Aggressive Care Following Hospital Admission for Acute Myocardial Infarction: Analysis of Effects on Mortality Using Instrumental Variables

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Abstract

Certain regions adopt an aggressive approach (routine cardiac catheterization and frequent invasive revascularization) to care for acute myocardial infarction (AMI), while other regions adopt a conservative approach (selective use of invasive procedures). Administrative data provide a means to estimate the effects of these variations on patient outcomes, but they are limited by their potential for confounding bias due to unobserved case-mix variation as treatment assignment is not random. This study applied instrumental variables, a methodology that can account for this bias, to estimate the effectiveness of aggressive care in a Canadian patient population. The study used administrative data of hospital admissions and health services for all patients admitted for a first AMI in Quebec in 1988 (n=8674). Incremental (marginal) mortality up to 4 years after admission was measured using distances to hospitals offering aggressive care as instrumental variables.

Patients living closer to hospitals offering aggressive care were more likely to receive aggressive care than patients living further away (e.g. 26% versus 19%, respectively, received catheterization within 90 days). However, instrumental variable estimation found that aggressive care was not associated with marginal mortality benefits in comparison to conservative care (e.g. adjusted difference at 1 year: 4%; 95% CI: -11% to 20%).

The aggressive approach to post-AMI care is not associated with marginal mortality benefits in Quebec.

Résumé

Tandis que certaines régions adoptent des méthodes agressives (cathétérisation cardiaque de routine et re-vascularisation fréquente) pour soigner l'infarctus du myocarde aigu (IMA), d'autres choisissent des méthodes moins agressives (utilisation sélective des procédures). Les données administratives fournissent un moyen d'estimer les effets de ces variations sur la survie des patients, mais elles sont limitées par un biais potentiel dû à une variation non-observée car les traitements ne sont pas assignés de façon aléatoire. Cette étude a utilisé des variables instrumentales, une méthodologie permettant la prise en compte de ce biais pour estimer l'efficacité des soins agressifs dans une population de patients canadiens. Cette étude a utilisé les données administratives des hospitalisations et des services de soins en santé pour tous les patients admis pour un premier IMA au Québec en 1988 (n=8674). L'augmentation de la mortalité (marginale), jusqu'à 4 années après l'admission, a été mesurée en utilisant comme variables instrumentales les distances domicile-hôpital offrant des soins agressifs.

Les patients vivant à proximité des hôpitaux offrant des soins agressifs ont été plus à même de recevoir des soins agressifs que les patients vivant plus loin (par exemple, 26% contre 19% ont respectivement bénéficié d'une cathétérisation dans les 30 jours). Cependant, selon l'estimation par la variable instrumentale, les soins agressifs n'étaient pas associés à une réduction de mortalité marginale, en comparaison avec les soins moins agressifs (par exemple, différence ajustée à un an: 4%; IC à 95%: -11% à 20%).

L'approche agressive des soins post-IMA n'est pas associée à une réduction sur la mortalité marginale au Québec.

Preface

This thesis was written as a collection of manuscripts submitted for publication, logically joined and integrated through supplementary, connecting texts. The following paragraphs describe the requirements of a thesis-by-manuscript at McGill University.

> Candidates have the option of including, as part of the thesis, the text of one or more papers submitted or to be submitted for publication, or the clearly-duplicated text of one or more published papers. These texts must be bound as an integral part of the thesis.
>
> If this option is chosen, connecting texts that provide logical bridges between the different papers are mandatory. The thesis must be written in such a way that it is more than a mere collection of manuscripts; in other words, results of a series of papers must be integrated.
>
> The thesis must still conform to all other requirements of the "Guidelines for Thesis Preparation". The thesis must include: a table of contents, an abstract in English and French, an introduction which clearly states the rationale and objectives of the study, a review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.
>
> Additional material must be provided where appropriate (e.g. in appendices) and in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.
>
> In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers.

Suggested Short Title

Mortality following aggressive care post-acute myocardial infarction.

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Dedication

To my family.

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1 Introduction

1.1 Acute Myocardial Infarction in Canada

Despite recent advances in the treatment of acute coronary syndromes such as acute myocardial infarction (AMI) and unstable angina, these diseases continue to place a significant burden on the health of Canadians. Both mortality from AMI and incidence rates of hospital admission for AMI have decreased slightly in recent years (Heart and Stroke Foundation of Canada 2000). However, as the number of elderly in the Canadian population is increasing, the absolute number of hospital admissions for AMI is rising. The age-standardized (to the 1991 Canadian population) rate of hospitalization for AMI in Canada decreased from 223.57 per 100 000 in 1985 to 190.17 per 100 000 in 1995. The absolute number of hospitalizations for AMI in Canada rose from 53 713 in 1985 to 57 230 in 1994. This increasing trend for the number of hospitalizations is expected to continue for fifteen years (Heart and Stroke Foundation of Canada 2000). Treatment of AMI is also technologically intensive and costly, and quality of life and the ability to return to work are negatively affected in survivors of AMI (Heart and Stroke Foundation of Canada 2000). Thus, identification of the approach to care of AMI that best improves patients' survival and other patient outcomes is critical for the provision of high-quality, cost-effective care.

1.2 Variations in Approaches to Care for Acute Myocardial Infarction

Numerous clinical trials have demonstrated the efficacy of certain cardiac procedures and medications in improving survival and other clinical outcomes after AMI (Yusuf et al. 1994). Evidence from these trials has been incorporated into various guidelines for clinical practice (ACC/AHA Guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines 1996; Fallen et al. 1995; Ryan et al. 1999), which have been developed to aid physicians in determining the appropriate course of treatment for AMI. Despite the widespread dissemination of these evidence-based guidelines, results from previous studies have shown that physicians' approach to care for AMI patients varies considerably across

geographic regions and practice settings. Most notably, certain regions consistently adopt an aggressive approach to care following acute myocardial infarction (AMI) - using invasive procedures such as cardiac catheterization in all patients and revascularization in most patients – while other regions consistently adopt more conservative approaches – using invasive cardiac procedures more selectively. For example, hospitals in most regions of the United States adopt an aggressive approach, while hospitals in most regions of Canada adopt a conservative approach (Pilote et al. 1994; Rouleau et al. 1993; Tu et al. 1997). In addition, the availability of invasive cardiac procedures at tertiary care hospitals has been shown to be one of the strongest determinants of their use (Pilote et al. 1996). These variations persist even in the absence of differences between the regions or practice settings in patient characteristics that would indicate differences in the approach to care. They also persist despite the fact that the current evidence-based guidelines endorse the conservative approach. For instance, the extensive guidelines published by the American College of Cardiology/American Heart Association currently recommend that cardiac catheterization and percutaneous transluminal coronary angioplasty (PTCA) should be performed primarily for patients with complicated AMI (ACC/AHA Guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines 1996; Ryan et al. 1999). These complications include spontaneous or mild exertion-induced myocardial ischemia during recovery, persistent hemodynamic instability, and mechanical complications of AMI, such as acute mitral regurgitation. These guidelines also point out that there is no convincing evidence to support routine cardiac catheterization and PTCA after successful thrombolytic therapy.

The geographic variations in the approach to care for AMI has raised the concern that certain patients are not receiving the recommended care, while other patients are receiving unnecessary care, which can put patients at unneeded risk and is not cost-effective. It is therefore important that the factors influencing the practice variations, and the effects of these variations on patient outcomes, be evaluated.

1.3 Trends in Care for Acute Myocardial Infarction in Canada

Although there are little data to support the use of invasive procedures in patients with non-complicated AMI, the aggressive approach is being increasingly adopted in Canada. For example, the age- and sex-adjusted 1-year cumulative incidence rate of cardiac catheterization after a first AMI in Quebec rose from 28% in 1988 to 43% in 1998 (Pilote et al. 2000). The same increasing trend has been observed in rates of use of PTCA and CABG. The 1-year cumulative incidence rate of PTCA rose from 8% to 23% and that of CABG from 6% to 9% from 1988 to 1998, respectively (Pilote et al. 2000). Similar trends have been observed in Ontario (Tu et al. 1999). Given that AMI is highly prevalent in Canada and that its current management bears a substantial and increasingly technological focus, the question of whether or not an aggressive versus a conservative approach to care after AMI improves patient outcomes holds major policy and health care implications.

1.4 Methodologic Approaches to Determine the Effects of Post-AMI Care

The question of whether or not an aggressive versus a conservative approach to care after AMI results in improved patient outcomes has been previously addressed in randomized controlled trials and observational studies. The randomized controlled trial is the gold standard of study designs for comparing two different medical interventions. By randomly allocating subjects to different groups that will each receive a particular treatment intervention, the study design aims to ensure that both groups are similar in all respects except for the intervention received, thus minimizing bias (Hornberger and Wrone 1997). This design allows the estimation of the *efficacy* of the treatment intervention on patient outcomes. That is, it allows the investigator to evaluate whether the treatment intervention can have an effect on outcome under the optimal, experimental-like conditions of the randomized controlled trial (Kramer 1988).

Despite the advantages of the randomized controlled trial design, there has also been increasing interest in the use of outcomes research methodology to determine the effects of different approaches to post-AMI care on patient outcomes. These outcomes research studies are observational, studying actual practice patterns and their effects in patient populations, and typically involve the use of a large administrative database (Ray

1997). This interest has developed in part because ethical, practical and cost considerations can limit the use of randomized clinical trials that compare the aggressive and conservative approaches to post-AMI care (Hornberger and Wrone 1997). In addition, the fact that clinical trials enroll selected patient populations, such as patients who are younger and healthier than the average patient with AMI, has been criticized as inadequate for clinical decision-making and policy development (Tu et al. 1997). In these respects, administrative databases are at an advantage in comparison to randomized controlled trials for they provide a relatively inexpensive, readily accessible means to obtain population-based, long-term follow-up data for a large numbers of patients. Finally, investigators have become interested in evaluating the factors influencing observed regional and international practice variations and the effects of these variations on patient outcomes (Roper et al. 1988). Outcomes research studies using administrative databases can help address such questions, providing an important complement to results from clinical trials by evaluating the *effectiveness* of approaches to care in addition to treatment efficacy. That is, they allow investigators to evaluate whether the treatment intervention can have an effect on outcome under "real-world" conditions (Kramer 1988).

1.5 Limitations of Administrative Database Research

Despite the interest in using administrative databases to answer questions related to the effectiveness of AMI care, this approach has several limitations (Byar 1991; Wen et al. 1995). One important limitation is that there is a strong potential for confounding bias due to differences between comparison groups in terms of patient characteristics that have not been captured in the database. For instance, there may be many patient characteristics not captured in the database that are associated with physicians' decisions as to whether or not to treat their patients aggressively. If these characteristics are also associated with patients' outcomes, they will bias outcome measures if they are not accounted for. This bias is termed *confounding by indication*. When the confounding variables are not captured in a database, they cannot be accounted for using standard statistical methods. It is therefore necessary to use alternative approaches to account for these unobserved confounding variables related to treatment assignment.

1.6 Alternative Approaches to Control Confounding Bias in Administrative Database Research

Several alternative approaches to control confounding bias in administrative database research have been previously applied and described in the literature. Some of these approaches involve "risk-adjustment" methods, which rely upon adjustment for measured, observable variables selected by investigators as potential confounding variables. These approaches include the "Clinical Classification for Health Policy Research" method described by Cowen et al. (Cowen et al. 1998) or the "clinical comorbidity index" designed by Deyo et al. (Deyo et al. 1992). Along similar lines, the "two-stage sampling design" described by Collet et al. (Collet et al. 1998) relies upon detailed chart review data collected for a sample of subjects included in a large administrative database to adjust for potential confounding variables.

One important limitation of the "risk-adjustment" approaches is that they cannot ensure that all potential confounding variables have been accounted for. Other, unmeasured variables may still confound outcome measures.

1.7 Instrumental Variables: An Additional Alternative Approach

Instrumental variables methodology is another approach that does not rely upon adjustment for measured potential confounders. This methodology was developed and has been widely applied in economics research (Bowden and Turkington 1984), and it has recently begun to be applied in medical outcomes research (Gowrisankaran and Town 1999; Ho et al. 2000; McClellan et al. 1994). In the instrumental variables-estimation strategy, an "instrument" or "instrumental variable" is selected by the investigator that can be used in analyses to form groups of subjects that are unrelated to confounding variables, but have different probabilities of receiving a particular treatment or approach to care. In this sense, instrumental variables-estimation allows a "pseudo-randomization" of study subjects, giving it an important advantage over the "risk-adjustment" approaches. In other words, the instrumental variable is used in lieu of randomization to determine treatment status and to attempt to ensure that, on average, the characteristics of study subjects receiving and not receiving treatment are similar. The effect of treatment is thus isolated from the effects of the confounding variables, and so it is possible to

estimate the magnitude of effect that the variation in treatment induced by the instrumental variable has on the outcome of interest.

In recognition of its potential advantages, the instrumental variable approach was previously applied to estimate the effectiveness of the aggressive approach to post-AMI care in elderly United States Medicare beneficiaries (McClellan et al. 1994). By demonstrating that outcome measures obtained using instrumental variables methodology were likely less biased than outcome measures using standard methodology, this study suggested that instrumental variables methodology has strong potential as a methodologic tool that can be used to estimate the effectiveness of post-AMI care using administrative data. Given this potential, instrumental variables methodology should be reapplied in different patient populations to further address the current debate concerning the appropriate approach to post-AMI care.

1.8 Study Rationale

Although randomized clinical trials can provide important evidence as to the efficacy of various approaches to post-AMI care, observational methods can also be used to study actual patterns of care for AMI and their effectiveness on patient outcomes. Administrative data on acute care hospital admissions and in- and out-patient services that are increasingly readily available can provide a means to evaluate this effectiveness. However, administrative database research is limited by its strong potential for confounding bias due to unobserved case-mix variation. Therefore, it is important that methodological approaches that can control for this bias be explored. This thesis responds to these avenues for future research by applying instrumental variables methodology to data from administrative sources in order to estimate the effectiveness of an aggressive versus a conservative approach to treatment of AMI in a Quebec patient population.

2 Literature Review

2.1 Preface to Manuscript # 1

Numerous studies have investigated whether an aggressive approach to treatment of acute coronary syndromes results in improved clinical outcomes in comparison to a conservative approach. These studies have been experimental in design – randomized controlled trials – as well as observational – such as retrospective cohort studies using data from registries or administrative sources. As the central aim of this thesis was to compare mortality outcomes for patients with AMI who were treated with the aggressive versus the conservative approach, it was important to review the previous literature on this topic. The following manuscript is a review of the key methodologic features and results of randomized controlled trials and observational studies that have compared clinical outcomes in patients treated with an aggressive versus a conservative approach following hospital admission for acute coronary syndromes.

This manuscript will be submitted to *Annals of Internal Medicine* in May, 2001. The subject matter presented here is timely and original in content; while there have been reviews published on the efficacy of specific procedures post-AMI, to our knowledge this review is the first to synthesize evidence of the efficacy and effectiveness of an aggressive approach to the treatment of acute coronary syndromes in comparison to a conservative approach.

2.2 Authors' Contributions

As first author, I conducted the literature search, was actively involved in the study design, abstraction and interpretation of data, and drafted and revised the manuscript. Dr. Louise Pilote, as thesis supervisor, contributed to all stages of the research, including study planning and execution, interpretation of data, and critical revision of the manuscript.

2.3 Manuscript #1

Aggressive versus Conservative Treatment for Uncomplicated Acute Coronary Syndromes: A Review of Clinical Trials and Observational Studies

(Suggested Short Title: Aggressive versus Conservative Treatment for Acute Coronary Syndromes)

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Abstract

There is current debate as to whether or not patients with uncomplicated acute coronary syndromes should be treated with an aggressive – routine cardiac catheterization and invasive revascularization of coronary arteries with suitable anatomy - or a conservative approach – cardiac catheterization and revascularization only for patients who demonstrate clear clinical indications. We reviewed randomized controlled trials and observational studies that have compared clinical outcomes in patients treated with an aggressive versus a conservative approach for uncomplicated acute coronary syndromes. This review found consistency of results across study designs, type of acute coronary syndrome, ages of patients enrolled, and duration of follow-up. Four randomized controlled trials enrolled exclusively patients with ST-segment elevation AMI, and in each of these trials the aggressive approach was not associated with reductions in mortality or rates of reinfarction. Four randomized controlled trials enrolled patients with non-ST-segment elevation AMI. In the two earliest of these trials (1994-1998) there were no differences in clinical outcomes between the comparison arms, while in the two most recent trials (1999-2000) the aggressive approach was associated with increased survival and less reinfarction. Increased prescription of certain medications known to improve survival and advances in technology available at the time these two trials were conducted may account for these findings. In each of the eighteen observational studies, the aggressive approach was not associated with improvements in clinical outcomes. However, a few of these studies suggested that the aggressive approach may be associated with improvements in "softer" outcomes, such as quality of life and functional status. Thus, evidence to date suggests that the aggressive approach does not result in improved clinical outcomes in comparison to the conservative approach for patients with ST-segment elevation AMI. Newer studies may be needed to determine whether this lack of association holds under current practice. Further study is also needed to determine whether the aggressive approach improves clinical outcomes for patients with non-ST-segment elevation AMI and unstable angina under current practice. Whether or not the aggressive approach improves quality of life and functional status remains an unanswered question, and so future studies should incorporate these outcome measures.

Introduction

There is current debate as to whether or not patients admitted to hospital with uncomplicated acute coronary syndromes should be treated with an aggressive or a conservative approach (1). The aggressive approach entails routine cardiac catheterization for all patients, followed by revascularization with percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG) if suitable coronary anatomy is demonstrated. In contrast, the conservative approach entails cardiac catheterization and revascularization with PTCA or CABG only for patients who demonstrate clear clinical indications for such treatment (2). Those who favor the aggressive approach argue that routine cardiac catheterization can be used to stratify patients according to their level of risk for future cardiac events, permitting timely and effective intervention (3). Those who favor the conservative approach argue that routine cardiac catheterization poses unnecessary risks to patients and wastes health care resources (4,5). They advocate that other non-invasive approaches to risk-stratification, such as the use of exercise treadmill testing, be adopted.

Numerous studies have investigated whether the aggressive approach to treatment of uncomplicated acute coronary syndromes results in improved clinical outcomes in comparison to the conservative approach. Understanding of this previous research could help resolve the current debate as to the appropriate course of treatment for patients with acute coronary syndromes. Such an understanding could also guide future research agendas. With these aims in mind, we reviewed the randomized controlled trials and observational studies that have compared clinical outcomes in patients treated with an aggressive versus a conservative approach for uncomplicated acute coronary syndromes.

