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PREDICTORS OF ADVERSE EVENTS WITHIN ONE-YEAR FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

BY

PADMAJA RAVIKANTI KAUL 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

Medical Sciences - Public Health Sciences

Edmonton, Alberta

Fall 2000

UNIVERSITY OF ALBERTA

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *Predictors of Adverse Events Within One-year Following Percutaneous Coronary Intervention* submitted by *Padmaja Ravikanti Kaul* in partial fulfillment of the requirements for the degree of *Doctor of Philosophy* in *Medical Sciences – Public Health Sciences.*

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ABSTRACT

This thesis is comprised of two studies. The primary objective of Study 1 was to identify baseline and procedural factors associated with one-year mortality following percutaneous coronary intervention (PCI). Models to identify predictors of 30-day mortality and one-year repeat revascularization were also developed. All three models were validated using a split-sample method. The objective of Study 2 was to examine the additional impact of secondary prevention strategies on repeat revascularization within one-year.

The patient population for Study 1 consisted of 4,695 Alberta residents who underwent PCI between July 1995 and December 1997. Data from the Alberta Provincial Program for Outcomes Assessment in Heart Disease (APPROACH) study were used for the analyses. The 425 patients in Study 2 were a subset of Study 1 patients enrolled in the Enhancement for Secondary Prevention in Coronary Heart Disease (ESP study) at the time of PCI.

Based on logistic regression analysis, cardiogenic shock, low ejection fraction, left main disease, intra-aortic balloon pump use, chronic obstructive pulmonary disease, lesions in the proximal LAD, renal disease, and emergency procedures were found to be positively associated with both short and long-term mortality. Increasing age, congestive heart failure, malignancy and peripheral vascular disease were also predictors of long-term mortality. Interestingly, hyperlipidemia and both current and past smoking were associated with lower

mortality. The models were shown to have good discriminatory power, as measured by the c-statistic, both in the development datasets and in the validation datasets.

With respect to repeat revascularization, the model developed in Study 1 and the Cox proportional hazard model developed as part of Study 2 found, in addition to many variables found to be predictive of mortality, that female sex was associated with a greater likelihood of repeat revascularization within one-year. The Cox model also found patients who were monitored closely post-discharge had more repeat procedures within one-year compared to those who received regular care.

These studies address a gap in the current literature around long-term outcomes associated with PCI in the post-stenting era. The identification of patients at high risk for adverse events can be used for discharge planning and patient education.

For my father

ACKNOWLEDGEMENTS

My sincere thanks to my supervisor, Dr. Duncan Saunders, and to the members of my supervisory committee, Dr. William Ghali, Dr. Stephen Newman, and Dr. Vladimir Dzavik, for selflessly giving me their time during evenings, weekends and vacations. They carefully reviewed several drafts of the thesis and provided invaluable guidance. This document is vastly improved as a result of their direction.

I thank the members of the APPROACH project (Dr. Merril Knudtson, Ms. Colleen Norris and Mr. Jason Badry) and the ESP project (Dr. Sonny Belenkie, Dr. Steve Edworthy, Ms. Bonnie Baptie, and Mr. Rafael Talavera) for generously allowing me the use of their data.

I thank my colleagues, Dr. Wei-Ching Chang, Dr. Yuling Fu, and Dr. Paul Armstrong, for training me to be a better researcher and for offering me opportunities to extend my education.

And most importantly, I thank my husband, Aditya, for his constant encouragement and unwavering support through what must surely have been trying times.

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GLOSSARY

PTCA:	Percutaneous Transluminal Coronary Angioplasty (also referred to as "angioplasty")
PCI:	Percutaneous Coronary Intervention (Includes balloon angioplasty and coronary stenting)
AMI:	Acute myocardial infarction
MI:	Myocardial infarction
CABG:	Coronary Artery Bypass Graft
NYHA:	New York Heart Association
CCS:	Canadian Cardiovascular Society
PVD:	Peripheral vascular disease
CHF:	Congestive heart failure
COPD:	Chronic obstructive pulmonary disease
CAD:	Coronary artery disease
IABP:	Intra-aortic balloon pump

CHAPTER 1: INTRODUCTION

1. INTRODUCTION

1.1 HEART DISEASE IN THE WORLD

A search of the World Wide Web using a popular search engine (Lycos®) on the key words "heart disease" identifies 828,403 websites. This topic's high web frequency is indicative of the continuing interest, on the part of the patient, provider and health care systems, in one the most prevalent chronic diseases in the world. According to the 1999 World Health Report, ischemic heart disease is ranked number one among leading causes of mortality and burden of disease among World Health Organization (WHO) member states [1].

There have been both temporal and geographic variations in mortality rates associated with coronary heart disease (CHD). In the United States, death rate attributed to CHD rose from 200 per 100,000 in 1950 to approximately 300 per 100,000 in 1966 [2]. The increasing rate of CHD mortality in years prior to 1960 was the main driving force in establishing the Framingham Heart Study, which has become a cornerstone of risk factor epidemiology in cardiovascular diseases [3-4]. This time-period saw the rise in cardiovascular related mortality in most industrialized countries [5]. As advances in public health resulted in the control of infectious diseases, all cause mortality began to be dominated by diseases of a chronic nature such as CHD and cancer.

