high.pred~dnorm(sex.high, tau.sex);
b0.sex.xhigh.pred~dnorm(sex.xhigh, tau.sex);

site.low<-b0.site.new+0*b0.urban.site;
site.mid<-b0.site.new+1*b0.urban.site;
b0.site.low.pred~dnorm(site.low, tau.site);
b0.site.mid.pred~dnorm(site.mid, tau.site);

oldmi.low<-b0.oldmi.new+0*b0.urban.oldmi;
oldmi.mid<-b0.oldmi.new+1*b0.urban.oldmi;
b0.oldmi.low.pred~dnorm(oldmi.low, tau.oldmi);
b0.oldmi.mid.pred~dnorm(oldmi.mid, tau.oldmi);

md.low<-b0.md.new+15*b0.vol.md;
md.mid<-b0.md.new+40*b0.vol.md;
md.high<-b0.md.new+65*b0.vol.md;
md.xhigh<-b0.md.new+90*b0.vol.md;
b0.md.low.pred~dnorm(md.low, tau.md);
b0.md.mid.pred~dnorm(md.mid, tau.md);
b0.md.high.pred~dnorm(md.high, tau.md);
b0.md.xhigh.pred~dnorm(md.xhigh, tau.md);

bp.low<-b0.bp.new+15*b0.vol.bp;
bp.mid<-b0.bp.new+40*b0.vol.bp;
bp.high<-b0.bp.new+65*b0.vol.bp;
bp.xhigh<-b0.bp.new+90*b0.vol.bp;
b0.bp.low.pred~dnorm(bp.low, tau.bp);
b0.bp.mid.pred~dnorm(bp.mid, tau.bp);
b0.bp.high.pred~dnorm(bp.high, tau.bp);
b0.bp.xhigh.pred~dnorm(bp.xhigh, tau.bp);
```

```
stat6.low<-b0.stat6.new+15*b0.vol.stat6;
stat6.mid<-b0.stat6.new+40*b0.vol.stat6;
stat6.high<-b0.stat6.new+65*b0.vol.stat6;
stat6.xhigh<-b0.stat6.new+90*b0.vol.stat6;
b0.stat6.low.pred~dnorm(stat6.low, tau.stat6);
b0.stat6.mid.pred~dnorm(stat6.mid, tau.stat6);
b0.stat6.high.pred~dnorm(stat6.high, tau.stat6);
b0.stat6.xhigh.pred~dnorm(stat6.xhigh, tau.stat6);

}

Parsing model declarations.
Loading data value file(s).
Warning -- expected data read before end of file
Loading initial value file(s).
Parsing model specification.
Checking model graph for directed cycles.
Generating code.
Generating sampling distributions.
Generating initial values
Checking model specification.
Choosing update methods.
compilation took  00:00:47
Bugs>update(500)     time for   500   updates was  00:02:17
Bugs>update(10000)     time for   10000  updates was  00:49:11
stats(b0.age65)
stats(b0.sex)
stats(b0.site)
stats(b0.stat6)
stats(b0.md)
Bugs>stats(b0.age65)
         -6.135E-1  2.117E-1 -1.017E+0 -1.993E-1 -6.130E-1    10000
Bugs>stats(b0.sex)
         -1.859E-2  2.033E-1 -3.858E-1  3.752E-1 -2.887E-2    10000
Bugs>stats(b0.site)
          1.100E+0  2.163E-1  6.737E-1  1.499E+0  1.101E+0    10000
Bugs>stats(b0.stat6)
         -5.874E-1  2.379E-1 -1.037E+0 -1.085E-1 -5.870E-1    10000
Bugs>stats(b0.md)
          5.948E-1  3.164E-1 -4.274E-4  1.247E+0  5.847E-1    10000
Bugs>stats(b0.bp)
         -7.407E-1  1.785E-1 -1.095E+0 -4.010E-1 -7.363E-1    10000
Bugs>stats(b0.oldmi)
          8.256E-1  2.251E-1  3.829E-1  1.276E+0  8.276E-1    10000
Bugs>stats(b0.age65.pred)
         -6.108E-1  5.529E-1 -1.801E+0  5.789E-1 -6.127E-1    10000
Bugs>stats(b0.sex.pred)
         -1.893E-2  2.900E-1 -5.689E-1  5.308E-1 -3.158E-2    10000
Bugs>stats(b0.site.pred)
          1.088E+0  6.194E-1 -2.587E-1  2.369E+0  1.113E+0    10000
Bugs>stats(b0.stat6.pred)
         -5.993E-1  4.880E-1 -1.624E+0  4.284E-1 -6.002E-1    10000
Bugs>stats(b0.md.pred)
          6.031E-1  1.152E+0 -1.718E+0  2.983E+0  5.785E-1    10000
```