Methods

Publications included in the review were identified by first searching for all relevant articles published in the English language between January 1, 1987 to November 30, 2000 (the date of the latest available citations as of January 31, 2001) in the MEDLINE database. The keywords used to identify the studies were *myocardial infarction* or *angina* (as both a subject heading and a keyword) combined with one of the following other keyword phrases: *aggressive treatment, aggressive management,*

conservative treatment, conservative management, invasive treatment, invasive management, non-invasive treatment, non-invasive management, regional variation, angiography, catheterization laboratory and *availability*. The reference lists in all publications selected from this search were then screened to obtain other relevant studies. Next, we conducted a manual search of the table of contents of the issues of several journals that had been published since November 30, 2000. These journals were: *American Heart Journal, American Journal of Cardiology, Annals of Internal Medicine, Archives of Internal Medicine, British Medical Journal, Circulation, JAMA, Journal of the American College of Cardiology, Lancet,* and *The New England Journal of Medicine*. Finally, to identify any relevant studies that had not yet been published, we conducted a manual search of the abstracts published in the supplements for the most recent annual meetings of the American Heart Association, American College of Cardiology and the European Society of Cardiology.

There were pre-determined criteria for selecting the publications to be included in this review. The randomized controlled trials must have randomly allocated patients with uncomplicated ST-segment elevation AMI, uncomplicated non-ST-segment elevation AMI and/or unstable angina to either an aggressive or a conservative treatment strategy. The aggressive treatment strategy had to include routine cardiac catheterization. The conservative treatment strategy had to restrict cardiac catheterization only for patients demonstrating clear clinical indications, such as spontaneous or exercise-induced ischemia (6,7). In the randomized controlled trials, the decision to use PTCA or CABG, and other medical therapies could be dictated by guidelines of the study protocol, or left to the discretion of the treating physician. Any clinical definition of AMI or unstable angina was acceptable.

The observational studies selected for review must have compared outcomes for patients with acute coronary syndromes (any definition) across geographic regions or hospitals with and without availability of cardiac catheterization. This review focused on these two types of comparison groups because they perhaps best provide a natural experiment. That is, they allow comparisons of outcomes across populations that differ substantially in the approach to treatment, but should not differ substantially in terms of other characteristics associated with the outcomes, such as severity of the infarct. The

availability of cardiac catheterization at the hospital of admission has also been shown to be one of the strongest determinants of its use (8). For the purposes of this review, the region(s) with the highest cumulative rates of use of cardiac catheterization over the follow-up period were included in the "aggressive" comparison group, while the other region(s) were included in the "conservative" comparison group.

The clinical outcomes of interest for this review were the cumulative incidences of reinfarction and death throughout the follow-up period. Therefore, all studies reviewed had to include these data. In addition, for relevance to current practice, all studies reviewed had to have been conducted when thrombolytic drugs were used in regular clinical practice following hospital admission for acute coronary syndromes. Studies that focused on comparisons across a sub-group of patients with another medical condition, such as stroke, were not reviewed.

Randomized Controlled Trials

ST-Segment Elevation Acute Myocardial Infarction

Whereas acute coronary syndromes have traditionally been classified by the appearance or non-appearance of Q-waves during electrocardiography, contemporary classification criteria are based on the thinking that the thrombotic events producing acute coronary syndromes manifest themselves in a clinical spectrum ranging from silent ischemia to sudden death (9). Unstable angina, non-ST-segment elevation AMI and ST-segment elevation AMI are part of this spectrum, ranging from less to more severe, respectively. The four earliest trials (published between 1988 and 1993) to compare aggressive versus conservative treatment for uncomplicated acute coronary syndromes enrolled exclusively patients with ST-segment elevation AMI (10-16) (Table 1). These trials enrolled from 201 to 3339 patients, and had follow-up periods that ranged from three months to three years. In each of the four trials, the protocols outlining treatment for patients allocated to the conservative arm were similar. Patients were given non-invasive medical therapy according to local practice or the study protocol, and only received cardiac catheterization if they demonstrated clear clinical indications. Where the trials differed most was in terms of the time delay before use of routine catheterization for patients allocated to the aggressive arm. Thus, these trials evaluated the most appropriate

timing of aggressive treatment in addition to whether or not aggressive treatment improved patient outcomes.

European Cooperative Study Group trial

Simoons et al. (for the European Cooperative Study Group) conducted a trial that enrolled 367 patients in six European countries to determine whether "immediate" catheterization followed by PTCA of an infarct-related artery with suitable coronary anatomy would open occluded vessels and reduce residual coronary stenosis after thrombolytic therapy, and if these effects would improve clinical outcomes such as reinfarction (10). The 183 patients allocated to the aggressive arm received cardiac catheterization as soon as the catheterization laboratory was available following thrombolytic therapy (range: 0.1-2.75 hours). In addition to measuring the clinical course over the follow-up period, enzymatic infarct size and global left ventricular function were measured for all patients by catheterization and ventriculography prior to hospital discharge. After three months of follow-up, it was found that outcomes were more favorable overall for patients in the conservative arm. Cumulative mortality rates were substantially higher in the aggressive arm than in the conservative arm (8.2% versus 3.3%), and so the trial was stopped prematurely. Enzymatic infarct size and left ventricular function did not differ between the treatment arms. Based on this evidence, the investigators concluded that "immediate" aggressive treatment of patients with uncomplicated ST-segment elevation AMI was unnecessary. In addition, they provided evidence to suggest that immediate aggressive treatment was associated with a high rate of early reocclusion and/or early recurrent ischemia.

TIMI II

Two additional trials attempted to determine whether a "delayed" aggressive approach would improve clinical outcomes after uncomplicated ST-segment elevation AMI. In the Thrombolysis in Myocardial Infarction II (TIMI II) trial, which was conducted in the United States, the 1681 patients allocated to the aggressive arm received cardiac catheterization 18 to 48 hours after thrombolytic therapy (11,15,16). This trial was the largest of the four trials that enrolled patients with ST-segment elevation AMI

(n=3339), and had the longest follow-up period (three years). The primary endpoint was survival free of reinfarction at 42 days, but incidence of clinical events and angina status were also measured throughout the follow-up period. The trial found no difference in cumulative mortality or reinfarction at any time during follow-up between the aggressive versus conservative arms (one year mortality: 6.9% versus 7.4%, p=0.59, one year reinfarction: 9.4% versus 9.8%, p=0.81). There were also no differences in angina status between the treatment arms. Thus, the TIMI II trial provided evidence that aggressive treatment does not improve clinical outcomes following uncomplicated ST-segment elevation AMI, even if this treatment is delayed for up to 48 hours post-thrombolysis.

SWIFT

The Should We Intervene Following Thrombolysis (SWIFT) trial, which enrolled 800 patients and was conducted in Britain and Ireland, also compared the "delayed" aggressive approach with the conservative approach after up to one year of follow-up (14). In this trial, the 397 patients allocated to the aggressive arm received cardiac catheterization within 48 hours after randomization. As in the TIMI II trial, there was no difference in mortality or reinfarction at any time during follow-up between the aggressive versus conservative arms (one year mortality: 5.8% versus 5.0%, p=0.64, one year reinfarction: 15.1% versus 12.9%, p=0.42). The authors did point out, however, that these results could not be necessarily be applied to patients excluded from the trial, such as those with reinfarction or cardiogenic shock, who were likely at higher risk of clinical events than the patients included in the trial. In contrast, previous infarction and cardiogenic shock were not exclusion criteria in the TIMI II trial (e.g. approximately 14% had a previous infarction).

TIMI II A sub-study

The TIMI II A sub-study compared both the "immediate" and "delayed" aggressive strategies with the conservative approach (12). In this sub-study, which enrolled 586 patients, there were two aggressive arms, one where patients received cardiac catheterization as soon as possible following thrombolytic therapy, and one where patients received catheterization within 18-48 hours. All patients received catheterization

prior to discharge. By one year of follow-up, clinical outcomes were similar for patients in the aggressive and conservative arms, regardless of the timing of aggressive treatment (e.g. "immediate" aggressive versus conservative, mortality: 8.2% versus 10.2%, reinfarction: 9.5% versus 9.6%). Thus, the TIMI II-A sub-study provided additional evidence to suggest that both the "immediate" and "delayed" aggressive approach do not improve clinical outcomes after uncomplicated ST-segment elevation AMI.

Barbash et al.

Finally, in a trial conducted by Barbash et al. in Israel, routine catheterization was delayed for at least 72 hours after admission for the patients in the aggressive arm (13). The rationale behind this delayed use of catheterization was that aggressive treatment given too soon after thrombolytic therapy, when the risk of reocclusion is still high, may not result in clinical benefits, while aggressive treatment given at a time when this risk is reduced may improve clinical outcomes. This trial was the smallest of all the trials that enrolled patients with ST-segment elevation AMI (n=201), but it had a follow-up period of one year. Reinfarction and mortality were the primary endpoints, and left ventricular function, angina status and frequency of rehospitalization were also measured at clinic visits made at regular intervals throughout the follow-up period. As in the previous trials, there was no difference in cumulative mortality or reinfarction at one year between the aggressive versus conservative arms (mortality: 8.2% versus 3.8%, p=0.15; reinfarction: 3.0% versus 3.8%). As there were no clinical benefits resulting from delayed aggressive treatment for patients with uncomplicated ST-segment elevation AMI, the investigators concluded that the conservative approach was preferable.

The four trials that enrolled patients with uncomplicated ST-segment elevation AMI have provided convincing evidence that aggressive treatment of uncomplicated ST-segment elevation is not associated with reductions in mortality or incidence of reinfarction. Other than due to the consistency of their results, these trials have provided convincing evidence because of their design. For instance, there was no evidence to suggest that randomization did not result in comparability of patient characteristics between the comparison arms. Attempts were also made to balance the numbers of patients allocated to each treatment arm at each study center, and when determining study

endpoints, steps were taken to blind the investigators of the treatment status of patients in each arm. Follow-up rates were also high (approximately 95% or higher) and analyses were by intention to treat.

Although the trials have provided strong evidence that aggressive treatment of uncomplicated ST-segment elevation does not improve clinical outcomes, these trials had a number of limitations that should be addressed. One important limitation is crossover from the conservative to the aggressive arm. In the four trials, between 13% and 38% of patients allocated to the conservative arm received cardiac catheterization during the initial hospitalization. By the end of follow-up, these rates were up to 100% in the trials that gave catheterization to all patients prior to discharge (European Cooperative Study and TIMI IIA), and were 48% in the TIMI II trial. Rates of PTCA were also quite high for patients allocated to the conservative arms (up to 24% in TIMI II A and Barbash trials), while rates of CABG were similar for patients in each comparison arm. This crossover brings to question whether the patients in the conservative arm actually received "conservative treatment", an important consideration when comparing outcome measures between the comparison arms. However, the fact that similar outcomes were observed for trials with different rates of crossover provides support for the conclusions of these trials.

Other limitations of these trials are common to many randomized controlled trials. For instance, with the exception of the TIMI II trial, these trials enrolled relatively few numbers of patients and had relatively short follow-up periods, probably due to constraints on costs and feasibility. The patients enrolled were also not comparable with the general population of patients with uncomplicated ST-segment elevation AMI, being quite young (average age in the trials was approximately 55 years while average age in general population is approximately 65 years (9)) and at low-risk of future events on average. As it is possible that aggressive treatment may be of more benefit to the older, high-risk patient, there may be limitations as to the generalizability of the trials' findings in actual clinical practice. However, the fact that similar findings have been demonstrated in observational studies, which enroll less selected patient populations, suggests that these limitations may be unfounded.

A possible shortcoming of these trials is that they were all published before

1993. Treatment of acute coronary syndromes has changed and continues to change over time, reducing survival rates for all patients and improving the outcomes of invasive cardiac procedures. For instance, there has been increasing prescription of medications known to improve survival after AMI, such as beta-blockers and angiotensin-converting enzyme inhibitors (17). Results of invasive procedures have also improved by the use of stenting and platelet GP IIB/IIIa inhibition during percutaneous coronary interventions (9). Newer studies may be needed to determine whether this lack of association holds under current practice.

One final shortcoming of these trials is that they did not measure outcomes other than "hard" clinical outcomes. Although clinical outcomes such as mortality and reinfarction are important, much of medical care is also directed at relieving symptoms in order to improve quality of life and functional status. There is also some observational evidence that suggests the aggressive approach may be associated with improvements in these outcomes (18-20). As these four trials did not measure quality of life and functional status, whether the aggressive approach to treatment of uncomplicated ST-segment elevation AMI results in improvements in these "softer" outcomes remains an unanswered question.

Non ST-segment elevation AMI and Unstable Angina

The four most recent randomized controlled trials to compare aggressive versus conservative treatment for uncomplicated acute coronary syndromes, which were published between 1994 and 2000, enrolled patients with non-ST-segment elevation AMI and unstable angina (21-27). In part, this shift in focus reflects continuing uncertainty as to the appropriate course of treatment for patients within the lower-risk range of the clinical spectrum of acute coronary syndromes. Patients with non-ST segment elevation AMI or unstable angina represent a heterogeneous group with a wide-ranging level of risk (9). These patients are at increased risk for subsequent coronary events in comparison to patients with ST-segment elevation AMI. Those who favor the aggressive approach for patients with non-ST-segment elevation AMI or unstable angina suggest that routine catheterization and PTCA will reduce this risk. Those who favor the

conservative approach suggest that early percutaneous coronary interventions actually put patients at additional risk for adverse clinical events.

This shift in focus also reflects changes in the pathophysiology of patients with acute coronary syndromes that have resulted from the widespread administration of thrombolytic therapy. Many patients originally presenting with ST-segment elevation at admission present ST-segment depression following the receipt of thrombolytic therapy (9). Thus, the prevalence of patients with non-ST-segment elevation AMI and unstable angina has increased and is now greater than the prevalence of patients with ST-segment elevation AMI. This shift in prevalence has prompted increasing interest in determining the appropriate course of treatment for patients with acute coronary syndromes that do not present with ST-segment elevation.

The four trials that enrolled patients with non-ST segment elevation AMI or unstable angina enrolled from 920 to 2457 patients and had follow-up periods that ranged from six months to two years (Table 2). Again, some trials differed in the timing of the receipt of routine catheterization. Another important difference is that the two latest trials were conducted at a time when results of invasive procedures were improved by the use of stenting and platelet GP IIB/IIIa inhibition during percutaneous coronary interventions (1999-2000). In each of these four trials, the protocols outlining treatment for patients allocated to the conservative arms were similar to those in the trials that enrolled patients with ST-segment elevation AMI.

TIMI III B

The earliest trial was the Thrombolysis in Myocardial Infarction III B (TIMI III B) trial, which enrolled 1473 patients and was conducted in the United States (21,22). The results of this trial at six weeks and one year of follow-up were published in 1994 and 1995, respectively. Similar to the TIMI II trial, patients allocated to the aggressive arm (n=740) received catheterization within 18 to 48 hours after thrombolysis. The primary endpoint in this trial was a composite endpoint of death, reinfarction or an unsatisfactory exercise treadmill test at six weeks. The clinical outcomes, as well as angina status and incidence of rehospitalization, were also measured throughout the follow-up period. After both six weeks and one year, there were no differences in

mortality or rates of reinfarction between patients in the aggressive and the conservative arms (one year mortality: 4.1% versus 4.4%, p=0.79; one year reinfarction: 8.3% versus 9.3%, p=0.51). However, rates of readmission at one year were lower in the aggressive arm than in the conservative arm (26% versus 33%, p<0.001), while angina status was similar between the two arms. Based on these results, the TIMI III B investigators concluded that either strategy was appropriate for the treatment of patients with non-ST-segment elevation AMI or unstable angina.

VANQWISH

The second earliest trial - the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial – was published in 1998 (23). The VANQWISH trial enrolled 920 patients with non-ST-segment elevation AMI admitted at 15 Veterans Affairs hospitals in the United States. This trial adopted the same approach to aggressive treatment as the TIMI III B trial, except that investigators at each study site decided whether or not to proceed with immediate revascularization when coronary anatomy was suitable. In the TIMI III B trial, the decision was based on coronary anatomy alone. As in the TIMI III B trial, Boden et al. found no differences in mortality or reinfarction between patients in the aggressive and conservative arms over the course of follow-up (hazard ratio for mortality at mean follow-up of 23 months, 0.72; 95% CI: 0.51 to 1.01; reinfarction: 15.6% versus 17.5%). However, at one year, mortality was higher in the aggressive arm than in the conservative arm (12.6% versus 7.9%, p=0.025). These investigators concluded that the aggressive approach does not improve clinical outcomes for patients with non-ST-segment elevation AMI. It should be noted, however, that the results of this trial have been highly controversial (28-31). Critics have questioned the applicability of these results to clinical practice because of the high mortality rates observed in the trial, the underuse of medical therapies such as beta-blockers by the patients enrolled, and the relatively low rates of use of revascularization procedures at the Veterans Affairs hospitals. Nevertheless, this trial has added to the body of evidence that suggests the aggressive approach does not improve clinical outcomes for patients with uncomplicated acute coronary syndromes.

FRISC II

The FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial was the first to provide evidence that the aggressive approach may be associated with improvements in clinical outcomes for patients with non-ST-segment elevation AMI and unstable angina (24,25). This trial enrolled 2457 patients at 58 Scandinavian hospitals, and stenting and platelet GP IIB/IIIa inhibition were available during the time it was conducted. Results observed after six months and one year of follow-up were published in 1999 and 2000, respectively. In this trial, the 1222 patients allocated to the aggressive arm received cardiac catheterization within a few days of enrollment. The design of this trial was factorial. After being allocated to receive either aggressive or conservative treatment, patients in each arm were further randomly allocated to receive either treatment with dalteparin, or treatment with placebo for 3 months. At one year, aggressive treatment was associated with mortality benefits and lower rates of reinfarction in comparison to conservative treatment (mortality: 2.2% versus 3.9%, $p=0.016$; reinfarction: 8.6% versus 11.6%, $p=0.015$). In addition, patients allocated to the aggressive arm had less angina at six months, and fewer readmissions at both six months and one year, (angina: 22% versus 39% at six months, $p<0.001$; readmissions: 37% versus 57% at one year, $p<0.0001$). Based on the results of this trial, the investigators endorsed the aggressive approach to treatment of non-ST-segment elevation AMI and unstable angina.

TACTICS – TIMI 18

The most recent trial - the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction 18 (TACTICS - TIMI 18) trial - has also provided evidence that the aggressive approach is associated with improved clinical outcomes for patients with non-ST-segment elevation AMI and unstable angina (26,27). Although complete results for this trial have not been published, an abstract based on the results of this trial was published in 2000. This trial, which enrolled 2220 patients in the United States, allocated patients in the aggressive arm to receive cardiac catheterization within 4 to 48 hours after

randomization. Besides being conducted when stenting and platelet GP IIB/IIIa inhibition were available, this trial was different from others in that data on quality of life and costs incurred were collected prospectively along with data on clinical outcomes. As in the FRISC II trial, the aggressive approach was associated with improvements in clinical outcomes in comparison to the conservative approach (death or reinfarction at six months: 7.3% versus 9.5%, $p<0.05$). The data on quality of life and costs incurred have not yet been published.

Despite some questions as to the generalizability of the results of the VANQWISH trial, the design of these trials was sound. These trials also enrolled larger numbers of patients, who were less restricted in terms of age in comparison to the patients enrolled in the ST-segment elevation trials. Thus, these trials are better suited to detect clinically meaningful differences in rare clinical outcomes such as mortality, and the results are perhaps more generalizable to actual clinical practice. However, these trials also had limitations. For example, with the exception of the FRISC II trial, crossover from the conservative arm to the aggressive arm was even more frequent in these trials than in the trials that enrolled patients with ST-segment elevation AMI. For example, in the TIMI III B trial, cumulative rates of catheterization for patients in the conservative arm were 57.3% during the initial hospitalization. These differences may reflect physicians' beliefs that aggressive treatment is more beneficial for patients with non-ST-segment elevation AMI and unstable angina than for patients with ST-segment elevation AMI. However, they could also reflect the temporal trends for increasing use of invasive cardiac procedures that have been observed in the United States (32) and other countries (17,33). This crossover should be kept in mind when comparing outcomes across the two treatment arms.