However, the latter part of the 20th century brought better news. Mortality rates associated with CHD were declining in the developed world [5]. For example, in the United States, by 1985, age-adjusted CHD death rates had decreased to about 70% of the 1950 CHD death rate [2]. These downward sloping mortality trends gave rise to several questions regarding their authenticity and the extent to which they were influenced by the modification of coronary risk factors.

In order to answer some of these questions the WHO initiated an epidemiological study: the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA). The WHO-MONICA project was established in the early 1980s and as part of the project, patients between the ages of 25 and 64 years from 38 populations in 21 countries have been followed-up for 10 years [6].

The analyses of 10-year WHO-MONICA project data revealed that cigarette smoking, blood pressure and total blood cholesterol, considered "classical" modifiable factors, accounted only partially for the variation in population trends in CHD [7]. Kuulasmaa and colleagues speculated on the influence of other factors such as changes in the treatment of CHD. In fact, in a parallel publication, the researchers documented that changes in coronary care and secondary prevention strategies over this 10-year period were strongly linked with the declining coronary endpoints [8].

One of the most effective treatments of CHD marked its 20th anniversary in September 1997 - Percutaneous Transluminal Coronary Angioplasty (PTCA). Since its introduction twenty years ago in Zurich, Switzerland, by Dr. Andreas Gruentzig, millions of angioplasties have been performed all over the world. In the United States, which is probably the most enthusiastic user of this technology, it is estimated that over 300,000 coronary angioplasties are performed annually [9].

1.2 The Canadian Perspective

In Canada, although the numbers of PTCA procedures are more modest, the rate at which utilization is increasing is dramatic. In 1988, 9,970 PTCAs were performed in Canada for a rate of 39/100,000 population. By 1991, the number of procedures had risen to 14,617 for a rate of 54/100,000 population. Although this translated into a 38.5% increase in utilization, it was still less than half the 1991 rate of PTCA procedure use in the US (130/100,000) [10]. This disparity between the two countries in the use of this procedure, particularly among the elderly, has been documented elsewhere. In an analysis of 1992 claims data, Verrilli and colleagues found the US-to-Canada ratio for PTCA use was 1.87 for patients aged between 65 and 69 years and 7.68 for patients over the age of 80 years [11].

Johansen et al analyzed hospital discharge data for fiscal years 1992/93 and 1993/94 to examine variations in angioplasty across Canadian provinces. PTCA rates among patients diagnosed with acute myocardial infarction ranged between 3.8 percent in Newfoundland to 17.7 percent in Alberta. In general, patients under the age of 60 years were more likely to undergo angioplasty compared to older patients. The overall rate of angioplasty within six-months of a myocardial infarction was 8.7% [12].

In addition to age, sex appears to be a factor in the utilization of PTCA procedures. In a study of 131 women and 440 men referred by cardiologists for revascularization procedures between January 1989 and June 1991 in Metropolitan Toronto, Naylor et al found that women, despite more severe symptoms, were more likely to be turned down for revascularization [13]. The sex-related differences in rates, however, were more pronounced for bypass surgery than for PTCA. In a similar US study of 49,623 and 33,159 discharges in 1987 for coronary heart disease in Massachusetts and Maryland, respectively, Ayanian and colleagues examined sex-related differences in the use of procedures after controlling for age and other baseline characteristics [14]. They found that men were more likely to undergo revascularization procedures than women, however, whether these rates represent a more appropriate use of the procedure among women or indicative of inappropriate use of the technology among men is unclear.

1.3 ANGIOPLASTIES IN ALBERTA

In both the 1991 [10] and the 1992-94 [12] Canadian studies, Alberta had the highest rate of PTCA procedures among all the provinces. In 1988, the PTCA rate per 100,000 population in Alberta was 59 and it had risen to 75 by 1991. The next highest utilization rate was found in Nova Scotia [74/100,000 in 1991]. Among acute myocardial infarction patients, PTCA rate in Alberta was 17.7%, significantly higher than the 11.1% in British Columbia, which was the province with the next highest rate of PTCA use. Angioplasty use among Alberta patients following acute myocardial infarction continued to rise between fiscal years 1993/94 and 1997/98, and the positive trend was particularly pronounced among males under the age of 65 years [15].

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2. PERCUTANEOUS CORONARY INTERVENTION

2.1 POPULARITY AND LIMITATIONS

The adoption of PTCA as an established treatment for coronary artery disease (CAD) can be attributed to several factors. Primary among them is the low morbidity and mortality associated with the procedure. Other factors include expanding the use of this procedure from the original set of patients with stable angina and single vessel disease to patients with unstable angina, multi-vessel disease, complex lesions and acute myocardial infarction [1]. This expansion has been made possible, in large part, by technological improvements and increased operator experience [2].