```
Bugs>stats(b0.bp.pred)
        -7.412E-1  3.120E-1 -1.368E+0 -1.159E-1 -7.330E-1   10000
Bugs>stats(b0.oldmi.pred)
         8.229E-1  6.306E-1 -4.924E-1  2.215E+0  8.158E-1   10000
Bugs>stats(b0.age65.low.pred)
        -3.331E-1  5.726E-1 -1.607E+0  7.626E-1 -2.988E-1   10000
Bugs>stats(b0.age65.mid.pred)
        -4.903E-1  5.332E-1 -1.697E+0  5.660E-1 -4.683E-1   10000
Bugs>stats(b0.age65.high.pred)
        -6.562E-1  5.149E-1 -1.762E+0  4.358E-1 -6.555E-1   10000
Bugs>stats(b0.age65.xhigh.pred)
        -8.087E-1  5.477E-1 -1.920E+0  4.269E-1 -8.253E-1   10000
Bugs>stats(b0.site.low.pred)
         4.953E-1  4.137E-1 -3.966E-1  1.316E+0  5.021E-1   10000
Bugs>stats(b0.site.mid.pred)
         1.881E+0  4.196E-1  1.007E+0  2.739E+0  1.878E+0   10000
Bugs>stats(b0.oldmi.low.pred)
         7.046E-1  7.323E-1 -8.076E-1  2.213E+0  7.174E-1   10000
Bugs>stats(b0.oldmi.mid.pred)
         1.052E+0  7.369E-1 -4.738E-1  2.714E+0  1.031E+0   10000
Bugs>stats(b0.md.low.pred)
         7.939E-1  1.232E+0 -1.650E+0  3.316E+0  7.642E-1   10000
Bugs>stats(b0.md.mid.pred)
         6.514E-1  1.198E+0 -1.758E+0  3.061E+0  6.504E-1   10000
Bugs>stats(b0.md.high.pred)
         5.149E-1  1.200E+0 -1.957E+0  2.933E+0  5.073E-1   10000
Bugs>stats(b0.md.xhigh.pred)
         2.996E-1  1.238E+0 -2.227E+0  2.812E+0  3.044E-1   10000
Bugs>stats(b0.bp.low.pred)
        -6.113E-1  3.897E-1 -1.386E+0  9.904E-2 -5.910E-1   10000
Bugs>stats(b0.bp.mid.pred)
        -6.976E-1  3.543E-1 -1.438E+0  9.649E-3 -6.829E-1   10000
Bugs>stats(b0.bp.high.pred)
        -7.808E-1  3.362E-1 -1.491E+0 -1.257E-1 -7.751E-1   10000
Bugs>stats(b0.bp.xhigh.pred)
        -8.660E-1  3.600E-1 -1.597E+0 -1.377E-1 -8.723E-1   10000
Bugs>stats(b0.sex.low.pred)
         1.034E-1  3.622E-1 -5.784E-1  8.144E-1  9.166E-2   10000
Bugs>stats(b0.sex.mid.pred)
         4.108E-2  3.218E-1 -5.924E-1  6.622E-1  4.446E-2   10000
Bugs>stats(b0.sex.high.pred)
        -1.788E-2  2.989E-1 -6.501E-1  5.668E-1 -1.379E-2   10000
Bugs>stats(b0.sex.xhigh.pred)
        -8.029E-2  3.194E-1 -7.638E-1  5.069E-1 -6.854E-2   10000
Bugs>stats(b0.stat6.low.pred)
        -2.503E-1  4.961E-1 -1.320E+0  6.885E-1 -2.093E-1   10000
Bugs>stats(b0.stat6.mid.pred)
        -4.780E-1  4.335E-1 -1.395E+0  3.633E-1 -4.443E-1   10000
Bugs>stats(b0.stat6.high.pred)
        -6.915E-1  4.087E-1 -1.555E+0  8.882E-2 -6.834E-1   10000
Bugs>stats(b0.stat6.high.pred)
        -6.915E-1  4.087E-1 -1.555E+0  8.882E-2 -6.834E-1   10000
Bugs>stats(sigma.age65)
         3.917E-1  2.837E-1  3.786E-2  1.033E+0  3.389E-1   10000
Bugs>stats(sigma.sex)
```