There were some differences between the patients enrolled in the trials that could account in part for the differences in findings between the two earliest and two latest trials. For example, it is possible that a benefit from aggressive treatment was found in the FRISC II trial and not in the VANQWISH trial because the patients in the FRISC II trial were healthier, on average, than patients in the VANQWISH trial. The VANQWISH trial enrolled more smokers, while the FRISC II trial enrolled patients with less severe infarcts, as indicated by ST-shifts and enzyme markers. However, the TACTICS-TIMI 18

trial enrolled patients who were less healthy than patients in the FRISC II trial, and a benefit from aggressive treatment was observed. Other potentially important differences relate to the type of thrombolytic therapy administered. Careful attention should be paid to this potential explanation once the full results of the TACTICS-TIMI 18 trial are published.

It should also be noted that with the exception of the TACTICS – TIMI 18 trial, the trials did not measure non-clinical outcomes such as quality of life and functional status. These outcomes may be of particular relevance to patients with non-ST-segment elevation AMI and unstable angina, for they are at high risk of subsequent coronary events, which could negatively affect quality of life and functional status.

In sum, the evidence as to the appropriate approach to treatment of non-ST-segment elevation AMI and unstable angina is inconclusive. It may well be that the advances in available technology such as stenting and platelet GP IIB/IIIa inhibition have contributed to improved outcomes for patients with non-ST-segment elevation AMI and unstable angina treated with the aggressive approach, and that the aggressive approach should now be endorsed for these patients. However, additional trials are needed to confirm or reject these findings, and these trials should include measures of quality of life and functional status.

Observational Studies

Hospitals with and without Availability of Cardiac Catheterization

Six observational studies have compared clinical outcomes for patients with ST-segment elevation AMI and non-ST-segment elevation AMI who were admitted to hospitals with and without availability of cardiac catheterization (34-39) (Table 3). The rationale behind making such comparisons is based on observations that the availability of cardiac catheterization at the hospital of admission is one of the strongest determinants of its use (8). In accordance with this observation, these studies found higher rates of use of catheterization for patients admitted at hospitals with availability of the procedure than for patients admitted at hospitals without availability of this procedure. This trend was also found for rates of use of PTCA and CABG. These differences in treatment were

found even after adjustment for potential confounders, or despite the fact that the measured characteristics of patients admitted at each type of hospital were similar.

Similar to the results of the randomized controlled trials, in all but one of these studies (37) the differences in treatment between the comparison groups were not associated with differences in mortality. Cumulative rates of reinfarction were only presented in one publication (38), and there were also no differences in these rates across the comparison groups. This absence of association held regardless of the duration of follow-up or the ages of the patients enrolled, and after adjustment for potential confounders. In addition, this absence of association held regardless of the source of data obtained for the study. For example, three of the studies used registry data (34,36,39). Two additional studies obtained data from administrative sources (37,38). One final study used data on procedures and outcomes that were obtained prospectively from hospital charts and vital status data from the Israeli National Population Register (35).

The only study that found an association between the availability of catheterization at the hospital of admission and mortality was conducted by Wright et al., who used registry data (37). Wright et al. compared outcomes for 24, 229 male veterans discharged from Veterans Affairs hospitals in the United States using data from the Veterans Affairs Patient Treatment File, a hospital discharge abstract database. They found that mortality rates were lower for patients admitted to hospitals with availability of catheterization than for patients admitted to hospitals without availability of catheterization (30.1% versus 33.4% at two years, $p<0.0001$; adjusted OR, 0.86; 95% CI: 0.81 to 0.92). It has been suggested that the lower overall procedure use at the Veterans Affairs hospitals in comparison to other hospitals may account for the association between availability of catheterization and reductions in mortality observed in this study (36,37). That is, with more selective use of the aggressive approach, the patients who received aggressive treatment were likely to receive significant benefit from it. Limited access to transfer between the hospitals with and without catheterization laboratories participating in this study may also partly explain this finding (36,37). Further studies in regions with lower overall procedure use are necessary to confirm or reject these hypotheses.

In sum, the results of these observational studies provide more evidence to suggest that aggressive treatment of patients with ST-segment elevation AMI and non-ST-segment elevation AMI is not associated with improvements in clinical outcomes. These observational studies provide an important complement to the results from the clinical trials by evaluating the effectiveness of approaches to treatment in addition to treatment efficacy. The studies also enrolled larger numbers of patients who were perhaps more representative of the general AMI patient population than the patients selected for randomized controlled trials, and they provide long-term follow-up data. Despite these advantages, however, the observational studies are at an important disadvantage over the randomized controlled trials because treatment assignment was not random. Also, the sources of data for such studies, and in particular the data from administrative sources, provide limited information about patient characteristics that could confound outcome measures. For instance, it is likely that healthier patients are selected to undergo catheterization, and that this selection cannot be fully accounted for by adjustments for age, sex and cardiac history (34). Finally, few studies have addressed the accuracy of the data sources used in these observational studies (40). Therefore, although the consistency of the results of these studies is convincing, the limitations of their design should be considered when interpreting their outcome measures.

Geographic Regions

In addition to variations in treatment of acute coronary syndromes across hospitals with and without cardiac catheterization facilities, marked variations in the approach to treatment of acute coronary syndromes have been observed across different geographic regions. These variations persist even in the absence of differences between the regions or practice settings in patient characteristics that would indicate differences in the approach to care. Thus, by providing a natural experiment, these comparisons are also useful in evaluating the impact of variations in treatment on clinical outcomes in actual clinical settings.

Twelve studies compared clinical outcomes for patients with acute coronary syndromes who were admitted in different geographic regions (Table 4). In seven of these studies, comparisons were made between patients admitted in regions in the United

States versus regions in Canada (18,41-46). In two other studies, the comparisons were made between different regions within the United States (47,48). The remaining three studies made comparisons across a number of different countries (49-51).

Other than the geographic regions compared, these studies differed in terms of the types of acute coronary syndrome sustained by the patients enrolled, the sources of data for the study, and the age ranges of the patients enrolled (Table 4). However, a number of trends were consistently evident across these studies. One trend was that the approach to treatment of acute coronary syndromes in the United States was more aggressive than the approach in the other countries. For example, we conducted a retrospective cohort study that compared treatment and outcomes between patients with ST-segment elevation AMI admitted to two university hospitals in the United States and Canada: Stanford (Calif) University Hospital (Stanford University) in the United States and Royal Victoria Hospital (McGill University) in Canada (41). In this study, which was published in 1994, cumulative rates of catheterization, PTCA and CABG at two years were higher for patients admitted to the Stanford University hospital than for patients admitted to the McGill University hospital (catheterization: 52.7% versus 29.8%; PTCA: 33.5% versus 12.6%; CABG: 14.2% versus 11.2%). These findings were also evident in a later (1997), larger study by Tu et al. that enrolled only patients over aged 65 years (44). These investigators compared outcomes at 180 days between patients admitted with ST-segment elevation or non-ST-segment elevation AMI in the United States and in the province of Ontario, Canada, using data obtained by linking various government administrative databases from the respective regions (catheterization: 39.5% versus 10.4%; PTCA: 14.0% versus 2.8%; CABG: 14.5% versus 3.5%). The differences in treatment between the United States and Canada have raised questions as to whether or not invasive cardiac procedures are overused in the United States or underused in Canada (1).

Another trend evident in these studies was that variations in the approach to treatment also exist within single countries. Both Pilote et al. (47) and Guadagnoli et al. (48) found that there was significant variation in rates of use of catheterization within different regions of the United States. Pilote et al. found that rates of catheterization during the initial hospitalization were highest in the South Central Region and lowest in

the New England region (81% versus 52%, respectively). Guadagnoli et al. found that rates of use of catheterization at 90 days were higher in Texas than in New York (45% versus 30%, respectively). Again, these differences in treatment raise questions about potential overuse of cardiac procedures in certain regions and underuse in others.

Although these studies demonstrated variations in the approach to treatment across the different geographic regions, the differences in treatment were not associated with differences in clinical outcomes. In fact, there was a lack of difference in clinical outcomes even when the overall approach to treatment in the regions observed was not particularly aggressive (e.g. Tu et al. (44)). Assuming aggressive care had an impact on clinical outcomes, greater benefits would be expected in regions with more conservative care overall, for any aggressive care is likely to be more targeted towards the patients who will receive significant benefit.

As an example of the lack of benefit observed, Van der Werf et al., who used data from the Global Utilization of Streptokinase and tissue plasminogen activator for Occluded Coronary Arteries (GUSTO-1) study (52), found that there was no difference in mortality at 30 days between patients admitted in the United States and patients admitted in the fourteen other countries that participated in the trials (unadjusted rates: 6.8% versus 7.2%, p=0.9; adjusted comparisons: p=0.047) (49). This absence of association also held in a multi-country study by Yusuf et al. (50), who obtained data from the Organisation to Assess Strategies for Ischaemic Syndromes (OASIS) registry. Yusuf et al. compared rates of death from cardiovascular disease or reinfarction at six months for patients with non-ST-segment elevation AMI or unstable angina admitted in Brazil or the United States (most aggressive regions) and patients admitted in Canada, Australia, Hungary or Poland (least aggressive regions) (10.5% versus 10.8%, p=0.68). Only in a study by Langer et al. did it appear that the more aggressive treatment observed for patients admitted in the United States might result in improved clinical outcomes in comparison to the more conservative treatment observed for patients admitted in Canada (reinfarction: 6.9% versus 7.4%; mortality: 2.2% versus 4.0%) (42). However, after adjusting for baseline differences these differences were no longer evident (relative risk of death: 0.9; 95% CI: 0.6 to 1.2). Thus, with the exception of the

FRISC II and TACTICS-TIMI 18 trials, these observational studies agree with the results of the randomized controlled trials.

In contrast to the randomized trials and the other observational studies reviewed, quality of life and functional status were measured in a few of the studies that compared outcomes for patients admitted in different geographic regions. These measurements suggest that quality of life and functional status may be better for patients admitted in the regions with more aggressive treatment than for patients admitted in regions with less aggressive treatment. For example, Mark et al. found that general health was higher at one year for patients admitted in the United States than for patients admitted in Canada (mean general health score as rated on a scale from 1 to 100 with 100 indicating perfect health status: 80 versus 75, $p<0.001$) (18). This study was another sub-study of the GUSTO-1 trial. Both Mark et al. (18) and Pilote et al. (19) also found that functional status and angina status were better for patients admitted in the United States than for patients admitted in Canada. In contrast to these two studies, Guadagnoli et al. (48) found that patients admitted in Texas (aggressive region) were less likely to perform "instrumental activities of daily living" than patients admitted in New York (conservative region). However, they found no differences in perceptions of general health between the two regions. Finally, Rouleau et al. found that patients admitted in the United States had lower cumulative rates of activity-limiting angina than patients admitted in Canada (33% versus 27%, $p<0.007$) (43). One important limitation of these comparisons is that cultural differences rather than treatment differences between the two countries may have explained the findings. In addition, at the time these studies were conducted the predictors of quality of life and functional status had not been clearly defined. Lack of knowledge about these predictors makes it difficult to assess whether or not the statistical adjustments adequately accounted for differences between the patients in different regions that could bias unadjusted outcome measures. Thus, further studies are needed to determine whether differences in approaches to treatment of acute coronary syndromes affect quality of life and functional status.

In summary, although marked geographic variations in the approach to treatment of acute coronary syndromes have been observed, the results from these studies suggest that the variations do not impact clinical outcomes. However, results from a few studies

suggest that more aggressive treatment in certain geographic regions may be associated with improvements in quality of life and functional status. Again, although the consistency of the results of these studies is convincing, the limitations inherent to their observational design must be taken into consideration. For instance, there may have been important differences in health care delivery, health status of patients enrolled, as well as cultural differences between the regions compared that could bias outcome measures. It is unlikely that these differences can be entirely accounted for by standard statistical adjustments. Despite these limitations, being in agreement with previous randomized controlled trials, these studies provide more evidence to suggest that aggressive treatment does not improve clinical outcomes for patients with uncomplicated acute coronary syndromes.

Summary

Of eight randomized controlled trials and eighteen observational studies that have compared clinical outcomes in patients treated with an aggressive versus a conservative approach for acute coronary syndromes, only two of the randomized controlled trials (FRISC II and TACTICS – TIMI 18) found that the aggressive approach improved clinical outcomes. These two trials enrolled exclusively patients with non-ST-segment elevation AMI and unstable angina and, unlike the other trials, were conducted at a time when results of invasive procedures had been improved by the use of stenting and platelet GP IIB/IIIa inhibition during percutaneous coronary interventions. The fact that patients without ST-segment elevation may be most likely to benefit from aggressive treatment because they are at higher risk for recurrent ischemia and death, together with the advances in available treatments may explain the discrepancy between these two trials and the others reviewed. The fact that patients allocated to the conservative arm in the FRISC II trial were treated more conservatively than patients allocated to the conservative arm in other trials may also partly explain this trial's positive findings.

This review highlights the consistency of the results of the studies reviewed across study designs, type of acute coronary syndrome, ages of patients enrolled, and duration of follow-up. It also highlights a number of important limitations of the previous studies, such as crossover, lack of generalizabilty to certain patient populations or current

practice, small sample size and limited follow-up, and the possibility for confounding bias due to unmeasured differences between the treatment groups. In addition, only a few observational studies and one randomized controlled trial included quality of life or functional status outcomes as part of their study design. It may well be that the aggressive approach results in improvements in these non-clinical outcomes, but there is now insufficient evidence to support or refute this conclusion.

In summary, evidence to date suggests that the aggressive approach to treatment of uncomplicated acute coronary syndromes does not result in improved clinical outcomes in comparison to the conservative approach. However, recent improvements in invasive technology and increased prescription of medications known to improve survival following acute coronary syndromes may improve clinical outcomes following aggressive treatment. In particular, these improvements may benefit patients with non-ST-segment elevation and unstable angina. Newer studies may be needed to determine whether this lack of association holds under current practice. Further study is also needed to determine whether the aggressive approach improves clinical outcomes for patients with non-ST-segment elevation AMI and unstable angina under current practice. Whether or not the aggressive approach improves quality of life and functional status remains an unanswered question, and so future studies should incorporate these outcome measures.

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Table 1. Use of Invasive Cardiac Procedures and Clinical Outcomes for Patients with ST-Segment Elevation Acute Myocardial Infarction Randomized to Aggressive (Agg) or Conservative (Con) Treatment Post-thrombolysis.

First Author [Reference]	Year	Sample Size	CATH (in-hospital)		One Year Cumulative Incidence Rate* (%)									
					CATH		PTCA		CABG		Reinfarction		Death	
			Agg	Con	Agg	Con	Agg	Con	Agg	Con	Agg	Con	Agg	Con
CATH within 2.75 hours in Aggressive arm														
European Cooperative Study														
Simoons [10]	1988	367	98.4	0	†	†	91.8	-	4.9	3.8	6.6	9.8	8.2	3.3
TIMI II A‡														
Rogers [12]	1990	392	99.0	17.8	†	†	75.8	23.9	19.1	18.3	9.5	9.6	8.2	10.2
CATH within 18-48 hours in Aggressive arm														
TIMI II A‡														
Rogers [12]	1990	391	90.2	17.8	†	†	64.3	23.9	14	18.3	6.5	9.6	7.7	10.2
SWIFT														
SWIFT Group [14]	1991	800	95.0	13.4	-	-	42.6§	3.0§	14.9§	1.7§	15.1	12.9	5.8	5.0
TIMI II														
Williams [15]	1992	3339	97.2	27.5	98.0	45.2	61.2	20.5	17.5	17.3	9.4	9.8	6.9	7.4
Catheterization ³ 72 hours in Aggressive arm														
Barbash [13]	1990	201	94.8	37.5	-	-	54.6	24.0	11.3	3.8	3.0	3.8	8.2	3.8

- Denotes data not available.

CATH denotes cardiac catheterization, PTCA denotes percutaneous transluminal coronary angioplasty, CABG denotes coronary artery bypass graft surgery.

* All follow-up periods were one year, except for the European Cooperative Study, which was stopped prematurely at 3 months.

† As per study protocol, all patients were to receive cardiac catheterization just prior to hospital discharge (not included in in-hospital rates). However, cumulative incidence rates of catheterization were not presented.

‡ The TIMI II A substudy had three comparison arms: "immediate invasive", "delayed invasive" and "conservative".

§ Denotes cumulative rates during the initial hospitalization. Cumulative incidence rates for the entire follow-up period were not available.

Table 2. Use of Invasive Cardiac Procedures and Clinical Outcomes for Patients with Non-ST-Segment Elevation Acute Myocardial Infarction (AMI) and Unstable Angina Randomized to Aggressive (Agg) or Conservative (Con) Treatment Post-thrombolysis.

					One Year Cumulative Incidence Rate* (%)									
			CATH (in-hospital)		CATH		PTCA		CABG		Reinfarction		Death	
First Author [Reference]	Year	Sample Size	Agg	Con	Agg	Con	Agg	Con	Agg	Con	Agg	Con	Agg	Con
CATH within 4-48 hours in Aggressive arm														
TIMI III B														
Anderson [22]	1995	1473	97.8	57.3	99	73	39	32	30	30	8.3	9.3	4.1	4.4
VANQWISH †														
Boden [23]	1998	920	94.2	24.0	95.7‡	48.5‡	21.2‡	12.0‡	20.6‡	19.0‡	-	-	12.6	7.9
TACTICS-TIMI 18														
Cannon [27]	2000	2220	97.0	51.0	-	-	-	-	-	-	4.8	6.9§	3.3	3.5
CATH within 7 days in Aggressive arm														
FRISC II														
Wallentin [25]	2000	2457	96	10	99	52	44	21	38	23	8.6	11.6§	2.2	3.9§

- Denotes data not available.

CATH denotes cardiac catheterization, PTCA denotes percutaneous transluminal coronary angioplasty, CABG denotes coronary artery bypass graft surgery.

* All cumulative incidence data correspond to follow-up periods of one year except for the TACTICS - TIMI 18 trial, which correspond to follow-up periods of six months.

† Patients with non-ST-segment elevation AMI only.

‡ Refer to results over the entire course of follow-up (mean of 23 months). Data for one year of follow-up were not available.

§ $P<0.05$ for comparison.

Table 3. Use of Invasive Cardiac Procedures and Clinical Outcomes for Patients with Acute Coronary Syndromes: Data from Observational Studies Comparing Patients Admitted to Hospitals With (Agg) or Without (Con) Availability of Cardiac Catheterization.