The major limitations of PTCA are the high incidence of restenosis and the need for repeat revascularization procedures. These generally occur within three to nine months of the PTCA [3-6]. Restenosis is defined as the angiographic re-narrowing at the site of the PTCA and is often accompanied by recurrence of symptoms of angina. Varying rates of repeat revascularization procedures have been reported in the literature. Table I provides a summary of some of the

Table 1. Summary of current literature on outcomes following PTCA procedure

Ref. No.	Study, year	Place	Follow-up time	# patients	%Death	%MI	%CABG	%Repeat PTCA	Comments
3	Meier et al. [1984]	Atlanta, USA	mean - 5 mos	510	...	...	...	18.6%	Patients undergoing PTCA for the first time.
13	Black et al. [1988]	Atlanta, USA	5 years	2,921	...	...	...	13.4%	Single vessel disease, angioplasties of saphenous vein grafts excluded.
7	de Feyter et al. [1988]	Rotterdam, Netherlands	2 years	200	2.5%	4.0%	6.0%	11.5%	Patients with unstable angina
9	King et al. [1994]	Atlanta, USA	3 years	198	7.1%	14.6%	22.0%	41.0%	RCT comparing CABG and PTCA outcomes
11	Talley et al. [1988]	Atlanta, USA	5 years	338	3.8%	5.6%	12.4%	21.9%	Data shown is of only successful PTCAs.
12	Detre et al. [1989]	Pittsburgh, USA	1 year	1,409	1.9%	2.6%	6.4%	20.7%	Data shown is of only successful PTCAs.
14	RITA trial participants [1993]	Nottingham, UK	Median - 2.5 years	510	2.4%	6.7%	18.8%	18.2%	Comparison of long-term effectiveness of CABG vs. PTCA
15	Thompson et al. [1993]	Jacksonville, FL, USA	mean - 25 months	982	9.2%	4.8%	10.6%	15.4%	Patients > 65 yrs, with successful PTCA. Exc. PTCA as treatment for AMI.
19	Weintraub et al. [1994]	Atlanta, USA	7 - 8 years	9,910	4.4%	8.4%	12.8%	28.2%	First-time elective PTCA patients.
16	Ruygrok et al. [1996]	Rotterdam, Netherlands	8 to 14 years	837	23.4%	17.1%	25.7%	26.4%	All patients undergoing PTCA between 1980 - 85 at a single center
10	Mick et al. [1994]	Cleveland, OH, USA	Median - 4.1 years	4,632	8.2%	6.6%	17.6%	29.3%	PTCA for acute ischemic events excluded.
17	Kelsey et al. [1993]	Pittsburgh, USA	4 years	2,136	7.7%	12.2%	17.6%	25.8%	1985 - 86 NHLBI Registry data
8	BARI Investigators [1996]	Pittsburgh, USA	5 years	915	13.7%	10.9%	31.0%	34.0%	Comparison of CABG vs. PTCA, patients with multi-vessel disease only.
18	Gruentzig et al. [1987]	Atlanta, USA	5 - 8 years	133	6.8%	...	14.3%	20.0%	Data shown is of only successful PTCAs.

studies' findings. The rates of Coronary Artery Bypass Graft (CABG) after a successful PTCA have ranged from 6% within two years [7] to 31% within five years [8]. Repeat angioplasty rates ranged from 11.5% in two years [7] to 41% in three years [9].

It is evident from the literature that incidence of cardiac events, including myocardial infarction, CABG, repeat PTCA, or death following a successful first PTCA, is of concern. It is, therefore, of clinical importance to determine risk factors associated with repeat cardiac events in the PTCA population.

2.2 The Angioplasty Procedure

The literal translation of Percutaneous Transluminal Coronary Angioplasty is as follows: "Percutaneous" meaning through the skin; "Transluminal" meaning within the vessel; "Coronary" identifying the type of vessel being treated; and "Angioplasty" referring to the technique used to widen narrowed coronary arteries. Historically, "balloon angioplasty" has been the most common PTCA procedure. In layman's terms the procedure can be described as follows. A guiding catheter is inserted either into the femoral artery (in the groin), or the brachial artery (in the arm). The catheter is maneuvered to where the coronary arteries branch off to the heart. Dye is then injected into the catheter to identify the site where the vessel(s) has narrowed. A balloon catheter is then inserted

into the guiding catheter to the occlusion site. A guide wire in the balloon catheter is advanced through the coronary artery, until its tip is beyond the site of the obstruction. The balloon catheter is then moved over the guide wire until the balloon is in the occluded area of the vessel and inflated. The inflation of the balloon results in the splitting and compressing of the obstructing plaque and slight stretching of the wall of the vessel. When the artery has been sufficiently opened, the balloon is deflated and removed.