```
          1.786E-1  1.544E-1  2.721E-2  6.006E-1  1.259E-1    10000
Bugs>stats(sigma.site)
          2.621E-1  2.037E-1  3.231E-2  7.555E-1  2.111E-1    10000
Bugs>stats(sigma.stat6)
          2.174E-1  2.108E-1  2.645E-2  7.847E-1  1.358E-1    10000
Bugs>stats(sigma.oldmi)
          5.517E-1  3.450E-1  3.350E-2  1.286E+0  5.348E-1    10000
Bugs>stats(sigma.md)
          1.092E+0  3.544E-1  4.632E-1  1.869E+0  1.066E+0    10000
Bugs>stats(sigma.bp)
          2.194E-1  1.910E-1  3.005E-2  7.343E-1  1.567E-1    10000
Bugs>stats(b0.intercept.new)
         -3.993E-1  2.316E+0 -5.009E+0  3.856E+0 -3.572E-1    10000
Bugs>stats(b0.statut.intercept)
         -8.012E-1  2.312E+0 -5.099E+0  3.741E+0 -8.327E-1    10000
Bugs>stats(age65.low)
         -3.373E-1  3.158E-1 -9.940E-1  2.835E-1 -3.230E-1    10000
Bugs>stats(age65.mid)
         -4.957E-1  2.361E-1 -9.836E-1 -4.823E-2 -4.880E-1    10000
Bugs>stats(age65.high)
         -6.541E-1  2.102E-1 -1.073E+0 -2.621E-1 -6.554E-1    10000
Bugs>stats(age65.xhigh)
         -8.124E-1  2.550E-1 -1.290E+0 -2.812E-1 -8.255E-1    10000
Bugs>stats(site.low)
          5.060E-1  2.490E-1  3.911E-2  1.020E+0  5.095E-1    10000
Bugs>stats(site.mid)
          1.886E+0  2.671E-1  1.369E+0  2.413E+0  1.882E+0    10000
Bugs>stats(oldmi.low)
          7.042E-1  3.239E-1  4.540E-2  1.333E+0  7.167E-1    10000
Bugs>stats(oldmi.mid)
          1.054E+0  3.565E-1  3.729E-1  1.790E+0  1.048E+0    10000
Bugs>stats(md.low)
          8.204E-1  4.538E-1 -5.166E-2  1.724E+0  8.115E-1    10000
Bugs>stats(md.mid)
          6.524E-1  3.398E-1 -4.548E-3  1.337E+0  6.478E-1    10000
Bugs>stats(md.high)
          4.845E-1  3.482E-1 -1.923E-1  1.202E+0  4.785E-1    10000
Bugs>stats(md.xhigh)
          3.165E-1  4.725E-1 -6.129E-1  1.273E+0  3.091E-1    10000
Bugs>stats(bp.low)
         -6.108E-1  2.666E-1 -1.106E+0 -1.169E-1 -5.962E-1    10000
Bugs>stats(bp.mid)
         -6.956E-1  1.985E-1 -1.084E+0 -3.381E-1 -6.863E-1    10000
Bugs>stats(bp.high)
         -7.804E-1  1.735E-1 -1.130E+0 -4.653E-1 -7.745E-1    10000
Bugs>stats(bp.xhigh)
         -8.652E-1  2.077E-1 -1.280E+0 -4.648E-1 -8.673E-1    10000
Bugs>stats(sex.low)
          1.023E-1  2.786E-1 -4.286E-1  6.534E-1  9.509E-2    10000
Bugs>stats(sex.mid)
          4.215E-2  2.132E-1 -3.780E-1  4.617E-1  4.347E-2    10000
Bugs>stats(sex.high)
         -1.801E-2  1.861E-1 -3.886E-1  3.426E-1 -1.697E-2    10000
Bugs>stats(sex.xhigh)
         -7.818E-2  2.123E-1 -5.085E-1  3.105E-1 -6.887E-2    10000
```

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