First Author [Reference]	Year	Sample Size	Cumulative Incidence Rates* (%)									
			CATH		PTCA		CABG		Reinfarction		Death	
			Agg	Con	Agg	Con	Agg	Con	Agg	Con	Agg	Con
ST- and non-ST-segment elevation AMI												
Every [34]	1993	5867	65.7	36.3	28.2	9.1	12.3	8.5	-	-	9.6	11.0
Behar [35]	1995	1014	25.6†	10.1†	11.7†‡	4.6†‡	-	-	-	-	17.8	16.9
Wright [37] §	1997	24229	50.5‖	25.6‖	10.3‖	3.7‖	10.2‖	7.0‖	-	-	30.1	33.4 ¶
Every [36]	1997	12331	67.1†	39.3†	32.5†	13.2†	12.5†	9.5†	-	-	26	29 ¶
Krumholz [38] **	1998	2521	46.0	38.8	13.0	9.9	14.4	18.1	14.8	10.4 ††	45.1	44.5
Rogers§ [39]	2000	305812	64.9†	-	31.4†	-	14.5†	-	2.7†	2.4†¶	22.2	23.5
Non-ST-segment elevation AMI and unstable angina												
Yusuf [50]	1998	7987	61‡‡	30‡‡	21‡‡	9‡‡	22‡‡	11‡‡			11.3§§	9.9§§††

- Denotes data not available.

CATH denotes cardiac catheterization, PTCA denotes percutaneous transluminal coronary angioplasty, CABG denotes coronary artery bypass graft surgery. AMI denotes acute myocardial infarction.

* Follow up periods for the studies were as follows: Every (1993), initial hospitalization; Rogers, 90 days; Behar, 1 year; Wright, 2 years; Every (1997) and Krumholz, 3 years.

† Denotes cumulative rates during the initial hospitalization. Cumulative incidence rates for the entire follow-up period were not available.

‡ Data refer to cumulative incidence of PTCA or CABG.

Table 3. Use of Invasive Cardiac Procedures and Clinical Outcomes for Patients with Acute Coronary Syndromes: Data from Observational Studies Comparing Patients Admitted to Hospitals With (Agg) or Without (Con) Availability of Cardiac Catheterization.

§ Comparison is actually hospitals with CABG, PTCA and catheterization versus hospitals without CABG, PTCA and catheterization.

‖ Denotes cumulative rates over 90 days after admission. Cumulative incidence rates for the entire follow-up period were not available.

¶ P<0.0001 for comparison.

** Patients ≥ 65 years old.

†† P<0.05 for comparison.

‡‡ Denotes cumulative rates over 180 days after admission. Cumulative incidence rates for the entire follow-up period were not available.

§§ Rates correspond to composite endpoint of cardiovascular disease death and reinfarction.

Table 4. Observational Data of Use of Invasive Cardiac Procedures and Clinical Outcomes for Patients with Acute Coronary Syndromes: Data from Observational Studies Comparing Patients Admitted in Geographic Regions with More Aggressive (Agg) or Conservative (Con) Treatment.

			Cumulative Incidence Rate* (%)									
			CATH		PTCA		CABG		Reinfarction		Death	
First Author [Reference]	Year	Sample Size	Agg	Con	Agg	Con	Agg	Con	Agg	Con	Agg	Con
ST-segment elevation AMI only												
Pilote [41]	1994	518	60.5	41.8	33.5	18.2	14.2	11.2	13.3	7.7	27.9	27.0
Mark [18]	1994	3000	72†	25†	29†	11†	14†	3†	3.7†	4.5†	9.3	9.7
Van de Werf [49]	1995	41021	-	-	30.6	10.4	13.1	2.8	3.7†	4.3†‡	6.8	7.2
Pilote [47]	1995	21772	81†	52†	34†	22†	17†	9†	3.9†	4.1†	8.6	10.1
Langer [42]	1999	8803	85†	8†	56†	3†	-	-	6.9	7.4‡	2.9	4.3§
ST-segment and non-ST-segment elevation AMI												
Rouleau [43]	1993	2231	78.0	48.2	26.5	11.4	21.6	12.6	13.4	14.1	22.7	22.2
Guadagnoli [48] ‖	1995	3689	45¶	30¶	15¶	7¶	15¶	13¶	-	-	37	36
Tu [44] ‖	1997	233702	39.5**	10.4**	14.0**	2.8**	14.5**	3.5**	-	-	34.3	34.4
Matsui [51]	1999	694	86.6†	52.2†	61.9†	33.3†	10.3†	5.2†	-	-	11.9	19.4
Non-ST-segment elevation AMI and unstable angina												
Anderson [45]	1997	2375	67.3	69.2	23.9	30.7	19.2	17.3	5.0	4.2	6.8	7.5
Yusuf [50]	1998	7987	69.4	39.2	23.6	12.9	25.2	14.6	-	-	10.5††	10.8††
Fu [46] ‡‡	2000	1410	81†	42†	37†	16†	23†	8.9†	9.3**	11.8**	10.5	10.6
Fu [46] §§	2000	1762	77†	46†	25†	14†	19†	13†	5.8**	8.8**‡	6.7	7.6

- Denotes data not available.

CATH denotes cardiac catheterization, PTCA denotes percutaneous transluminal coronary angioplasty, CABG denotes coronary artery bypass graft surgery. AMI denotes acute myocardial infarction.

Table 4. Observational Data of Use of Invasive Cardiac Procedures and Clinical Outcomes for Patients with Acute Coronary Syndromes: Data from Observational Studies Comparing Patients Admitted in Geographic Regions with More Aggressive (Agg) or Conservative (Con) Treatment.

* Follow up periods for the studies were as follows: Van der Werf, 30 days; Yusuf, 6 months; Mark, Pilote (1995), Langer, Matsui, Anderson, Fu and Tu, 1 year; Pilote (1994) and Guadagnoli, 2 years; Rouleau, 24 to 60 months.

† denotes cumulative rates during the initial hospitalization. Cumulative incidence rates for the entire follow-up period were not available.

‡ $P<0.05$ for comparison.

§ $P<0.0001$ for comparison (adjusted P-value > 0.05).

‖ Patients ≥ 65 years old.

¶ denotes cumulative rates over 90 days after admission. Cumulative incidence rates for the entire follow-up period were not available.

** denotes cumulative rates over 180 days after admission. Cumulative incidence rates for the entire follow-up period were not available.

†† Rates correspond to composite endpoint of cardiovascular disease death and reinfarction.

‡‡ Patients with non-ST-segment elevation AMI only.

§§ Patients with unstable angina only.

2.4 Instrumental Variables Methodology: An Approach to Estimate the Marginal Effects of Post-AMI Care

The preceding review included examples of studies that were observational in design and utilized data from administrative sources to compare the effectiveness of an aggressive versus a conservative approach to post-AMI care. Several advantages of these observational studies were identified. For instance, in comparison to the randomized controlled trials reviewed, the administrative database studies contained larger numbers of patients, had longer follow-up periods, and studied broader patient populations. The results of these studies also complemented those of the previous randomized controlled trials, providing estimates of the effects of physicians' actual practice patterns on clinical outcomes.

Despite the attractiveness of the administrative database studies, they have the important drawback that they are limited by their strong potential for confounding bias due to unobserved case-mix variation. Instrumental variables-estimation is a methodology that can account for this bias. It is this methodology that was applied in this thesis, using data from administrative sources in order to compare the effectiveness of the aggressive versus the conservative approach to post-AMI care in Quebec. The following section describes instrumental variables methodology, and presents an example of its previous application.

2.4.1 Instrumental Variables-estimation

Instrumental variables methodology has been widely applied in economics research (Bowden and Turkington 1984), and has recently begun to be applied in areas of medical outcomes research (Gowrisankaran and Town 1999; Ho et al. 2000; McClellan et al. 1994). Instrumental variables-estimation is a regression-based technique that is used to yield unbiased and consistent measures of effect (regression coefficient) in situations when standard regression analysis does not yield valid measures of effect due to correlation between explanatory variables and the error term. This problem is common in economics research because of the difficulty in performing controlled experiments. For example, economists are often interested in analyzing the effectiveness of a government program (Econometric Issues for Survey Data 1997). In these situations, ordinary least

squares regression analysis has been the standard tool used to evaluate the effect of the program on outcomes such as income, employment or health. To be valid, however, regression analysis relies on the assumption that the conditional mean of the error term in the regression equation is zero (Econometric Issues for Survey Data 1997; Zohoori and Savitz 1997). If a variable that is correlated with the explanatory variable in the model is omitted because it is unobservable or the data are unavailable, then this assumption will not be met. Therefore, the error term will be correlated with one or more of the observed explanatory variables and the regression coefficient obtained from the regression analysis will be biased and inconsistent. Of note, in economics research of this kind, it is probable that many factors have at least some correlation with the explanatory variable and it is likely impossible to have knowledge of, or obtain information on, all of these factors. It is only when a variable that is highly correlated with the explanatory variable is omitted from a regression model that the bias in the regression coefficient will be strong enough to lead to false inference. It is in these cases when a statistical methodology such as instrumental variables-estimation should be applied.

Because government programs are not typically implemented randomly, in economics research evaluating the effectiveness of a government program the explanatory variable coding for such a program will almost certainly be correlated with the error term in a regression model. The regression coefficient obtained from such an analysis may therefore underestimate or overestimate the true effect of the program on the outcome of interest. Instrumental variables-estimation can circumvent this problem provided that an "instrumental variable" can be found that is correlated with the explanatory variable but uncorrelated with the error term (Econometric Issues for Survey Data 1997; Zohoori and Savitz 1997). This estimation is commonly performed by including the instrumental variable in a two-stage least squares regression model. In the first stage of this model, the instrumental variable(s) is regressed on each explanatory variable. In the second stage the outcome variable is regressed on the predicted value from the first-stage regression and any other independent variables included in the model. If the instrumental variable is valid, this estimation strategy will purge the regression model of the effects of the correlation between the explanatory variable and the error term, resulting in an unbiased and consistent measure of effect.

Thus, to be valid, the instrumental variable must meet the two basic conditions that were noted above: 1) the instrumental variable must be correlated with the explanatory variable, and 2) it must be uncorrelated with the error term.

2.4.2 Instrumental Variables Methodology in Outcomes Research

In medical outcomes research, correlation between explanatory variables and the error term will occur because of unobserved differences between comparison groups that influence both receipt of treatment and outcome (Harris and Remler 1998; Newhouse and McClellan 1998). For instance, when determining whether or not to care for patients with an aggressive versus a conservative approach, physicians may reserve aggressive care for the healthiest patients, who would have better outcomes even without this care. In this situation, standard regression analysis would overstate the beneficial effects of the aggressive approach to care of AMI patients (Harris and Remler 1998). This bias is referred to as confounding bias, and the correlated variables (such as those related to health status) are referred to as confounding variables.

Valid instrumental variables that can be used in outcomes research studies are observable factors that are associated with the receipt of a particular treatment or approach to care but do not directly affect patient outcomes (Harris and Remler 1998; Newhouse and McClellan 1998). For instrumental variables-estimation, study subjects are grouped based on their values of the chosen instrumental variable. If the instrumental variable is valid, then groups of subjects are formed that are similar in all aspects except for their likelihood of receiving the particular treatment of interest. In this sense, the instrumental variables approach is a method of "pseudo-randomization". The instrumental variable is used in lieu of a randomization to determine treatment status and to attempt to ensure that, on average, the characteristics of study subjects receiving and not receiving treatment are similar. The effect of treatment is thus isolated from the effects of the confounding variables, and so it is possible to estimate the magnitude of effect that the variation in treatment induced by the instrumental variable has on the outcome of interest. In two-stage least squares regression analysis, the outcome measure (regression coefficient) will represent the average effect of treatment for the study subjects whose treatment assignment was determined by the instrumental variable.

2.4.3 Marginal Estimates of Effectiveness

By measuring only the effect of treatment for study subjects whose treatment status was determined by the instrumental variable, instrumental variables-estimation produces incremental, or *marginal*, measures of effectiveness (Harris and Remler 1998). The subjects whose treatment status was determined by the instrumental variable are referred to as the *marginal* sub-population.

As an example, suppose an instrumental variable can have two values, 1 and 2. Subjects with a value 1 for this instrumental variable are placed into group 1. Subjects with a value 2 for this instrumental variable are placed into group 2. Now suppose that 45% of subjects in group 1 received a particular treatment, while 55% of subjects in group 2 received this treatment. Instrumental variable estimates will represent the effect of changing the rate of receipt of treatment by 10% - a marginal or incremental effect. In this example, some subjects in each group would always receive the treatment, while some subjects would never receive the treatment, regardless of their value for the instrumental variable. Instrumental variables-estimation provides no information about the effects of treatment for these subjects; it only provides information about the remaining, marginal subjects.

The estimates of effect typically obtained from randomized controlled trials are usually different from those obtained by applying instrumental variables-estimation in observational studies. In a randomized controlled trial, randomization attempts to ensure that the two comparison groups differ only in terms of the treatment that they receive. If there is perfect compliance, then 100% of the subjects in one group receive the treatment, while 0% of subjects in the other group receive the treatment. Thus, by simply subtracting the cumulative rates of the outcome of interest for patients in each comparison group, the average effect of treatment for the study population under investigation is measured. In contrast, instrumental variables estimates correspond to the marginal effect of treatment for the marginal sub-population. Should it be possible to recruit for the trial only those patients who make up the marginal sub-population, estimates that correspond to the effect of treatment for the marginal sub-population could also be obtained in randomized controlled trials. However, in many situations the

marginal sub-population is unlikely to be observable, limiting the potential to conduct such trials.

The differences between instrumental variables estimates and estimates obtained from randomized controlled trials highlight the fact that marginal outcome measures may be more relevant to health policy concerning post-AMI care (Harris and Remler 1998; McClellan and Newhouse 2000; Newhouse and McClellan 1998). The reason for this relevance is that instrumental variables-estimation answers questions in "matters of degree – how widely should a treatment be used?" (McClellan and Newhouse 2000). Randomized controlled trials are more apt to answer health questions in "absolute terms – should a particular treatment be used?" In particular, trials are more apt to answer such questions in situations when the marginal sub-population cannot be directly observed. Given that cardiac catheterization, PTCA and CABG do result in improvements in clinical outcomes for some patients, health policy questions concerning AMI treatment may be better answered in "matters of degree". In addition, questions concerning health policy are likely most relevant to the marginal patients, for whom the appropriate treatment is most uncertain.

2.4.4 A Previous Study of the Marginal Effects of Aggressive Care for AMI

McClellan et al. investigated whether an aggressive approach to post-AMI care reduced mortality in marginal, elderly United States Medicare beneficiaries who were admitted for AMI in 1987 (McClellan et al. 1994). It was hypothesized that outcome measures obtained from standard statistical methods would be biased because the Medicare database used for the study did not include many variables likely to be strongly correlated with receipt of aggressive care, such as severity of the infarct. Therefore, the investigators used differential distance between different types of hospitals (the difference between a patient's distance to the nearest hospital offering cardiac catheterization minus the patient's distance to the nearest hospital of any type) as an instrumental variable to account for the confounding bias. The choice of this instrumental variable was based on the assumption that AMI patients who lived closer to a hospital with availability of catheterization would be more likely to be admitted to these hospitals, and therefore be more likely to receive this procedure. In addition, it was assumed that

differential distance to a hospital with availability of catheterization was not correlated with confounding variables.

McClellan et al. demonstrated that there was likely appreciable bias in outcome measures obtained from standard statistical methods due to unobserved differences between comparison groups, and that instrumental variables-estimation could result in outcome measures that were likely to be less biased. To demonstrate this, they first compared unadjusted differences in cumulative mortality rates between patients who received catheterization within 90 days of admission and those who did not. Patients who received catheterization had mortality rates that were much lower than those for patients who did not receive catheterization within 90 days. However, there were also large differences in observable patient characteristics, such as age and comorbidities, between the comparison groups. The authors then used analysis of variance (ANOVA) methods to estimate the effect of receipt of catheterization within 90 days on mortality after adjusting for these observable differences. These estimates reduced the large mortality differences between comparison groups by up to 25%. However, by determining and comparing the average effect of hospital capability of catheterization on the use of this procedure using ANOVA and instrumental variables-estimation, they estimated that 15-20% of the differences in use of catheterization across hospital types was due to unobserved differences in case-mix. They then proceeded to use the instrumental variables to "pseudo-randomize" subjects into groups that had different likelihoods of receiving catheterization, but were similar in terms of other observed and unobserved characteristics. Comparison of groups of subjects that differed only in differential distance showed that receipt of catheterization within 90 days was associated with a reduction in mortality rates 1 to 4 years after AMI of at most 5 percentage points. These results were in contrast to those obtained from the ANOVA tests, where the receipt of catheterization was associated with a reduction in mortality of up to 28 percentage points. Two later observational studies conducted by McClellan (McClellan 1996) and Brooks, McClellan and Wong (Brooks et al. 2000) also showed small, but statistically significant, marginal benefits in mortality resulting from aggressive care using this methodology.

Taken alone, the different measures of effect obtained from the more standard ANOVA tests and instrumental variables-estimation would likely lead to substantial

differences in inference made as to the effectiveness of aggressive care. In particular, the measures of effect obtained from the ANOVA tests would have overestimated the beneficial effects of aggressive care. Assuming that the instrumental variable used was valid (tests of validity were performed), the study by McClellan et al. study provides a good example of the potential for instrumental variables-estimation as a methodological tool for measuring the effectiveness of post-AMI care using administrative data.

2.4.5 The Marginal Effects of Aggressive Care in Canada versus the United States

Although instrumental variables methodology holds promise as a tool to measure the effectiveness of different approaches to care for AMI, it has not been applied in AMI patient populations other than elderly insurance beneficiaries in the United States. To more fully evaluate the generalizability of outcome measures obtained using this methodology, it is important that it be re-applied in other age groups and patient populations. In particular, this methodology should be re-applied in populations from regions that adopt different approaches to post-AMI care. Regions that adopt different approaches to post-AMI care overall will be operating on different margins. We would expect the marginal mortality benefits resulting from aggressive care in regions with more conservative care overall (lower margin) to be greater than the marginal mortality benefits resulting from aggressive care in regions with more aggressive care overall (higher margin). For instance, the marginal benefits of aggressive care should be greater in Canada than in the United States. Greater benefits would be expected in Canada because with more conservative care overall, any aggressive care is likely to be more targeted towards the patients who will receive significant benefit. In regions with more aggressive care overall, more patients will receive aggressive care with more modest significant benefit. As instrumental variables methodology has already been applied to an elderly population of patients admitted for AMI in the United States, this study provides an opportunity to make such comparisons by applying the same methodology to a population of patients of any age-group who were admitted for AMI in Quebec.

3 Study Objectives

3.1 Research question

Is an aggressive approach to care following hospital admission for AMI more effective in reducing mortality than a conservative approach?

3.2 Study objectives

Primary objective:

- To evaluate the incremental (marginal) effectiveness of aggressive care on mortality in patients admitted for a first AMI in Quebec using instrumental variables methodology.