Balloon angioplasty, however, is only one of many techniques/devices used in coronary angioplasty. Directional coronary atherectomy (DCA) involves a catheter equipped with a small mechanically driven cutter. The cutter shaves the plaque and stores it in a collection chamber and is removed when the catheter is withdrawn. In Mechanical rotational atherectomy (MRA), a rotating diamond-shaped burr shaves the coronary plaque into tiny particles. These particles can pass through the coronary circulation. Some catheters have also been equipped with special lasers that photo-dissolve obstructions in the arteries.

In light of the expansion of the types of devices used in coronary angioplasty, practitioners have deemed it appropriate to coin the broader term Percutaneous Coronary Intervention (PCI), that encompasses procedures using balloons, atherectomy devices, lasers and stents. Through the rest of this document, the terms PCI and coronary angioplasty are used interchangeably.

2.3 The Introduction of Stents

One of the most important advances in the practice of interventional cardiology has been the introduction of coronary stents. The major limitation of the balloon and other angioplasty devices is the risk of abrupt closure following the removal of the catheter from the site of the occlusion. Coronary stenting is a direct solution to this problem. A coronary stent is a small latticed stainless steel tube, which is mounted on a balloon catheter. At the site of the occlusion, the balloon expands, thus causing the stent to expand and press against the coronary artery wall. The balloon is then deflated and withdrawn, however, the stent stays in place permanently, holding the blood vessel open.

2.4 Balloon-Angioplasty versus Stents

The first coronary stent was implanted in 1987 and for the first few years high bleeding rates, longer hospital stays, and high costs marked stent use. However, in 1994, the results of two randomized controlled trials, one European and one North American, were published in the New England Journal of Medicine [20, 21]. These trials showed a reduction in restenosis and repeat revascularization

rates among patients who underwent stenting compared to those who underwent balloon-angioplasty.

As practitioners became more adept in the deployment of stents, the initial high rates of adverse events declined rapidly and the introduction of adjunct therapy reduced lengths of stay and bleeding complications [22]. These positive attributes have led to a tremendous increase in the utilization of stents during angioplasty. In a study examining trends in interventional device use and outcomes, Peterson et al used the National Cardiovascular Network's Coronary Interventional Database [23]. Between January 1994 and December 1997, data on 76,904 procedures at 12 US hospitals were analyzed. During this time-period there was a 12-fold increase in the use of stents (5.4% in 1994 to 69% in 1997). These trends were accompanied by static mortality rates, improved procedural success and complication rates and decreased length of hospital stay.

In Canada, the Total Occlusion Study of Canada (TOSCA) randomized 410 patients with non-acute native coronary occlusions to PTCA or stenting and found stenting to be associated with higher patency and lower restenosis and target-vessel revascularization at 6-months [24].

At the population level, rates of stent use have been documented for the province of Ontario [22]. In 1996, 39% of patients undergoing catheter-based revascularization received stents. This annual rate however masks the surge in stenting compared to previous years. For example, in the last quarter of 1995, the

rate of stent use was 32%, and by the last quarter of 1996 the rate had risen to 52% of all catheter-based interventions.

The excessive use of stents in coronary intervention has been met with considerable criticism. In an editorial in the New England Journal of Medicine in 1998 titled "Coronary-Artery Stents - Gauging, Gorging, and Gouging", Eric Topol of the Cleveland Clinic Foundation chastised interventional cardiologists for embracing a new technology before all the evidence from the clinical trials was in [25]. Clinical trial data reveal that stenting is associated with a higher number of deaths and myocardial infarctions, however, because these end-points are infrequent, the studies do not have enough statistical power to detect differences. And the more popular outcome that has been used to indicate stents' superiority: the need for fewer repeat revascularizations, can be considered a "soft-endpoint" with potential for bias due to cardiologists forgoing repeat procedures in patients whom they know to have a stent.

The strong argument for stenting that can be constructed from efficacy trials is also weakened by evidence from effectiveness studies. Narins et al document data from four studies of stenting in the "real world" where stenting was extended to patients who would have been considered ineligible for inclusion into the original randomized controlled trials comparing balloon angioplasty and stenting [26]. Several interesting findings are mentioned. First, very few of the patients who undergo stenting in the real world would have been eligible for

either the Balloon-Expandable-Stent Implantation with Balloon Angioplasty study (BENESTENT) [20] or the Stent Restenosis Study (STRESS) [21] trials: eligibility ranged from 7% of 522 patients [27] to 27% of 316 patients [28]. Second, rates of angiographic restenosis, restenosis requiring target lesion revascularization (TLR), and a composite of death, myocardial infarction or TLR at one year were all almost twice as high in the ineligible patients than in the eligible patients [29, 30].

2.5 The Role of GP IIb/IIIa Inhibitors

Despite controversies, it appears that utilization of stents will continue to increase. This can be attributed, in part, to recent evidence on the complementary benefits of platelet glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors when used in conjunction with coronary stents. Several randomized controlled trials have established that the use of GP IIb/IIIa inhibitors in PCI, irrespective of the device used, is associated with better outcomes [31]. However, the EPISTENT trial was the first trial to compare the following three therapies: 1) stent plus placebo; 2) stent plus abciximab (a GP IIb/IIIa inhibitor); and 3) balloon angioplasty and abciximab [32]. The primary end-point was death, myocardial infarction, or the need for urgent revascularization within 30 days. Of 2,399 patients enrolled, 809 were randomized to stent plus placebo, 794 to stent plus abciximab, and 796 to balloon angioplasty plus abciximab. The rate of

primary end-point in the three treatment arms was 10.8%, 5.3% and 6.9%, respectively, indicating that the stent plus abciximab had a significantly lower rate of adverse events compared to the other two treatments. At six months, the rates of death or myocardial infarction were 11.4%, 5.6% and 7.8%, respectively, indicating that the benefit of stenting with GP IIb/IIIa inhibitor was sustained during the long-term [33].

The beneficial effect of stent and abciximab was also established among patients with a history of diabetes [34]. In a subgroup analysis of 491 diabetic patients enrolled in the EPISTENT trial, patients in the stent plus abciximab group had the lowest rate of death or myocardial infarction at six months (6.2% compared to 12.7% in the stent plus placebo arm and 7.8% in the balloon-angioplasty plus abciximab arm).

2.6 Angioplasty Compared to Bypass Surgery

Some data from randomized controlled trials in the pre-GP IIb/IIIa inhibitor era suggest that angioplasty may not be the best therapy for diabetic patients. In a subgroup analysis of diabetic patients enrolled in the Bypass Angioplasty Revascularization Investigation (BARI), a randomized controlled trial of PTCA versus CABG in patients with multi-vessel disease, five-year cause-specific mortality rate among CABG patients was 5.8% compared to 20.6% who underwent PTCA procedures [35]. Other large observational studies have

provided evidence to support the hypothesis that bypass surgery may be a more effective alternative in the treatment of diabetic patients with multi-vessel disease [36-38].

However, overall there appears to be little difference in mortality between patients treated with angioplasty and those treated with bypass surgery [39]. In a meta-analysis of eight randomized trials comparing bypass surgery and angioplasty, Pocock et al found that the number of deaths for all available follow-up were 73 for CABG patients and 79 for PTCA patients (OR = 1.08; 95% CI 0.79 - 1.50) [40]. However, the major difference lay in the number of repeat interventions in the first year of follow-up. Thirty-three (33.7%) percent of PTCA patients underwent either a repeat PTCA or CABG as compared to 3.3% of CABG patients. This increase in the need for revascularization associated with PTCA shown in both the clinical trial setting and in clinical practice has major economic and quality of life implications [41,42].

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CHAPTER 2. LITERATURE REVIEW

1. TRENDS IN OUTCOMES ASSOCIATED WITH PCI

Before beginning a discussion on the predictors of adverse outcomes following PCI, it is useful to examine the trends in the incidence of adverse events associated with PCI over the last few decades. Table 1 provides a summary, from published literature, on some of the more established adverse outcomes associated with PCI, namely, in-hospital death, in-hospital myocardial infarction, and bypass surgery. Where available, the percentage of "successful" PCIs is provided.

Several interesting observations can be made from the data in Table 1. There was a dramatic change in outcomes associated with PCI between the first five years in which it was introduced (1977-81) and by the time it was being performed routinely (1985-86) [1]. From the time that angioplasty became a mainstream procedure, it has been associated with very low adverse event rates. High-risk patient populations accounted for the higher mortality rates of 3.4% found in the Moscucci study [11] and 2.6% in the Grassman study [7]. Among the 1,476 patients in the Moscucci study, 3.3% had cardiogenic shock and 14.3% had acute myocardial infarction. And all the patients in the Grassman study had acute myocardial infarction on admission.

Table 1. Summary of outcomes associated with percutaneous coronary interventions - data from published studies

Ref.	Author	Group	Time-period	Sample size	In-hospital Outcomes				Success
					Death	MI	CABG		
							Any	Emergency	
1.	Detre, et al	NHLBI	1977-81	1,155	1.2	4.9	26.5	5.8	61
		NHLBI	1985-86	1,802	1.0	4.3	5.6	3.4	78
2.	Mick, et al	--	1980-88	5,000	0.5	0.4	4.7	--	93
3.	Hannan, et al	NYS	1991	5,827	0.6	1.2	2.5	1.7	87
4.	Kimmel, et al	SCA&I	1992	10,622	0.4	0.6	--	1.5	--
5.	Malenka, et al	NNE	1989-93	12,232	1.0	1.5	3.2	2.1	93
4.	Kimmel, et al	SCA&I	1993	10,030	0.5	0.5	--	1.2	--
6.	King, et al	NACI	1990-94	1,985	1.8	1.5	3.5	--	83
7.	Grassman, et al*	SCA&I	1990-94	4,366	2.6	--	--	3.4	92
8.	Hannan, et al	NYS	1991-94	62,670	0.9	--	--	3.4	--
9.	Ellis, et al	--	1993-94	12,985	1.3	3.5	--	2.1	--
10.	McGrath, et al	NNE	1990-93	13,014	1.0	2.4	3.3	2.2	89
		NNE	1994-95	7,248	1.1	2.1	3.3	2.3	89
11.	Moscucci, et al	--	1994-96	1,476	3.4	0.8	0.9	--	--
10.	McGrath, et al	NNE	1995-97	14,490	1.2	2.0	1.8	1.3	92

*Acute myocardial patients only.