Secondary objectives:

- To compare the results observed in this study to those observed by McClellan et al. (1994) (McClellan et al. 1994), who addressed the same research question by applying instrumental variables methodology to elderly United States Medicare beneficiaries who were admitted for AMI in 1987. By making this comparison, we aimed to assess the generalizability of outcome measures obtained using instrumental variables methodology in different populations of AMI patients. Specifically, we compared patient populations from regions adopting different approaches to post-AMI care, as well as patient populations of different age groups.
- To compare the effectiveness of aggressive care on mortality in elderly ($\geq$ 65 years old at the time of admission for AMI) and younger ($<$ 65 years old) patients.

4 Study Methodology

4.1 Study Population and Sources of Data

Data on the treatment and clinical outcomes of all patients who sustained a first AMI in Quebec between January 1, 1988 and December 31, 1988 (n = 8995) were obtained retrospectively from two government administrative databases: the Quebec hospital discharge summary database (Med-Echo), and the Quebec Medicare database (*la Régie de l'assurance maladie du Québec* (RAMQ)). Data were obtained for a four-year follow-up period to December 31, 1992.

The Med-Echo database was used to identify patients for inclusion into the study cohort on the basis of a hospitalization with a main discharge diagnosis of AMI (ICD-9 code 410). To help ensure that the start of follow-up corresponded to the date of the first AMI for all subjects, the absence of a code for AMI was ascertained for at least 3 years preceding the diagnosis. The positive predictive value for coding an AMI in the Med-Echo database has been estimated to be 96% (95% confidence interval: 94% to 98%) (Levy et al. 1999). Patient demographic characteristics (age and sex) and the administrative code corresponding to the hospital to which each patient was admitted were identified from these data. Up to 15 secondary diagnoses are also entered into the Med-Echo database; these secondary diagnoses were used to obtain data on subjects' co-morbid diseases. The co-morbid diseases studied (based on ICD-9 codes) were: cancer (140-208), pulmonary disease (uncomplicated) (415.0, 416.8, 416.9, 491-4), dementia (290, 331-331.2), renal disease (uncomplicated) (403, 404, 585, 996.73, V45.1), diabetes (250) and cerebrovascular diseases (430-438). Postal codes (first three digits) for the patients' residence at the time of discharge from their initial hospitalization for AMI were also identified for 99.4% of the cohort. Canada Post's definition of a rural address (a zero in the second position of the postal code) was used to characterize each patient's residence as rural or urban. These data spanned the years from January 1, 1988 to December 31, 1992.

The RAMQ database was used to obtain data on each cardiac catheterization, PTCA and CABG performed on subjects during the follow-up period. These data included the date of the procedure and the administrative code corresponding to the

hospital where the procedure was performed. These data also spanned the years from January 1, 1988 to December 31, 1992.

Complete four-year survival data were obtained for 99.7% of the AMI cohort by merging data from both the Med-Echo and the RAMQ databases. The methods used to ascertain accurate survival data have been published elsewhere (Pilote et al. 2000).

4.2 Hospital Characteristics

As a preliminary step in the creation of the instrumental variables, we classified each acute care hospital in Quebec in four ways: according to whether or not they had 1) availability of cardiac catheterization, 2) availability of PTCA, 3) availability of CABG, and 4) treated a high or low volume of first AMI patients during 1988. In 1988, 13 hospitals in Quebec offered cardiac catheterization. Of these 13 hospitals, 12 offered PTCA and 9 offered CABG. Thus, the hospital categories were not mutually exclusive.

To classify a hospital according to volume, we calculated the number of first AMI patients admitted in 1988 for each hospital. We then examined the distribution of these numbers across all hospitals. We classified any hospital treating a number of first AMI patients greater than or equal to the 75^{th} percentile value for the distribution as a high volume hospital. We classified any hospital treating a number of first AMI patients less than the 75^{th} percentile value as a low volume hospital.

4.3 Instrumental Variables

The approach taken to create the instrumental variables used in our study was almost identical to that used previously for the United States Medicare population (McClellan et al. 1994). The four instrumental variables used in our study corresponded to the subjects' "differential distances" to the four classifications of hospitals. For example, one instrumental variable corresponded to the subjects' differential distance to a catheterization hospital. We created this variable by calculating the difference between the distance from a subject's residence to the nearest catheterization hospital, and the distance from this subject's residence to the nearest acute care hospital of any type. The three other instrumental variables corresponded to the difference between the distance from a subject's residence to 1) the nearest CABG hospital, 2) the nearest PTCA hospital,

and 3) the nearest high-volume hospital, and the subject's distance to the nearest acute care hospital of any type. The choice of these instrumental variables was based on two main assumptions: 1) that AMI patients who lived closer to catheterization, PTCA, CABG, or high-volume hospitals than to other types of hospitals were more likely to receive aggressive care, and 2) that differential distances to each hospital type were not associated with any subject characteristics such as health status, which could be associated with the receipt of aggressive care and mortality.

To construct the instrumental variables, we collected latitude and longitude data from Statistics Canada. We used spherical geographic coordinates derived from these data to construct straight-line distances from the center of each patient's residential postal code region to the center of the postal code regions for each acute care hospital in Quebec. These distances were calculated using the following three steps.

Step 1:

Let i represent postal code region x

Let j represent postal code region y, where we would like to calculate the distance (D) over the surface of the globe between i and j.

$\theta_i = \text{longitude}(i) \bullet (\Pi \div 180)$

$\varphi_i = \text{latitude}(i) \bullet (\Pi \div 180)$

$\theta_j = \text{longitude}(j) \bullet (\Pi \div 180)$

$\varphi_j = \text{latitude}(j) \bullet (\Pi \div 180)$

Step 2:

$X_i = \sin(\theta_i) \bullet \cos(\varphi_i)$

$Y_i = \cos(\theta_i) \bullet \cos(\varphi_i)$

$Z_i = \sin(\varphi_i)$

$X_j = \sin(\theta_j) \bullet \cos(\varphi_j)$

$Y_j = \cos(\theta_j) \bullet \cos(\varphi_j)$

$Z_j = \sin(\varphi_j)$

Step 3:

L = square root of $[(X_i - X_j)^2 + (Y_i - Y_j)^2 + (Z_i - Z_j)^2]$

$D = 2 \bullet R \bullet \arcsin(L \div 2)$, where $R = 4042$ = the radius of the earth (miles)[1]. All distances were measured in miles to allow comparison with the results reported by McClellan et al. (McClellan et al. 1994).

Previous work suggests that these straight-line distances are highly correlated with travel time (Econometric Issues for Survey Data 1997). These data were available for 99.9% of the study subjects.

In keeping with the methods employed by McClellan et al. (McClellan et al. 1994), we excluded from our analyses subjects who were admitted to a hospital more than 100 miles (160.9 km) from their place of residence. It was assumed that these patients were travelling at the time of their AMI.

4.4 Analytic Approach

4.4.1 Independent Variables

The main independent variable used in this study was a binary variable corresponding to whether or not subjects received cardiac catheterization within 90 days after their admission for a first AMI. Receipt of this invasive procedure was used to indicate the receipt of aggressive care. Our data show that most AMI patients in Quebec who receive catheterization will receive this procedure within 90 days following the date of their admission for AMI (median time in 1988 = 34 days). In addition, only small numbers of patients will sustain a recurrent AMI within this time period (7 % in 1988).

Other independent variables were: age, sex, rural or urban residence and the co-morbid diseases (see text for descriptions).

[1] Corrected so as to give the correct distance between Montreal and Toronto using our co-ordinates.

4.4.2 Outcome Variables

There were 7 outcome variables used in this study: binary variables corresponding to mortality at 1 day, 7 days, 30 days, and 1, 2, 3 and 4 years following the date of admission for AMI. These time periods were chosen in order to permit direct comparisons with the outcome measures reported by McClellan et al. (McClellan et al. 1994). In addition, relatively few patients received catheterization within the first week following admission. Therefore, examining mortality outcomes at the time periods earlier than 90 days permitted insight into whether or not any mortality differences between comparison groups could be associated with factors other than receipt of catheterization. For example, large mortality differences observed only 1 day after admission could more likely be due to factors such as the greater likelihood of care from a cardiologist at catheterization hospitals, rather than receipt of catheterization.

4.4.3 Descriptive Statistics

As a first step in the analytic approach, we compared demographic characteristics, co-morbid diseases, invasive procedures received and mortality between subjects who received cardiac catheterization within 90 days after their admission for a first AMI and subjects who did not.

4.4.4 Adjusted Analyses Using Standard ANOVA Methodology

Second, we used a standard statistical method - ANOVA - to estimate the association between catheterization within 90 days of admission for AMI, and mortality at 1 day, 7 days, 30 days, and 1, 2, 3 and 4 years. We created three ANOVA models for each mortality variable: an unadjusted model, a model adjusted for age, sex and rural or urban residence, and a model adjusted for age, sex, rural or urban residence and co-morbid diseases. Age was entered into the ANOVA models as a polychotomous variable with 12 categories. There were ten categories corresponding to 5-year age intervals starting from age 40 years until age 89 years. There was also one category corresponding to ages under 40 years, and one category corresponding to ages of 90 years and over.

Although ANOVA methods were used for comparability with the methods used by McClellan et al. (McClellan et al. 1994), it was recognized that logistic regression could

be more appropriate for analyses with a dichotomous independent variable. Therefore, logit models including the same independent variables were also run, and results from these models were compared to the ANOVA results (data not shown, but were comparable). In addition, we examined ANOVA models that included interaction terms (age group and sex) for the presence of significant interactions (data not shown, but no significant interactions were found).

4.4.5 Two-group (Unadjusted) Comparisons across Differential Distance Groups

Third, we placed subjects into two groups based on their differential distance to each type of hospital. We classified subjects with a differential distance above the median differential distance for all subjects as having a high differential distance to each hospital type. We classified subjects with a differential distance below or equal to the median differential distance as having a low differential distance. We then compared the demographic and clinical characteristics of each group, as well as the invasive procedures received and mortality, across each differential distance group. Incremental (marginal) differences in mortality across the low and high differential distance groups (η_{IV}) were calculated according to the following formula:

$$\eta_{IV} = \frac{m\,(\text{near}) - m\,(\text{far})}{c\,(\text{near}) - c\,(\text{far})}$$

where m and c denote conditional mean outcome (mortality) and catheterization rates in each differential distance group, respectively.

4.4.6 Two-stage Least Squares Regression Analysis Including Instrumental Variables

We used two-stage least squares regression analysis to estimate the marginal effects of the aggressive approach to post-AMI care on mortality. For these analyses, we created four new sets of instrumental variables. Each set of instrumental variables corresponded to groups of subjects based on their differential distance to one of the four hospital types. For example, we created eight binary variables to form eight approximately equal-sized

groups of subjects based on their differential distances to catheterization hospitals. Each variable was coded as 1 if the subjects' differential distance to a catheterization hospital fell within a specified range (in miles (1 mile = 1.61 km) and rounded off: 0, 0.02-1.7, 1.7-2.8, 2.9-5.2, 5.4-18.7, 18.8-35.1, 35.3-67.4, 68.2-473.0), and 0 otherwise. The cut-off points for the intervals were chosen in order to create approximately equal-sized groups. We also created eight binary variables based on subjects' differential distances to CABG (in miles and rounded off: 0-0.05, 0.08-1.7, 1.8-3.3, 3.4-5.2, 5.4-18.7, 18.8-35.1, 35.3-67.4, 68.2-473.0) and PTCA hospitals (in miles and rounded off: 0, 0.02-1.7, 1.7-2.8, 2.9-5.2, 5.4-18.7, 18.8-35.1, 35.3-67.4, 68.2-473.0). Because the differential distance groups for PTCA hospitals had ranges identical to those for catheterization hospitals, we did not include the groups for PTCA hospitals in any subsequent analyses. We created three binary variables based on subjects' differential distance to a high-volume hospital (in miles and rounded off: 0, 0.05-5.5, 5.6-531.6).

Finally, we created two-stage least squares regression models. These models are represented by the following two equations (Brooks et al. 2000):

"Treatment" choice equation

$$T_i = \alpha + \beta_1 \bullet X_i + \beta_2 \bullet Y_i + \beta_3 \bullet A_i + (\theta_i + \epsilon_i) \qquad (1)$$

Outcome equation

$$O_i = \delta + \gamma_1 \bullet X_i + \gamma_2 \bullet Y_i + \gamma_3 \bullet T_i + (\theta_i + v_i) \qquad (2)$$

T_i = 1 if patient receives catheterization within 90 days of admission, 0 otherwise;
X_i = measured patient demographic characteristics (e.g., age, sex);
Y_i = measured patient clinical characteristics (e.g., co-morbid diseases);
A_i = a set of binary variables grouping patients based on values of instrumental variables that affect outcomes only through their impact on treatment choice.
O_i = 1 if health outcome occurs (e.g., mortality within one year), 0 otherwise;

θ_i = unmeasured "confounding variables" that are related to both choice of treatment and outcomes;

ϵ_i, ν_i = the net impact of unmeasured variables that distinctly affect treatment choice and health outcome, respectively;

These methods estimated the average marginal effects of aggressive care on mortality for subjects within the same age group, and with the same sex and co-morbid diseases. We included different combinations of instrumental variables in the different regression models in order to account for differential access to aggressive care at catheterization, CABG and high-volume hospitals both separately and simultaneously. The main independent variables included in models estimating effects on mortality at 1 day, 7 days and 30 days were receipt of catheterization within 1 day, 7 days and 30 days, respectively. In order to evaluate the marginal effects of aspects of aggressive care other than invasive treatments, such as emergency response systems (McClellan et al. 1994), some models also included rural residence and/or admission to a high volume hospital as independent variables. A complete list of each regression equation ran in this study is attached (Appendix 1).

We completed each set of analyses for all study subjects, for subjects <65 years of age at the time of admission for AMI, and for subjects ≥ 65 years of age at the time of admission for AMI. We performed all analyses using Stata 4.0 (Stata Press, College Station, Texas).

4.5 Validity of Instrumental Variables

The choice of these instrumental variables was based on two main assumptions: 1) that AMI patients who lived relatively closer to catheterization, PTCA, CABG, or high-volume hospitals were more likely to receive aggressive care, and 2) that differential distances to each hospital type were not associated with any subject characteristics such as health status, which could be associated with the receipt of aggressive care and mortality (Harris and Remler 1998; Newhouse and McClellan 1998). The validity of the two assumptions made when selecting instrumental variables is crucial to the validity of the outcome measures obtained using instrumental variables-estimation methodology

(Bound 1995; Econometric Issues for Survey Data 1997; Staiger and Stock 1997). Previous studies have shown that the availability of cardiac catheterization laboratories in certain geographic regions is associated with a more aggressive approach to post-AMI care in these regions (Pilote et al. 1996). This evidence provides support for the first assumption. Examining *F*-statistics for the first-stage regression equations used for instrumental variables-estimation of treatment effects can provide further support for this assumption (Econometric Issues for Survey Data 1997). Statistically significant p-values (<0.05) for the *F*-statistics related to the association between the instrumental variable and receipt of aggressive care provide evidence that the instrumental variables selected are associated with variation in rates of receipt of aggressive care across the differential distance groups. We examined the *F*-statistics for the first-stage regression equations in this study. In addition, the relationship between subjects' differential distance to a hospital offering aggressive care and the probability that they will receive aggressive care should not only be strong, but also monotonic (Harris and Remler 1998). We investigated whether this association was monotonic for our study subjects by calculating the proportion of subjects receiving catheterization within 90 days in each differential distance group. The results are not shown, but they confirmed the relationship was monotonic.

For the second assumption to be violated, it would be necessary for patients with different health status or differences in other characteristics to have chosen to live closer to hospitals with availability of catheterization, PTCA and/or CABG, or to high-volume hospitals. There is no direct method available to validate this assumption (Harris and Remler 1998; McClellan and Newhouse 2000). However, as was demonstrated by McClellan et al. (McClellan et al. 1994), comparisons of observed patient characteristics across the differential distance groups can provide indirect evidence as to its validity if these characteristics are observed to be similar across each group. We employed these indirect methods in this study. In addition, the validity of this assumption for the United States has been investigated using medical chart review data by McClellan and Noguchi (McClellan and Noguchi 2000). These investigations have shown that differential distance is not associated with variables that strongly predict mortality after AMI, such as variables associated with the severity of AMI. This second assumption could also be

invalid because it is conceivable that patients might move closer to hospitals with availability of invasive cardiac procedures following a first AMI. However, our study population included only patients admitted for a first AMI, giving assurance that this limitation is not relevant to our study. Finally, this second assumption could be invalid because patients who are furthest from the hospitals may have a longer delay between onset of infarction and treatment, which may in turn affect their outcomes. Although we did not attempt to address this limitation in this study, McClellan et al. (1994) addressed this limitation by repeating their analyses only for those patients living in urban areas or with small absolute distances to hospitals. These analyses did not detect any differences in health status as a function of differential distance.

4.6 Ethics Approval

The Institutional Review Board of the Faculty of Medicine, McGill University, granted approval for this study on May 31, 2000 (Appendix 2).

5 Results

5.1 Preface to manuscript #2

The question of whether or not the aggressive approach to post-AMI care is more effective in comparison to a conservative approach requires evaluation. Applying instrumental variables methodology, we evaluated the marginal effects of an aggressive approach to post-AMI care on mortality in a Canadian patient population, obtaining data from an administrative database of all patients sustaining a first AMI in Quebec in 1988. By obtaining data from this time period, and by using the analytic approach used by McClellan et al. (McClellan et al. 1994), we were able to compare our results to those previously obtained for a population of patients admitted for AMI in the United States. Thus, we could assess the generalizability of outcomes measures obtained using instrumental variables methodology. One unique aspect of the Quebec database is that it includes AMI patients of all ages, while the United States Medicare database includes only AMI patients over age 64. Therefore, we were also able to apply instrumental variables methodology to a population of AMI patients from an age group that had never been studied previously.

The following manuscript describes the results of this research. A similar version of this manuscript was submitted to *JAMA* on January 3, 2001. It should be noted that Dr. Stan Shapiro's name did not appear on the submitted version of the manuscript. However, due to his subsequent contributions to the study, his name has been included on the version submitted with this thesis. Abstracts, based on the results from this study, were also submitted for presentation at: 1) the 17th annual meeting of the International Society of Technology Assessment in Health Care, 2) the 24th annual meeting of the Society of General Internal Medicine, 3) the Congress of Epidemiology 2001, 4) The Canadian Society of Internal Medicine Annual Scientific Meeting 2001. As of May 2, 2001, the abstracts submitted to the International Society of Technology Assessment in Health Care and to the Society of General Internal Medicine have been accepted for an oral presentation. The abstract submitted to the Congress of Epidemiology has also been accepted for a poster presentation.

5.2 Authors' Contribution

As first author, I was actively involved in the study design, analysis and interpretation of data, and drafting and critical revision of the manuscript. I created the data set used in analyses, carried out the statistical analyses, and wrote all manuscripts. Dr. Louise Pilote as thesis supervisor, contributed to all stages of the research. Her contributions were: obtaining funding and data acquisition, study planning and execution, interpretation of results, critical revision of the manuscript and the dissemination of study results. She also contributed her expertise in the area of cardiovascular epidemiology and health services research. Dr. Theresa Gyorkos, as co-supervisor, was also actively involved in study planning, critical revision of the manuscript and dissemination of study results, and she contributed her expertise in epidemiologic research. Dr. John Penrod, as thesis committee member, was involved in study planning, interpretation of results and critical revision of the manuscript. He also contributed extensively his economics expertise in the area of instrumental variables methodology. Dr. Stan Shapiro, as thesis committee member, was also involved in interpretation of results and critical revision of the manuscript, and he contributed his expertise in epidemiology and biostatistics to the planning of this study.