NHLBI: National Heart, Lung, and Blood Institute; NYS: New York State; SCA&I: Society for Cardiac Angiography and Interventions; NNE: Northern New England Cardiovascular Disease Study Group; NACI: New Approaches to Coronary Interventions; MI: myocardial infarction; CABG: Coronary Artery Bypass Surgery;

The increasing use of PCI as the primary therapy for acute MI is supported by evidence from clinical trials. In the Primary Angioplasty in Myocardial Infarction (PAMI) study, 395 patients presenting within 12 hours of the onset of myocardial infarction were randomized to immediate PTCA or intravenous tissue plasminogen activator (t-PA). The combined end-point of death or re-infarction was statistically significantly lower in the PTCA arm (5.1%) compared to the t-PA arm (12%) [12]. In an angioplasty sub-study of the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial, 1138 patients were randomized to PTCA or t-PA. The incidence of the primary end-point (a composite of death, re-infarction or disabling stroke within 30 days) was 9.6% in the PTCA arm and 13.7% in the t-PA arm. However, this statistically significant difference in rates was lost by 6-months (14.1% in PTCA and 16.1% in t-PA) [13]. In a trial using a different thrombolytic agent, 301 patients with acute myocardial infarction were randomized to PTCA or to intravenous streptokinase [14]. The combined end-point of death or re-infarction occurred in 15% of the patients in the streptokinase arm and in 3% of patients in the PTCA arm.

The clinical profile of the patient undergoing PCI has changed dramatically over the last twenty years. In addition to being used more and more in patients presenting with myocardial infarction, PCI procedures are being used in patients

who are older, have worse left ventricular function and more complex lesions [1, 10].

The rates of coronary artery bypass surgery (CABG) following PCI fell from 26.5% in the 70's to 5.6% in the 80's to 1.8% in 1995-97. McGrath et al attribute the latter decline to the increasing use of stents in PCI procedures [10]. In their study the drop in CABG rates coincided with the introduction of stents in 1995 and by 1996 and 1997, when stents were used in 45.2% and 62.4% of the cases, respectively, the rates dropped even more dramatically.

Other factors have probably contributed to the improving outcomes associated with PCI. Increasing operator volumes have been shown to be associated with better outcomes. In fact, between 1988 and 1993 the American College of Cardiology/American Heart Association (ACC/AHA) guidelines increased the recommended minimum procedures from 50 to 75 per year per physician [15, 16]. In a 1992 analysis of Medicare data, Jollis et al found that patients of physicians who did not meet the ACC/AHA minimum volume guidelines had worse outcomes [17].

Based on the promising data from clinical trials on the advantages of PCI adjunct therapies such as glycoprotein IIb/IIIa inhibitors [18, 19] and the ever evolving quest for newer more effective technologies, both in equipment and medications, one can expect PCI outcomes to continue to improve into the new century.

2. Studies on Identifying Predictors of In-hospital mortality Following PCI

Statistical constraints imposed by infrequent outcomes have required that studies examining predictors of adverse outcomes following PCI involve large sample sizes [20]. The establishment of PCI registry databases such as the National Heart, Lung and Blood Institute's (NHLBI) Coronary Angioplasty Registry, the New York State (NYS) Cardiac Database, the Society for Coronary Angiography and Intervention (SCA&I) Registry, the Duke Cardiovascular Database, the Northern New England (NNE) Cardiac database, and more recently the Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease (APPROACH) database have allowed extensive examination of risk-factors associated with the procedure.

Table 2 is a summary of the variables found to be risk-factors for in-hospital mortality following PCI in the studies identifying multivariable predictors of in-hospital mortality.

One of the first studies identifying risk factors for outcomes of PTCA was conducted by Hannan and colleagues [3]. The study was based on 5,827 patients who underwent coronary angioplasties between January 1, 1991 and June 30, 1991 in New York state. One of the outcomes examined was in-hospital

mortality. Only 37 (0.63%) patients died in-hospital and female gender, hemodynamic instability, defined as a condition requiring pharmacologic or

Table 2. Summary of independent predictors of in-hospital mortality. The "X" indicates that a particular variable was found to be a significant predictor in multivariable analysis.

Variables Years	Hannan 1991	Hannan 91-94	Ellis 93-94	O'Connor 94-96	Moscucci 94-96
Reference number	3	8	9	21	11
Sample Size	5,827	62,670	12,985	15,331	1,476
Demographics					
Age		X	X	X	X
Female gender	X	X	X		X
Disease stage and severity					
Acute MI		X	X	X	**
Hemodynamic instability*	X	X			
Previous PTCA		X			
Previous CABG		X			
Shock	X	X	X	X	X
Comorbidities					
Diabetes		X			
CHF		X		X	X
Renal disease				X	X
PVD				X	
Femoral popliteal disease		X			
Cardiac Anatomy					
Lesion complexity			X	X	
Ejection fraction	X	X		X	
Procedural variables					
Urgent procedure				X	
Emergent procedure				X	X
IABP		X		X	
Number of lesions		X	X		X

MI = myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Graft; CHF = congestive heart failure; PVD = peripheral vascular disease; IABP = intra-aortic balloon pump; *Defined as a condition requiring pharmacologic or mechanical support for blood pressure or cardiac output. **Study includes acute myocardial infarction patients only

mechanical support for blood pressure or cardiac output, and shock were associated with higher mortality. Ejection fraction was inversely related to in-hospital mortality.

In a subsequent study, Hannan and colleagues updated the analyses to include 62, 670 patients who underwent PCI between 1991 and 1994 [8]. Variables associated with higher mortality were: age, female sex, lower ejection fraction, congestive heart failure, previous myocardial infarction, hemodynamic instability, shock, renal failure, femoral popliteal disease, diabetes, intra-aortic balloon pump, two or three vessels attempted and previous open heart surgery. Also, patients who had undergone a prior coronary angioplasty were less likely to die in-hospital. The c-index associated with the model was 0.89 and the Hosmer-Lemeshow goodness of fit test was insignificant (p=0.11) indicating little departure from a perfect fit. (Detailed descriptions of the c-index and the Hosmer-Lemeshow goodness of fit test are provided in Chapter 5).

In the model generated by Ellis et al from the Cleveland Clinic Foundation using 12,985 patients who underwent PCIs during 1993 and 1994, the correlates of in-hospital mortality were: the logarithm of patient age in years, shock, acute myocardial infarction, lesion complexity defined as Type A and B1 = 1, Type B2 = 2, and Type C = 3 (used as a continuous variable), and the number of diseased vessels [9]. The coefficient of male sex was negative indicating that males were

less likely to die during the hospital stay compared to females. The model had good discriminatory power as suggested by the c-index of 0.85.

The most recent modeling studies are from O'Connor et al of the Northern New England Cardiac Disease Study Group [21] and Moscucci et al [11]. In the NNE study, data on 15,331 consecutive hospital admissions from six clinical centers were analyzed. Increasing age, acute myocardial infarction, shock, urgent or emergent priority, decreasing ejection fraction, renal disease, peripheral vascular disease, congestive heart failure, intra-aortic balloon pump, and lesions of type C were all associated with higher in-hospital mortality. The c-index for the model was 0.88 indicating that the model had a good ability to discriminate between patients who had the outcome and those who didn't. The Hosmer-Lemeshow goodness of fit test was not statistically significant.

In addition to validating the NNE and Cleveland Clinic models on an independent high-risk patient population of 1,476 acute myocardial infarction patients, Moscucci and colleagues also developed a separate model fit to their patient population. The following variables were found to be significant predictors of in-hospital mortality: emergency procedure, age, female gender, cardiogenic shock, number of diseased vessels, congestive heart failure and renal disease. Again, the model's c-index was 0.88 and the Hosmer-Lemeshow statistic was not significant.

3. LONG-TERM OUTCOMES FOLLOWING PCI

There are fewer studies examining predictors of longer-term outcomes of PCI. Table 3 offers a summary of findings from some of the studies.

Table 3. Summary of multivariable predictors of long-term mortality. The "X" indicates that a particular variable was found to be a significant predictor in multivariable analyses.

Description	Mick	Bell	Cowley	Weintraub
Reference	2	38	22	40
Sample size	5000	3027	3079	6318
Follow-up	4 years	1 year	18 months	5 year
Variables				
Demographics				
Age	X	X		X
Male gender	X		X	
Heart disease stage and severity				
CCS class	X	X	X	X
Prior MI		X		
Prior CABG		X		
AMI on admit		X		
CHF	X	X		X
Comorbidities				
Diabetes	X	X		X
Hypertension	X	X	X	X
Smoking hx			X	
Coronary anatomy and LV function				
Extent of disease	X	X	X	X
EF				X
Graft	X			
LM disease			X	

CCS = Canadian Cardiovascular Society; MI = myocardial infarction; CABG = coronary artery bypass graft; AMI = acute myocardial infarction; CHF = congestive heart failure; hx = history; EF = ejection fraction; LM = left main

One of the first studies of five-year survival was by Mick et al [2]. Based on data from 5000 consecutive patients who underwent PCI between 1980 and 1988, the authors developed a model to risk-stratify patients according to their long-term outcomes. At a median follow-up of 4.1 years, the mortality rate among these

patients was 7.3%. Independent predictors of long-term mortality were male gender, age, extent of disease (defined by an artery or major side branch with > 60% lumen narrowing and classified as single-, double-, or triple-vessel disease), CCS class, diabetes, congestive heart failure, hypertension and target lesion in bypass graft.