5.3 Manuscript #2

Does Aggressive Care Following Acute Myocardial Infarction Reduce Mortality? Analysis with Instrumental Variables to Compare Effectiveness in Canadian and United States Patient Populations

(Short Title: Mortality Following Aggressive Care Post-AMI)

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Word Count: 5891

Abstract

Context: In the United States, where an aggressive approach to care following acute myocardial infarction (AMI) is more commonly adopted in comparison to a conservative approach, the aggressive approach may be associated with small incremental (marginal) mortality benefits.

Objective: To evaluate the effectiveness of aggressive care following AMI in Canada. We hypothesized that the marginal benefits should be larger in Canada, as the country is operating on a lower margin because the approach to care is more conservative overall.

Design and Setting: Retrospective cohort study using administrative data of acute care hospital admissions and in- and out-patient services in Quebec (1988-1992). We used differential distances to hospitals offering aggressive care as instrumental variables to control for unobserved case-mix variation.

Patients: All patients who sustained a first AMI in Quebec in 1988 (n=8674).

Main Outcome Measures: Mortality up to 4 years after first AMI.

Results: Of the 4422 subjects who were $\geq$ 65 years old, 11% received cardiac catheterization within 90 days after admission. In a previous study that applied similar methodology to the 1987 United States (US) Medicare population of first AMI patients, 30% of subjects received catheterization within 90 days. As in the US study, we found that subjects living relatively close to hospitals offering aggressive care were more likely to receive aggressive care (26% of "close" versus 19% of "far" subjects received cardiac catheterization within 90 days; 95% CI around the difference: 5% to 9%). Unlike the US study, we found no differences in mortality across the "close" versus "far" differential distance groups (unadjusted differences at 1 year: 1%; 95% CI: -1% to 3%). This absence of association was found in elderly ($\geq$ 65 years) and younger age groups. Adjusted results also showed no differences between subjects receiving aggressive versus conservative care (at 1, 2 and 4 years: 4%, 2%, -4%; 95% CI: -11% to 20%, -15% to 18%, -26% to 8%, respectively).

Conclusions: Contrary to our hypothesis but consistent with results from numerous randomized trials and observational studies, the aggressive approach to post-AMI care does not appear to be associated with marginal mortality benefits even in Canada, where the approach to post-AMI care is conservative overall.

Key Words

Myocardial infarction; instrumental variables; administrative database; confounding bias; selection bias; mortality; outcomes research; epidemiology; methods; Canada; United States

Introduction

Certain regions consistently adopt an aggressive approach to care following acute myocardial infarction (AMI) - using invasive procedures such as cardiac catheterization in all patients and revascularization in most patients – while other regions consistently adopt more conservative approaches – using invasive cardiac procedures more selectively. For example, most regions of the United States adopt an aggressive approach, while most Canadian regions adopt a conservative approach [1-4]. Whether or not the aggressive approach reduces mortality in comparison to more conservative approaches remains a topic of intensive investigation [5]. There is therefore increasing interest in the use of outcomes research methodology to evaluate the effectiveness of different approaches to post-AMI care, using patient and provider data from administrative sources to observe practice patterns and clinical outcomes in existent patient populations.

Despite the interest in using administrative databases to answer questions related to the effectiveness of AMI care, this approach has several limitations [6,7]. One important limitation is that there is a strong potential for confounding bias due to differences between comparison groups in terms of patient characteristics that have not been captured in the database. When confounding variables are not captured in a database, they cannot be accounted for using standard statistical methods. It is therefore necessary to use alternative approaches to account for these unobserved differences.

One approach that has been proposed is the use of instrumental variables [8,9]. Instrumental variable methodology has been widely applied in economic research, and has recently begun to be applied in health outcomes research [10-12]. In the instrumental variable estimation strategy, an "instrument" or "instrumental variable" is selected by the investigator that can be used in analyses to form groups of subjects that are unrelated to confounding variables, but have different probabilities of receiving a particular treatment or approach to care. In this sense, instrumental variable estimation allows a "pseudo-randomization" of study subjects. For this pseudo-randomization to occur, the instrumental variable must be associated with the main independent variable of interest and must not be directly associated with the outcome variable of interest [13]. For instance, an investigator interested in evaluating the effectiveness of an aggressive approach to post-AMI care could select a variable that is associated with the receipt of aggressive

care, but otherwise is not associated with mortality post-AMI. The differences in care received across the instrumental variable groups then allows for estimation of the average effects of the care received for those subjects whose type of care received was determined by the instrumental variable. These subjects are referred to as the "marginal" sub-population. Incremental, or "marginal", effects of care are estimated for this sub-population using instrumental variable methodology [14].

McClellan et al. used instrumental variable estimation to investigate whether or not an aggressive approach to post-AMI care reduced mortality in marginal, elderly United States Medicare beneficiaries who were admitted for AMI in 1987 [15]. This study demonstrated the likelihood of appreciable bias in standard outcome measures due to unobserved differences between groups of subjects receiving aggressive or conservative care, and the likelihood of less bias in outcome measures following the application of the instrumental variable approach. Standard analytical methods indicated that there were large benefits from aggressive care (28% (standard error=0.3) reduction in cumulative mortality at four years), while outcome measures obtained using instrumental variable methodology showed only minimal benefits (5% (standard error=3.2) reduction in cumulative mortality at four years, not significant (p-values or confidence interval not presented)). Two later studies conducted by McClellan [16] and Brooks, McClellan and Wong [17] also showed small, but statistically significant, marginal benefits in mortality resulting from aggressive care using this methodology.

Although McClellan et al. demonstrated that instrumental variable methodology is promising, it has not been applied in AMI patient populations other than the elderly insurance beneficiaries in the United States. To more fully evaluate the generalizability of outcome measures obtained using this methodology, it is important that it be re-applied in other age groups and patient populations. In particular, this methodology should be re-applied in populations from regions that adopt different approaches to post-AMI care. Regions that adopt different approaches to post-AMI care will be operating on different margins. We would expect the marginal mortality benefits resulting from aggressive care in regions with more conservative care (lower margin) to be greater than the marginal mortality benefits resulting from aggressive care in regions with more aggressive care

(higher margin). For instance, the marginal benefits of aggressive care should be greater in Canada than in the United States.

The main objective of this study was to evaluate the marginal effects of an aggressive approach to post-AMI care on mortality in a Canadian patient population. The data were obtained from an administrative database of all patients sustaining a first AMI in Quebec in 1988. By obtaining data from this time period, and by using the analytic approach used by McClellan et al. [15], we were able to compare our results to those previously obtained for the United States Medicare population. One unique aspect of the Quebec database is that it includes AMI patients of all ages, while the United States Medicare database includes only AMI patients over age 64. Therefore, a sub-objective of this study was to compare the marginal effects of more aggressive care on mortality in patients < 65 years old to the effects in older patients.

Methods

Subjects

Data on the treatment and clinical outcomes of all patients who sustained a first AMI in Quebec between January 1, 1988 and December 31, 1988 (n = 8995) were obtained retrospectively from two government administrative databases: the Quebec hospital discharge summary database (Med-Echo), and the Quebec Medicare database (*la Régie de l'assurance maladie du Québec* (RAMQ)). All subjects were followed for up to 4 years until December 31, 1992.

The Med-Echo database was used to identify patients for inclusion into the study cohort on the basis of a hospitalization with a main discharge diagnosis of AMI (ICD-9 code 410). To help ensure that the start of follow-up corresponded to the date of the first AMI for all subjects, the absence of a code for AMI was ascertained for at least 3 years preceding the diagnosis. The positive predictive value for coding an AMI in the Med-Echo database has been evaluated to be 96% (95% CI: 94% to 98%) [18]. Patient demographic characteristics (age and sex) and the administrative code corresponding to the hospital to which each patient was admitted were identified from these data. Up to 15 secondary diagnoses are also entered into the Med-Echo database; these secondary diagnoses were used to obtain data on subjects' co-morbid diseases. The co-morbid diseases studied (based on ICD-9 codes) were: cancer (140-208), pulmonary disease (uncomplicated) (415.0, 416.8, 416.9, 491-4), dementia (290, 331-331.2), renal disease (uncomplicated) (403, 404, 585, 996.73, V45.1), diabetes (250) and cerebrovascular diseases (430-438). Postal codes (first three digits) for the patients' residence at the time of their discharge were also identified for 99.4% of the cohort. Canada Post's definition of a rural address (a zero in the second position of the postal code) was used to characterize each patient's residence as rural or urban. These data spanned the years from January 1, 1988 to December 31, 1992.

The RAMQ database was used to obtain data on each cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft surgery (CABG) performed on subjects during the follow-up period. These data included the date of the procedure and the administrative code corresponding to the hospital where

the procedure was performed. These data also spanned the years from January 1, 1988 to December 31, 1992.

Complete four-year survival data were obtained for 99.7% of the AMI cohort by merging data from both the Med-Echo and the RAMQ databases. The methods used to ascertain accurate survival data have been published elsewhere [19].

This study received ethical approval from the McGill University Institutional Review Board.

Hospital Characteristics

As a preliminary step in the creation of the instrumental variables, we classified each acute care hospital in Quebec in four ways: according to whether or not they had 1) availability of cardiac catheterization, 2) availability of PTCA, 3) availability of CABG, and 4) treated a high or low volume of first AMI patients during 1988. In 1988, 13 hospitals in Quebec offered cardiac catheterization. Of these 13 hospitals, 12 offered PTCA and 9 offered CABG. Thus, the hospital categories were not mutually exclusive.

To classify a hospital according to volume, we calculated the number of first AMI patients admitted in 1988 for each hospital. We then examined the distribution of these numbers across all hospitals. We classified any hospital treating a number of first AMI patients greater than or equal to the 75^{th} percentile value for the distribution as a high volume hospital. We classified any hospital treating a number of first AMI patients less than the 75^{th} percentile value as a low volume hospital.

Instrumental Variables

The approach taken to create the instrumental variables used in our study was almost identical to that used previously for the United States Medicare population [15]. The four instrumental variables used in our study corresponded to the subjects' "differential distances" to the four classifications of hospitals. For example, one instrumental variable corresponded to the subjects' differential distance to a catheterization hospital. We created this variable by calculating the difference between the distance from a subject's residence to the nearest catheterization hospital, and the distance from this subject's residence to the nearest acute care hospital of any type. The three other instrumental

variables corresponded to the difference between the distance from a subject's residence to 1) the nearest CABG hospital, 2) the nearest PTCA hospital, and 3) the nearest high-volume hospital, and the subject's distance to the nearest acute care hospital of any type. The choice of these instrumental variables was based on two main assumptions: 1) that AMI patients who lived relatively closer to catheterization, PTCA, CABG, or high-volume hospitals were more likely to receive aggressive care, and 2) that differential distances to each hospital type were not associated with any subject characteristics such as health status, which could be associated with the receipt of aggressive care and mortality.

To construct the instrumental variables, we collected latitude and longitude data from Statistics Canada. We used spherical geographic coordinates derived from these data to construct straight-line distances from the center of each patient's residential postal code region to the center of the postal code regions for each acute care hospital in Quebec. Previous work suggests that these straight-line distances are highly correlated with travel time [20]. These data were available for 99.9% of the study subjects.

In keeping with the methods employed for the United States Medicare population [15], we excluded subjects who were admitted to a hospital more than 100 miles (160.9 km) from their place of residence from our analyses. It was assumed that these patients were travelling at the time of their AMI.

Analytic Approach

In order to permit direct comparisons, the analytic approach was almost identical to that used for analyses applied to the United States Medicare population [15]. The main independent variable used in this study was a binary variable corresponding to whether or not subjects received cardiac catheterization within 90 days after their admission for a first AMI. Receipt of this invasive procedure was used to indicate the receipt of aggressive care. Our data show that most AMI patients in Quebec who receive catheterization will receive this procedure within 90 days following the date of their admission for AMI (median time in 1988 = 34 days). In addition, only small numbers of patients will sustain a recurrent AMI within this time period (7 % in 1988).

There were 7 outcome variables used in this study: binary variables corresponding to mortality at 1 day, 7 days, 30 days, and 1, 2, 3 and 4 years following the date of admission for AMI. These time periods were chosen in order to permit direct comparisons with the outcome measures reported by McClellan et al. In addition, relatively few patients received catheterization within the first week following admission. Therefore, examining mortality outcomes at the time periods earlier than 90 days permitted insight into whether or not any mortality differences between comparison groups could be associated with factors other than receipt of catheterization. For example, large mortality differences observed only 1 day after admission could be more likely due to the greater likelihood of care from a cardiologist at catheterization hospitals, rather than receipt of catheterization.

As a first step in the analytic approach, we compared demographic characteristics, co-morbid diseases, invasive procedures received and mortality between subjects who received cardiac catheterization within 90 days after their admission for a first AMI and subjects who did not.

Second, we used the same statistical method used by McClellan et al. - analysis of variance (ANOVA) - to estimate the association between catheterization within 90 days of admission for AMI, and mortality at 1 day, 7 days, 30 days, and 1, 2, 3 and 4 years. We created three ANOVA models for each mortality variable: an unadjusted model, a model adjusted for age, sex and rural or urban residence, and a model adjusted for age, sex, rural or urban residence and co-morbid diseases. Age was entered into the ANOVA models as a polychotomous variable with 12 categories. There were ten categories corresponding to 5-year age intervals starting from age 40 years until age 89 years. There was also one category corresponding to ages under 40 years, and one category corresponding to ages of 90 years and over. Although ANOVA methods were used for comparability with the methods used by McClellan et al. {1}, it was recognized that logistic regression could be more appropriate for analyses with a dichotomous independent variable. Therefore, logit models including the same independent variables were also run, and results from these models were compared to the ANOVA results. These analyses yielded comparable results, and only the ANOVA results are presented. In addition, we examined ANOVA models that included interaction terms (age group and

sex) for the presence of significant interactions (data not shown, but no significant interactions were found).

Third, we placed subjects into two groups based on their differential distance to each type of hospital. We classified subjects with a differential distance above the median differential distance for all subjects as having a high differential distance to each hospital type. We classified subjects with a differential distance below or equal to the median differential distance as having a low differential distance. We then compared the demographic and clinical characteristics of each group, as well as the invasive procedures received and mortality, across each differential distance group.

Finally, we used two-stage least squares regression analysis to estimate the marginal effects of the aggressive approach to post-AMI care on mortality. For these analyses, we created four new sets of instrumental variables. Each set of instrumental variables corresponded to groups of subjects based on their differential distance to one of the four hospital types. For example, we created eight binary variables to form eight approximately equal-sized groups of subjects based on their differential distances to catheterization hospitals. Each variable was coded as 1 if the subjects' differential distance to a catheterization hospital fell within a specified range (in miles (1 mile = 1.61 km) and rounded off: 0, 0.02-1.7, 1.7-2.8, 2.9-5.2, 5.4-18.7, 18.8-35.1, 35.3-67.4, 68.2-473.0), and 0 otherwise. We also created eight binary variables based on subjects' differential distances to CABG (in miles and rounded off: 0-0.05, 0.08-1.7, 1.8-3.3, 3.4-5.2, 5.4-18.7, 18.8-35.1, 35.3-67.4, 68.2-473.0) and PTCA hospitals (in miles and rounded off: 0, 0.02-1.7, 1.7-2.8, 2.9-5.2, 5.4-18.7, 18.8-35.1, 35.3-67.4, 68.2-473.0). Because the differential distance groups for PTCA hospitals had ranges identical to those for catheterization hospitals, we did not include the groups for PTCA hospitals in any subsequent analyses. We created three binary variables based on subjects' differential distance to a high-volume hospital (in miles and rounded off: 0, 0.05-5.5, 5.6-531.6).

Finally, we created two-stage least squares regression models. These methods estimated the average marginal effects of aggressive care on mortality for subjects within the same age group, and with the same sex and co-morbid diseases. Before running the models, we examined *F*-statistics for the association between the instrumental variables and receipt of catheterization (first-stage regression equations). Statistically significant p-

values (<0.05) for these statistics provide evidence that the instrumental variables selected are associated with variation in rates of use of catheterization across the differential distance groups[21], and therefore, that the first assumption made in choosing our instrumental variables is valid. There is no direct method available to validate the second assumption [14], but several analyses can provide indirect evidence. We employed these indirect methods in this study, and they are further described in the Results section.

We then included different combinations of instrumental variables in the different regression models in order to account for differential access to aggressive care at catheterization, CABG and high-volume hospitals both singularly and simultaneously. The main independent variables included in models estimating effects on mortality at 1 day, 7 days and 30 days were receipt of catheterization within 1 day, 7 days and 30 days, respectively. In order to evaluate the marginal effects of aspects of aggressive care other than invasive treatments, such as emergency response systems [15], some models also included rural residence and/or admission to a high volume hospital as independent variables.

We completed each set of analyses for all study subjects, for subjects <65 years of age at the time of admission for AMI, and for subjects ≥ 65 years of age at the time of admission for AMI. We performed all analyses using Stata 4.0 (Stata Press, College Station, Texas).

Results

Study Population

After the exclusion of patients who were admitted to a hospital more than 100 miles from their place of residence, and exclusions of those patients with missing residence postal code, mortality and/or latitude and longitude data, our study population consisted of 8674 subjects (96.43% of the original AMI cohort). The patients who were excluded from the cohort had demographic and co-morbid disease characteristics similar to those patients who were not excluded, but a smaller proportion of excluded patients were admitted to a catheterization hospital (15% for excluded patients versus 23% for study population). This difference probably reflects the fact that more latitude and longitude information was unavailable for rural regions. Similar proportions of patients received cardiac catheterization within 90 days after admission for AMI (20% for excluded patients versus 22% for study population). Differences in demographic characteristics and co-morbid diseases between patients who received and did not receive cardiac catheterization within 90 days were also comparable for excluded patients and for the study subjects.

Of the 8674 study subjects, a total of 1928 (22%) received cardiac catheterization within 90 days after admission for AMI. There were 4422 (51%) subjects who were $\geq$ 65 years old at the time of admission. Of these subjects, 11 % received cardiac catheterization within 90 days, while 34 % of the 4252 subjects who were < 65 years old received cardiac catheterization within 90 days.

There were marked differences in demographic characteristics, co-morbid diseases and characteristics of care received between subjects who received catheterization within 90 days and subjects who did not (Table 1). The trends in the differences observed for the whole cohort were also observed for the cohort of subjects who were <65 years old and the cohort of subjects who were $\geq$ 65 years old. Subjects who received catheterization were younger on average, and smaller proportions were female and resided in rural areas than subjects who did not receive catheterization. In addition, smaller proportions of subjects who received catheterization had co-morbid diseases. Greater proportions of subjects who received catheterization were admitted to

catheterization, PTCA, CABG, and high-volume hospitals, and greater proportions of these subjects received CAGB or PTCA within 90 days after admission for AMI.

Standard Outcome Measures and Evidence for Confounding Bias

There were large differences in mortality between subjects who received catheterization within 90 days and subjects who did not (Table 1). By 4 years following admission for AMI, only 14% of subjects who were catheterized within 90 days following admission for AMI had died, while 41% of subjects who were not catheterized within 90 days had died. After adjusting these differences for observable subject characteristics, the percentage-point differences in 4-year mortality rates between the two groups was reduced from 28% to 13% (both values favoring receipt of catheterization) (Table 2). However, given the marked differences between the groups in terms of observable characteristics, it is probable that there were also many other differences between the groups in terms of characteristics that were not captured in the database, such as AMI severity or acute complications. As these characteristics are associated with both selection for receipt of invasive procedures and mortality, it is likely that the standard outcome measures are biased, overestimating the true effects of aggressive care. In addition, differences in mortality between the two groups were evident only 1 day after admission for AMI (adjusted difference of 4%; 95% CI: 3% to 5%), when catheterization was not likely to have been received.

Unadjusted Comparisons across Differential Distance Groups

Two groups of subjects were formed based on the median differential distance to a catheterization hospital. Comparisons of demographic characteristics and co-morbid diseases across these differential distance groups (Table 3) showed differences that were substantially less marked than the differences observed for the same characteristics when comparisons were made according to the receipt of catheterization within 90 days (Table 1). Only small differences in observable subject characteristics were observed despite the fact that a greater proportion of patients in the low differential distance group received catheterization within 90 days after admission for AMI (26% versus 19% for high and low differential distance groups, respectively). As would be expected, greater proportions

of subjects in the low differential distance group were admitted to catheterization, PTCA, CABG and high volume hospitals, and greater proportions of these subjects received PTCA and CABG. These results provide additional support for the assumption that a subject's differential distance to a catheterization hospital is associated with their receipt of catheterization, but is not associated with other characteristics that could influence selection for receipt of catheterization, such as age and co-morbid diseases. Finally, unlike the large mortality differences observed across groups of subjects receiving and not receiving catheterization, there were no differences in mortality observed across the differential distance groups at any time period following admission for AMI.

Instrumental Variable Estimation: Two-stage Least Squares Regression Analysis

Before running two-stage least squares regression models to estimate the marginal effects of aggressive care on mortality, the validity of the instrumental variables used in these models was investigated by obtaining *F*– statistics for the first-stage regression equations. All *F*– statistics corresponded with a significant p-value, except for some of the models including receipt of catheterization within 1 day as an outcome measure (for study subjects $\geq$ 65 years old). Mortality at 1 day after AMI was therefore not used as an outcome measure in the two-stage least squares regression analyses for subjects $\geq$ 65 years old. These results provide evidence to support the hypothesis that differential distance to different types of hospitals is associated with aggressive care. The fact that the proportions of patients who received cardiac catheterization within 90 days decreased across greater differential distance groups provided additional evidence.

The instrumental variable estimates of marginal effects of aggressive care showed no mortality benefits from receipt of catheterization (Table 4). All confidence intervals included zero. For example, in the simplest model, which included only sets of instrumental variables corresponding to differential distance to catheterization hospitals, the average difference in mortality at 3 years was -4% (favoring receipt of catheterization; 95% CI: -20% to 13%). In the full model, which contained three sets of instrumental variables (differential distances to catheterization, CABG and high-volume hospitals) and examined the effects of both admission to a high-volume hospital and catheterization simultaneously, the average difference in mortality at 3 years was also -

4% (favoring receipt of catheterization and admission to a high-volume hospital; 95% CI: -29% to 22%). The results do not show any notable trends according to timing after AMI. However, interpretation of the estimates for mortality at 1 day is limited due to the inefficiency of the estimates. Finally, admission to a high-volume hospital (Table 4) and rural residence (data not shown) was not associated with mortality.

Marginal Effects of Aggressive Care in Canada versus the United States

By examining data for subjects $\geq$ 65 years old at the time of their admission for AMI, we were able to directly compare the marginal effects of aggressive care on mortality in Quebec and the United States. The United States analysis has been previously reported [15]. Table 5 shows that the trends in the demographic, co-morbid disease, treatment and mortality differences across high and low differential groups were similar to those observed for the United States Medicare population. However, fewer subjects in both the low and high differential groups in Quebec received invasive cardiac procedures than patients in the corresponding differential distance groups in the United States. For example, only 14% of subjects in the low differential distance group in Quebec received cardiac catheterization within 90 days, compared to the 26% of subjects who received catheterization within 90 days in the low differential distance group in the United States. Cumulative mortality rates were also slightly lower in Quebec than in the United States (e.g. mortality at 1 year: approximately 35% in Quebec versus approximately 40% in the United States). Data from both Quebec and the United States, however, showed that subjects living relatively close to a hospital offering cardiac catheterization were more likely to receive cardiac catheterization within 90 days of admission for AMI. Data from both sources also showed no large average differences in mortality across the high and low differential distance groups, although ANOVA analyses showed large differences in mortality across groups defined by receipt of catheterization (e.g. in Quebec at 1 year: -16%; 95% CI: -21% to –12%), favoring receipt of catheterization.

One difference from the United States study is that in the two-group comparisons, the Quebec subjects who were marginal from the standpoint of the instrumental variables did not show a mortality benefit, while the United States subjects did. For example,

McClellan et al. found a 6-point reduction in mortality at 4 years [-6.0=100x[58.1-58.5]/[26.2-19.5];P<0.05] for the marginal subjects. As McClellan et al. point out, however, the estimates do not control for other differences in care received across the two groups, such as greater access to emergency services associated with urban residence [15]. Similar to the results observed for the United States Medicare population, instrumental variable estimation showed no marginal benefits from receipt of catheterization in Quebec patients ≥ 65 years old (Table 6). The full model for the Quebec population gave an average difference in mortality at 2 years of -11% (favoring catheterization; 95% CI: -56% to 34%). The full model for the United States population gave an average difference in mortality at 2 years of –5.4% (favoring catheterization; SE: 3.3%; 95% CI approximately –11.9% to 1.1%).

Marginal Effects of Aggressive Care in Younger versus Older AMI Patients

As instrumental variable estimation methodology has never been previously applied to investigate the effectiveness of aggressive care in AMI patients under 65 years of age, we compared our instrumental variables estimates obtained for subjects ≥ 65 years old and subjects <65 years old at the time of admission. The trends in the differences in demographic characteristics, co-morbid diseases and care received between high and low differential distance groups were similar for both subjects ≥ 65 years old (Table 5) and subjects <65 years old (data not shown). As would be expected, however, the younger subjects had fewer co-morbid diseases, and were more likely to receive invasive treatment after their AMI. Despite these differences, both the two-group comparisons across high and low differential distance groups and the two-stage least squares regression analyses including greater numbers of differential distance groups (Table 6) showed no effects of receipt of catheterization on mortality in either younger or older subjects. For patients <65 years old, the full model gave an average difference in mortality at 2 years of -7% (favoring catheterization; 95% CI: -28% to 15%).

Comment

In this study, we applied instrumental variable methodology to evaluate the effectiveness of an aggressive approach versus more conservative approaches to care after AMI in a Canadian patient population. We found that an aggressive approach to care after AMI was not associated with incremental (marginal) benefits in mortality up to 4 years after the AMI in both elderly and younger patients. Our unadjusted comparisons across groups of patients who were more or less likely to receive aggressive care showed no average or marginal differences in mortality between the groups. The trends observed in differences across the comparison groups in subject characteristics and care received were consistent with those obtained by applying the same instrumental variable methodology to a population of elderly United States Medicare beneficiaries [15], giving face validity to the methodology. However, the mortality outcome measures are inconsistent with the United States study, which found small marginal mortality benefits resulting from aggressive care. These results are also contrary to our hypothesis that the marginal benefits of aggressive care should be greater in the Canadian patient population, where the approach to care is more conservative overall.

The negative results of this study are consistent with those from previous randomized controlled trials [22-26] and observational studies [1,27]. This study therefore provides additional evidence that there may be no mortality benefits resulting from aggressive care after AMI except in patients with specific indications for invasive cardiac procedures [28,29]. The fact that our results are generalizable across AMI patient populations of all ages provides support for this conclusion. In one of our previous studies, we also found that more aggressive care in certain regions of the United States was not associated with differences in mortality [30]. As there is variation across regions in approaches to post-AMI care, geographic region can be viewed as a kind of simple instrumental variable. Thus, our results are also consistent with this previous study.

The results of this study should be of interest to clinicians and policymakers who question whether or not invasive cardiac procedures are under- or over-utilized in different health care systems and/or regions. Just as there exist marked differences in the approaches to post-AMI care between the United States and Canada [1,3,31], there also exist marked differences within regions of these countries [30,32]. In addition, studies have shown

that rates of use of invasive procedures are increasing overall both in the United States [3] and in Canada [33]. In fact, one of our recent studies has shown that rates of use of invasive procedures in some regions of Quebec are approaching rates of use in the United States [19]. The outcome measures obtained in this study using instrumental variable methodology should be of particular relevance to people who question the "marginal value" of these changes. Newhouse and McClellan [8] and Harris and Remler [14] point out that results obtained from instrumental variable methodology could potentially be more useful than those from clinical trials, if one considers that clinicians and policymakers may be most uncertain about the benefits of aggressive treatment for marginal patients.

More generally, the results of this study should be of interest to any investigator interested in evaluating the effectiveness of health interventions using administrative data. As in the study by McClellan et al. [15], it was likely that outcome measures obtained using standard statistical measures were subject to confounding bias due to variables that were not captured in the database. We also found evidence to support the hypothesis that outcome measures obtained using the instrumental variable methodology were likely to be less biased. This evidence highlights and reinforces the potential usefulness of instrumental variable methodology as a tool for the investigation of the effectiveness of various approaches to post-AMI care.

Although the instrumental variable approach can be a useful methodologic tool when using administrative data for outcomes research, there are also several limitations to this approach that must be considered. One limitation is that instrumental variable estimates are less precise than estimates obtained from other methods [9,12,21]. For instance, the confidence intervals around our adjusted outcome measures were wide. In part, this lack of precision was probably due to the relatively small numbers of patients receiving invasive procedures in Quebec, particularly for the group of patients that were over age 65. However, even analyses applying this methodology to a greater number of AMI patients admitted in Quebec (over the years from 1988-1995) did not provide estimates with much more precision (data not shown). Since Quebec represents roughly one fourth of the Canadian population, even an expansion of this study to include additional Canadian regions is not likely to sufficiently improve the efficiency of the outcome measures obtained using this methodology. An international study that accounts for

variations across regions in approaches to post-AMI care may provide more efficient estimates but still allow for observation of outcomes in Canadian patient populations. In addition, it may be better to sacrifice some precision for a reduction in bias[9]. Such a decision must be made in the context of the individual study. In the case of our study, given the continued uncertainty about the effectiveness of the aggressive approach to post-AMI care and the strong probability for bias in standard measures of this effectiveness, instrumental variables estimates were a good alternative to standard outcome measures.

Although the validity of the assumptions made in choosing the instrumental variables used in a study is crucial to the validity of the outcome measures obtained in the study [14,21], the validity of the assumptions cannot be proven. For instance, we made the assumption that the instrumental variables were not associated with any subject characteristics such as health status, which could be associated with the type of care received and mortality. As was the case for the United States Medicare population, our comparisons of demographic characteristics and co-morbid diseases across "low" and "high" differential distance groups provided evidence that subjects did not differ substantially in terms of these observed characteristics. However, we cannot rule out the possibility that the subjects differed in terms of other unobserved characteristics. It is possible that as certain instrumental variables are repeatedly used in the same context but in different patient populations, the validity of the chosen instrumental variable will cease to be as great a concern.

In summary, in an application of instrumental variable methodology to the entire population of first AMI patients in Quebec in 1988, we observed that there was no association between an aggressive approach to post-AMI care and short- or long-term mortality. This lack of association was found in both elderly and younger patients, and these results are consistent with results from previous randomized controlled trials and observational studies, which included selected AMI patient populations. These results are also similar to results from a previous study that applied the same methodology to the 1987 United States Medicare population. Thus, this study lends support to the conclusion that the aggressive approach to post-AMI care is not beneficial. However, to more fully justify this conclusion, a larger, international study may be required to improve the

statistical efficiency of outcome measures obtained using instrumental variable methodology.

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Table 1. Characteristics of Patients with a First Acute Myocardial Infarction in Quebec in 1988

	No Catheterization within 90 Days (n=6746)	Catheterization within 90 Days (n=1928)	Unadjusted Difference (95% CI)
Demographic characteristics (%)			
Female	36	23	13 (11,16)
Mean age in years (SD)	66 (13)	56 (11)	10 (9,10)
Rural residence	27	21	5 (3,7)
Co-morbid diseases (%)			
Cancer	1	0	1 (0.6,1)
Pulmonary disease, uncomplicated	12	6	6 (5,8)
Dementia	1	0	1 (0.5,1)
Diabetes	18	13	5 (3,7)
Renal disease, uncomplicated	4	2	2 (1,3)
Cerebrovascular disease	6	2	4 (3,4)
Care received (%)			
Initial admit to catheterization hospital	19	39	-20 (-22,-18)
Initial admit to PTCA hospital[2]	17	33	-16 (-18,-14)
Initial admit to CABG hospital[3]	14	27	-13 (-16,-11)
Initial admit to high-volume† hospital[4]	58	73	-15 (-17,-13)
Catheterization within 7 days	0	32	-32 (-34,-30)
CABG within 90 days	0	17	-17 (-19,-16)
PTCA within 90 days	3	18	-16 (-17,-14)
Cumulative mortality (%)			
1 day	6	0	6 (5,6)
7 days	13	1	12 (11,13)
30 days	18	3	16 (14,17)
1 year	27	7	20 (19,22)
2 years	33	9	24 (22,25)
3 years	37	12	26 (24,28)
4 years	41	14	28 (26,29)

CABG denotes coronary artery bypass graft, PTCA denotes percutaneous transluminal coronary angioplasty.

All acute care hospitals in Quebec were classified according to availability of catheterization[1], PTCA[2] and/or CABG[3], as well as number of patients admitted for a first acute myocardial infarction in 1988[4]. Hospital categories were not mutually exclusive.

†At least 133 admissions for first acute myocardial infarction in 1988.

Table 2. Cumulative Effects of Catheterization Within 90 Days after Acute Myocardial Infarction* On Mortality, Not Accounting for Bias Due to Unobserved Differences Between Patients Receiving and Not Receiving Catheterization

	Percentage-point Changes in Mortality Rates (95% CI)						
	1-day	7-day	30-day	1-year	2-year	3-year	4-year
None (unadjusted differences)	-6 (-7,-5)	-12 (-14,-11)	-16 (-17,-14)	-20 (-22,-18)	-24 (-26,-21)	-26 (-28,-24)	-28 (-30,-25)
After adjustment for age, sex and rural or urban residence	-4 (-5,-3)	-8 (-10,-6)	-10 (-11,-8)	-11 (-13,-9)	-13 (-15,-11)	-14 (-16,-11)	-14 (-16,-12)
After adjustment for age, sex, rural or urban residence and co-morbid diseases	-4 (-5,-3)	-8 (-10,-6)	-9 (-11,-8)	-10 (-12,-8)	-12 (-14,-10)	-13 (-15,-10)	-13 (-15,-11)

*Analyses were performed using ANOVA.

Table 3. Patient Characteristics by Differential Distance* to a Catheterization Hospital

	Differential Distance ≤ 5.2 miles (n=4334)	Differential Distance > 5.2 miles (n=4340)	Unadjusted Difference (95% CI)
Demographic characteristics (%)			
Female	36	31	5 (3,7)
Mean age in years (SD)	65 (13)	63 (13)	1 (1,2)
Rural residence	6	45	-39 (-41,-37)
Co-morbid diseases (%)			
Cancer	1	1	0 (-0.1,1)
Pulmonary disease, uncomplicated	10	12	-2 (-4,-1)
Dementia	1	0	0 (-0.2,0.5)
Diabetes	18	16	2 (0,3)
Renal disease, uncomplicated	4	2	2 (1,2.3)
Cerebrovascular disease	5	5	1 (0,2)
Care received (%)			
Initial admit to catheterization hospital	39	7	32 (30,33)
Initial admit to PTCA hospital[2]	35	7	28 (26,30)
Initial admit to CABG hospital[3]	28	6	22 (21,24)
Initial admit to high-volume† hospital[4]	76	47	29 (27,31)
Catheterization within 7 days	10	4	5 (4,6)
Catheterization within 90 days	26	19	7 (5,9)
CABG within 90 days	4	4	1 (0,2)
PTCA within 90 days	7	5	2 (1,3)
Cumulative mortality (%)			
1 day	4	5	0 (-1,1)
7 days	10	10	1 (-1,2)
30 days	15	14	1 (-1,2)
1 year	23	22	1 (0,3)
2 years	28	27	1 (-1,3)
3 years	32	31	1 (-1,3)
4 years	36	35	1 (-1,3)

CABG denotes coronary artery bypass graft, PTCA denotes percutaneous transluminal coronary angioplasty.

All acute care hospitals in Quebec were classified according to availability of catheterization[1], PTCA[2] and/or CABG[3], as well as number of patients admitted for a first acute myocardial infarction in 1988[4]. Hospital categories were not mutually exclusive.

†At least 133 admissions for first acute myocardial infarction in 1988.

* Median differential difference to a catheterization hospital.

Table 4. Adjusted Estimates of Marginal Effects of an Aggressive Approach to Care after Acute Myocardial Infarction on Mortality: Two-Stage Least Square Regression Analyses Including Instrumental Variables

Model*	Instrumental Variables**	Independent Variable(s)	Marginal Differences (%) in Mortality (95% Confidence Interval) 1-day	7-day	30-day	1-year	2-year	3-year	4-year
1	CATH	Catheterization received	-14 (-82,54)	1 (-14,16)	0 (-12,13)	4 (-11,20)	2 (-15,18)	-4 (-20,13)	-9 (-26,8)
2	CATH CABG	Catheterization received	-9 (-74,56)	3 (-12,17)	0 (-12,12)	4 (-11,20)	1 (-15,18)	-4 (-21,13)	-10 (-27,7)
3	CATH CABG	Admit to high-volume hospital	0 (-2,1)	0 (-3,2)	-1 (-5,2)	-2 (-6,3)	0 (-4,4)	0 (-4,4)	1 (-4,5)
	High-volume	Catheterization received	-9 (-64,46)	5 (-13,22)	4 (-14,22)	11 (-13,35)	3 (-22,28)	-4 (-29,22)	-12 (-38,13)

CATH denotes cardiac catheterization, CABG denotes coronary artery bypass graft surgery.

* Results from some models not shown.

** Instrumental variables used in analyses were differential distances to the nearest catheterization hospital (CATH), CABG hospital (CABG), or high-volume hospital. Other variables included in each model were age group, sex and co-morbid diseases.

Table 5. Patient Characteristics According to Differential Distance* to a Catheterization Hospital For Patients ≥ 65 Years Old in Quebec and the United States

	Quebec		United States**	
	Differential Distance ≤ 4.7 miles	Differential Distance > 4.7 miles	Differential Distance ≤ 2.5 miles	Differential Distance > 2.5 miles
	n=2212	n=2210	n=102 516	n=102 505
Demographic characteristics (%)				
Female	49	44	51	50
Mean age in years (SD)	75 (7)	74 (6)	76 (7)	76 (7)
Rural residence	7	44	7	52
Co-morbid diseases (%)				
Cancer	2	2	2	2
Pulmonary disease, uncomplicated	12	15	10	11
Dementia	1	1	1	1
Diabetes	21	20	18	18
Renal disease, uncomplicated	6	4	2	2
Cerebrovascular disease	7	8	5	5
Care received (%)				
Initial admit to catheterization hospital	40	5	34	5
Initial admit to PTCA*** hospital[2]	36	5	42	11
Initial admit to CABG*** hospital[3]	28	4		
Initial admit to high-volume† hospital[4]	74	47	67	37
Catheterization within 7 days	6	2	21	11
Catheterization within 90 days	14	9	26	20
CABG within 90 days	3	3	9	7
PTCA within 90 days	4	2	6	4

Table 5 (continued). Patient Characteristics According to Differential Distance* to a Catheterization Hospital For Patients ≥ 65 Years Old in Quebec and the United States

	Quebec		United States**	
	Differential Distance ≤ 4.7 miles	Differential Distance > 4.7 miles	Differential Distance ≤ 2.5 miles	Differential Distance > 2.5 miles
	n=2212	n=2210	n=102 516	n=102 505
Cumulative mortality (%)				
1 day	6	7	8	9
7 days	16	15	17	19
1 year	35	34	40	41
2 years	41	41	47	48
3 years	47	46	53	54
4 years	52	52	58	59

CABG denotes coronary artery bypass graft, PTCA denotes percutaneous transluminal coronary angioplasty.

All acute care hospitals in Quebec were classified according to availability of catheterization[1], PTCA[2] and/or CABG[3], as well as number of patients admitted for a first acute myocardial infarction in 1988[4]. Hospital categories were not mutually exclusive.

* Median differential difference to a catheterization hospital in Quebec was 4.7 miles. Median differential distance to a catheterization hospital in the United States was 2.5 miles.

** Source: McClellan et al. *JAMA*. 1994;272:859-866.

*** All hospitals in the United States with availability of either CABG or PTCA were classified as "revascularization hospitals".

†At least 133 admission for first acute myocardial infarction in 1988 for Quebec hospitals. At least 75 admissions for first acute myocardial infarction in 1987 for United States hospitals.

Table 6. Adjusted Estimates of Marginal Effects of an Aggressive Approach to Care after Acute Myocardial Infarction on Mortality in Elderly (≥ 65 Years) and Younger (< 65 Years) Patients: Two-Stage Least Square Regression Analyses Including Instrumental Variables.

Model*	Instrumental Variables**	Independent Variable(s)	Marginal Differences (%) in Mortality (95% Confidence Interval)						
			1-day	7-day	30-day	1-year	2-year	3-year	4-year
	Elderly Patients								
1	CATH	Catheterization received	NA	-2 (-41,37)	-7 (-44,29)	3 (-38,45)	5 (-37,48)	-4 (-47,39)	-20 (-63,23)
2	CATH CABG	Catheterization received	NA	-4 (-42,34)	-20 (-54,13)	-2 (-40,36)	-1 (-40,37)	-10 (-48,29)	-27 (-66,12)
3	CATH CABG	Admit to high-volume hospital	NA	0 (-3,4)	0 (-4,5)	0 (-5,5)	2 (-3,8)	2 (-3,7)	1 (-4,7)
	High-volume	Catheterization received	NA	-6 (-47,35)	-22 (-62,18)	-2 (-46,41)	-11 (-56,34)	-17 (-62,28)	-34 (-79,12)
	Younger Patients								
1	CATH	Catheterization received	-9 (-55,37)	0 (-11,11)	-1 (-9,8)	-3 (-15,8)	-8 (-21,5)	-11 (-25,3)	-13 (-28,1)
2	CATH CABG	Catheterization received	-15 (-57,26)	0 (-10,11)	0 (-8,9)	-3 (-15,9)	-8 (-21,5)	-11 (-25,3)	-13 (-27,1)
3	CATH CABG	Admit to high-volume hospital	0 (-2,1)	-1 (-4,1)	-2 (-6,2)	-1 (-6,4)	0 (-5,5)	0 (-5,6)	2 (-4,8)
	High-volume	Catheterization received	-13 (-55,30)	3 (-9,16)	5 (-8,18)	1 (-19,21)	-7 (-28,15)	-11 (-34,12)	-18 (-43,6)

CATH denotes cardiac catheterization, CABG denotes coronary artery bypass graft surgery.
NA denotes not applicable because F-tests for first-stage regressions were not significant.
* Results from some models not shown.
** Instrumental variables used in analyses were differential distances to the nearest catheterization hospital (CATH), CABG hospital (CABG), or high-volume hospital. Other variables included in each model were age group, sex and co-morbid diseases.

6 Discussion and Conclusion

For this thesis, instrumental variables methodology was applied to data from administrative sources in order to estimate the effectiveness of an aggressive versus a conservative approach to post-AMI care in a Quebec patient population. We found that an aggressive approach to care after AMI was not associated with incremental (marginal) benefits in mortality up to four years after a first AMI. This absence of association held in both elderly ($\geq$ 65 years) and younger ($<$ 65 years) patients. Interestingly, this absence of association held even though the relatively conservative approach to post-AMI adopted overall across Canada might be expected to result in marginal benefits in mortality for the patients treated with the aggressive approach. As we found in our review, many randomized controlled trials and observational studies have demonstrated that there may be no benefit in terms of clinical outcomes resulting from the aggressive approach. Hence, certain patients may be receiving unnecessary care, which is not cost-effective. Given the important burden that acute coronary syndromes such as AMI place on the health of Canadians, as well as the health care system, clinicians and health policymakers should continue to address this important question, adopting clinical practice and health policy accordingly.

In addition to studying the effectiveness of different approaches to post-AMI care, it is also important that methodologic approaches that can improve the validity of outcome measures in such studies be explored. Through this study, evidence of the generalizability of outcome measures obtained using instrumental variables methodology was provided. Similar results were found in both United States and Canadian patient populations, and in elderly and younger Canadian patient populations. However, through the application of instrumental variables methodology, a number of limitations of this methodology were noted. One limitation is that instrumental variable estimates are less precise than estimates obtained from other methods. For instance, the confidence intervals around our adjusted outcome measures were wide. In part, this lack of precision was probably due to the relatively small numbers of patients receiving invasive procedures in Quebec, particularly for the group of patients that were over age 65. However, even analyses applying this methodology to a greater number of AMI patients admitted in Quebec (over the years from 1988-1995) did not provide estimates with much

more precision. Since Quebec represents roughly one fourth of the Canadian population, even an expansion of this study to include additional Canadian regions is not likely to sufficiently improve the precision of the outcome measures obtained using this methodology. An international study that accounts for variations across regions in approaches to post-AMI care may provide more efficient estimates but still allow for observation of outcomes in Canadian patient populations. In addition, it may be better to sacrifice some precision for a reduction in bias. Such a decision must be made in the context of the individual study. In the case of our study, given the continued uncertainty about the effectiveness of the aggressive approach to post-AMI care and the strong probability for bias in standard measures of this effectiveness, instrumental variables estimates were a good alternative to standard outcome measures.

The instrumental variables approach is also limited in that although the validity of the assumptions made in choosing the instrumental variables used in a study is crucial to the validity of the outcome measures, the validity of the assumptions cannot be proven. For instance, we made the assumption that the instrumental variables were not associated with any subject characteristics such as health status, which could be associated with the type of care received and mortality. As was the case for the United States Medicare population, our comparisons of demographic characteristics and co-morbid diseases across "low" and "high" differential distance groups provided evidence that subjects did not differ substantially in terms of these observed characteristics. However, we cannot rule out the possibility that the subjects differed in terms of other unobserved characteristics. It is possible that, as certain instrumental variables are repeatedly used in the same context but in different patient populations, the validity of the chosen instrumental variable will cease to be as great a concern.

One final limitation relates to the ease of interpretation of the outcome measures obtained using this methodology. In this study, outcome measures obtained using instrumental variables-estimation cannot be generalized to the entire population of AMI patients, but only to the marginal sub-population of patients whose receipt of aggressive care depended on their differential distance to hospitals providing more aggressive care. This issue of generalizability means that interpretation of outcome measures obtained from instrumental variables-estimation is not as straightforward as interpretation of

outcome measures from clinical trials, where the probability of receiving treatment is random for all study subjects. Instead, because the marginal sub-population cannot actually be identified in most cases, investigators using instrumental variables-estimation must use their clinical knowledge to understand how the outcome measure was generated. However, as was previously noted, once instrumental variables estimates are interpreted correctly they may actually be of more interest to policymakers and clinicians than estimates from clinical trials because they refer to the population of patients for whom the benefits of treatment are most uncertain.

6.1 Future Research

Both the literature review conducted for this thesis and the study itself revealed deficiencies in certain areas that provide opportunities for future research in the area of post-AMI care. For instance, the literature review put randomized controlled trials and observational studies that have compared clinical outcomes in patients with acute coronary syndromes treated with an aggressive versus a conservative approach into temporal context. Thus, it revealed that many of the studies on which current practice guidelines are based were conducted with few subjects and relatively short follow-up periods, and at a time when currently available advances in invasive cardiac technologies and other treatments were not available. New, large-scale trials should be conducted to evaluate the long- and short-term effects of aggressive care in the current health care context. In addition, the majority of the most recent studies have focussed on patients with non-ST-segment elevation AMI and unstable angina. Given the wide regional and international practice variations that persist even in treatment of ST-segment elevation AMI patients, new studies should also enroll these patients.

Another important finding of the review was that there is a paucity of randomized controlled trials that have evaluated the effects of aggressive versus conservative care on non-clinical outcomes, such as quality of life, functional status and costs incurred. New trials should include these study outcomes, in order to confirm or reject the findings of a few observational studies that have suggested that the aggressive approach results in improvements in these non-clinical outcomes.

Finally, the literature review provided an opportunity to compare and contrast results from studies with experimental and observational designs, highlighting the

advantages of the observational studies. The observational studies enrolled larger numbers of subjects, had longer follow-up periods, and provided data on patient populations that were less selected than in the randomized controlled trials. As changing trends in post-AMI care persist, observational studies should continue to be performed in order to evaluate the effectiveness of different approaches to such care in the current health care context.

As observational studies using administrative data provide a valuable opportunity to evaluate the effectiveness of post-AMI care, methodologic approaches that can improve the validity of outcome measures obtained through such studies should be explored. Through its application of instrumental variables methodology, this thesis was an important first step in this exploration. A next step would be to apply instrumental variables methodology to estimate the impact of the aggressive approach on other patient outcomes, such as reinfarction, readmissions, and, if possible, quality of life, functional status and costs. Again, it may be necessary to use a large international database to conduct such a study, in order to obtain instrumental variable estimates with better precision than were obtained in this study.

Finally, this thesis demonstrated that instrumental variables methodology can be a useful tool for estimating the effectiveness of health care interventions using administrative data. Given this potential, other epidemiologic investigators interested in estimating the effectiveness of health care interventions should be made aware of this methodology. If appropriate for their study questions, these investigators might consider adding instrumental variables methodology to their methodologic "tool box".

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8 Appendices

Appendix 1: Two-stage least squares regression equations.

Model Set 1:

mortality at "x" days = β_1(catheterization at "x" days) + β_2(age group) + β_3(sex) + β_4(cancer) + β_5(pulmonary disease, uncomplicated) + β_6(dementia) + β_7(diabetes) + β_8(renal disease, uncomplicated) + β_9(cerebrovascular disease) [$\gamma_{1\text{-}y\text{-}}$(differential distance group dummy "y") + γ_2(age group) + γ_3(sex) + γ_4(cancer) + γ_5(pulmonary disease, uncomplicated) + γ_6(dementia) + γ_7(diabetes) + γ_8(renal disease, uncomplicated) + γ_9(cerebrovascular disease)]

Where "x" = 1 day, 7 days, 30 days, 1 year, 2 years, 3 years or 4 years after admission (e.g. 7 different models).

Where there were dummies for 8 differential distance groups ("y"=2,3,4...8; "y"=1 was reference group), corresponding to the differential distance to the nearest catheterization hospital.

N.B. For this and all other model sets, see Methods sections for variable definitions.

Model Set 2:

mortality at "x" days = β_1(catheterization at "x" days) + β_2(age group) + β_3(sex) + β_4(cancer) + β_5(pulmonary disease, uncomplicated) + β_6(dementia) + β_7(diabetes) + β_8(renal disease, uncomplicated) + β_9(cerebrovascular disease) [$\gamma_{1\text{-}y\text{-}}$(differential distance group dummy "y") + $\gamma_{2\text{-}z\text{-}}$(differential distance group dummy "z") + γ_3(age group) + γ_4(sex) + γ_5(cancer) + γ_6(pulmonary disease, uncomplicated) + γ_7(dementia) + γ_8(diabetes) + γ_9(renal disease, uncomplicated) + γ_{10}(cerebrovascular disease)]

Where "x" = 1 day, 7 days, 30 days, 1 year, 2 years, 3 years or 4 years after admission (e.g. 7 different models).

Where there were dummies for 8 differential distance groups ("y"=2,3,4...8; "y"=1 was reference group), corresponding to the differential distance to the nearest catheterization hospital.

Where there were dummies for 8 differential distance groups ("z"=2,3,4...8; "z"=1 was reference group), corresponding to the differential distance to the nearest CABG hospital.

Model Set 3:

mortality at "x" days = β_1(catheterization at "x" days) + β_2(rural residence) + β_3(age group) + β_4(sex) + β_5(cancer) + β_6(pulmonary disease, uncomplicated) + β_7(dementia) + β_8(diabetes) + β_9(renal disease, uncomplicated) + β_{10}(cerebrovascular disease) [$\gamma_{1\text{-}y}$(differential distance group dummy "y") + $\gamma_{2\text{-}z}$(differential distance group dummy "z") + γ_3(age group) + γ_4(sex) + γ_5(cancer) + γ_6(pulmonary disease, uncomplicated) + γ_7(dementia) + γ_8(diabetes) + γ_9(renal disease, uncomplicated) + γ_{10}(cerebrovascular disease)]

Where "x" = 1 day, 7 days, 30 days, 1 year, 2 years, 3 years or 4 years after admission (e.g. 7 different models).

Where there were dummies for 8 differential distance groups ("y"=2,3,4...8; "y"=1 was reference group), corresponding to the differential distance to the nearest catheterization hospital.

Where there were dummies for 8 differential distance groups ("z"=2,3,4...8; "z"=1 was reference group), corresponding to the differential distance to the nearest CABG hospital.

Model Set 4:

mortality at "x" days = β_1(admission to a high volume hospital) + β_2(age group) + β_3(sex) + β_4(cancer) + β_5(pulmonary disease, uncomplicated) + β_6(dementia) + β_7(diabetes) + β_8(renal disease, uncomplicated) + β_9(cerebrovascular disease) [$\gamma_{1\text{-}k}$(differential distance group dummy "k") + γ_2(age group) + γ_3(sex) + γ_4(cancer) + γ_5(pulmonary disease, uncomplicated) + γ_6(dementia) + γ_7(diabetes) + γ_8(renal disease, uncomplicated) + γ_9(cerebrovascular disease)]

Where there were dummies for 3 differential distance groups ("k"=2 or 3; "k"=1 was reference group), corresponding to the differential distance to the nearest high volume hospital.

Model Set 5:

mortality at "x" days = β_1(admission to a high volume hospital) + β_2(rural residence) + β_3(age group) + β_4(sex) + β_5(cancer) + β_6(pulmonary disease, uncomplicated) + β_7(dementia) + β_8(diabetes) + β_9(renal disease, uncomplicated) + β_{10}(cerebrovascular disease) [$\gamma_{1\text{-}k}$(differential distance group dummy "k") + γ_2(age group) + γ_3(sex) + γ_4(cancer) + γ_5(pulmonary disease, uncomplicated) + γ_6(dementia) + γ_7(diabetes) + γ_8(renal disease, uncomplicated) + γ_9(cerebrovascular disease)]

Where there were dummies for 3 differential distance groups ("k"=2 or 3; "k"=1 was reference group), corresponding to the differential distance to the nearest high volume hospital.

Model Set 6:

mortality at "x" days = β_1(catheterization at "x" days) + β_2(admission to high volume hospital) + β_3(age group) + β_4(sex) + β_5(cancer) + β_6(pulmonary disease, uncomplicated) + β_7(dementia) + β_8(diabetes) + β_9(renal disease, uncomplicated) + β_{10}(cerebrovascular disease) [γ_{1*y*}(differential distance group dummy "y") + γ_{2*z*}(differential distance group dummy "z") + γ_{3*k*}(differential distance group dummy "k") + γ_4(age group) + γ_5(sex) + γ_6(cancer) + γ_7(pulmonary disease, uncomplicated) + γ_8(dementia) + γ_9(diabetes) + γ_{10}(renal disease, uncomplicated) + γ_{11}(cerebrovascular disease)]

Where "x" = 1 day, 7 days, 30 days, 1 year, 2 years, 3 years or 4 years after admission (e.g. 7 different models).

Where there were dummies for 8 differential distance groups ("y"=2,3,4...8; "y"=1 was reference group), corresponding to the differential distance to the nearest catheterization hospital.

Where there were dummies for 8 differential distance groups ("z"=2,3,4...8; "z"=1 was reference group), corresponding to the differential distance to the nearest CABG hospital.

Where there were dummies for 3 differential distance groups ("k"=2 or 3; "k"=1 was reference group), corresponding to the differential distance to the nearest high volume hospital.

Model Set 7:

mortality at "x" days = β_1(catheterization at "x" days) + β_2(admission to high volume hospital) + β_3(rural residence) + β_4(age group) + β_5(sex) + β_6(cancer) + β_7(pulmonary disease, uncomplicated) + β_8(dementia) + β_9(diabetes) + β_{10}(renal disease, uncomplicated) + β_{11}(cerebrovascular disease) [γ_{1*y*}(differential distance group dummy "y") + γ_{2*z*}(differential distance group dummy "z") + γ_{3*k*}(differential distance group dummy "k") + γ_4(age group) + γ_5(sex) + γ_6(cancer) + γ_7(pulmonary disease, uncomplicated) + γ_8(dementia) + γ_9(diabetes) + γ_{10}(renal disease, uncomplicated) + γ_{11}(cerebrovascular disease)]

Where "x" = 1 day, 7 days, 30 days, 1 year, 2 years, 3 years or 4 years after admission (e.g. 7 different models).

Where there were dummies for 8 differential distance groups ("y"=2,3,4...8; "y"=1 was reference group), corresponding to the differential distance to the nearest catheterization hospital.

Where there were dummies for 8 differential distance groups ("z"=2,3,4...8; "z"=1 was reference group), corresponding to the differential distance to the nearest CABG hospital.

Where there were dummies for 3 differential distance groups ("k"=2 or 3; "k"=1 was reference group), corresponding to the differential distance to the nearest high volume hospital.

Appendix 2: Certificate of Ethical Acceptability for Research Involving Human Subjects.