In the context of examining sex-differences in the long-term results of coronary angioplasty, Cowley et al used data on 705 women and 2374 men in the NHLBI PTCA Registry [22]. At two years, the mortality rate among men was 2.2% and among women it was 0.4%. Factors associated with late mortality were left main disease, male gender, class 3 or 4 angina, hypertension, multi-vessel disease, and smoking history.

Among 3027 patients who underwent successful angioplasty at Mayo Clinic, Bell et al found no significant differences among males and females in long-term mortality [38]. However, stage and severity of disease measures, namely CCS class, congestive heart failure, prior myocardial infarction, prior CABG, as well as acute myocardial infarction on admission, were all significantly associated with mortality. In addition, comorbidities such as diabetes and hypertension also played a role.

Weintraub et al's study was by far the largest with 6318 patients on whom 5-year survival data was available [40]. In a multivariable analysis, long-term mortality

was associated with older age, congestive heart failure, reduced ejection fraction, multi-vessel disease, diabetes, hypertension and angina.

Many of the other studies examining longer-term outcomes of PCI have been descriptive in nature [6] or have been conducted within the context of clinical trials [23-24]. There appear to have been no studies, to date, examining long-term outcomes in the post-stenting era.

4.1 Independent Predictors of Adverse Events Following PCI

Baseline predictors of adverse events following PCI can be classified into the following categories: demographic factors; disease stage and severity measures; comorbidities; cardiac anatomy and function; and procedural factors. The previous tables (Table 2 and 3) summarized findings of studies examining multivariable predictors of short and long-term outcomes. However, in addition to these studies there have been several observational studies examining particular risk factors. In the following sections literature around the more dominant risk factors for adverse events following PCI is discussed in detail. These include age, sex, diabetes, hyperlipidemia, congestive heart failure and cardiogenic shock.

4.1 Age

Over the last few decades, primarily due to improvements in medical care, life expectancy in developed countries has shown a tremendous increase. This has led to major demographic shifts, with the elderly accounting for an increasing percentage of the population. In response to this aging population's needs, rates of PCI among the elderly have increased substantially [25].

In the multivariable setting (Tables 2 and 3), age has been found to be a significant predictor of both short and long-term mortality [8,9,21,11,2,38,40]. Table 4 summarizes the findings of some additional observational studies that have examined age-related outcomes of PCI. As can be seen from the table, increasing age is consistently associated with higher mortality in the short-term and not surprisingly in the long-term as well. Octogenarians (patients over 80 years) are particularly susceptible to worse outcomes.

The positive relationship between increasing age and mortality is to be expected. The more relevant question may be whether outcomes associated with PCI are better or worse compared to those of alternative therapies among the elderly. Although this question is tangential to this thesis, it is worth mentioning that in the context of randomized controlled trials, patients over the age of 70 years who

Table 4. Summary of findings from studies examining outcomes of PCI by age categories

Ref	Author	Time-period	Age categories	Sample size	Death in-hospital	Length of Follow-up	Long-term outcomes	
							Death	Repeat PCI
26	Forman et al	1982 - 88	60-69	570	2%	3-years	4%	16%
			70-79	270	2%		10%	15%
			80+	67	6%		18%	6%
27	Kelsey et al	1985 - 86	< 65	1315	0.2%	2-years	3%	22%
			65 - 74	394	3.0%		8%	19%
			≥ 75	92	3.3%		13%	20%
28	Thompson, et al	1980 - 89	≥ 65	982	3.2%	25 months	9.2%	15.4%
29	Tan, et al	1981 - 93	≥ 70	163	2%	5 years	17%	16%
30	De Jaegere, et al	1983 - 88	≥ 70	166	4%	21 months	10%	13%
31	Gravina Taddei, et al	1980 - 96	< 50	3941	2%	10 years	13%	
			50 - 59	5919	2%		19%	
			60 - 69	6399	4%		46%	
			70 - 79	3285	6%		57%	
			> 80	511	11%		76%	

underwent PCI fared far better than patients who were treated medically with thrombolytic therapy [32, 33].

4.2 Sex

In the multivariable setting (Tables 2 and 3) female gender was associated with higher short-term mortality [8,9,11,21] but with lower longer-term mortality [2,22]. Historically, there has been speculation whether the worse outcomes observed have led to physicians being less inclined to prescribe invasive treatments to women. Among patients with established CAD, there is significant disparity in the rates of cardiac procedures among men and women. The odds of undergoing revascularization have been shown to be 30 to 40 percent higher for men admitted with a diagnosis of AMI compared to women [34]. As part of the Survival and Ventricular Enlargement (SAVE) study, a large post-infarction intervention trial, Steingart et al examined the sex-related differences in the treatment of high-risk patients presenting with similar cardiovascular events [35]. They found that despite reporting higher levels of disability, women were less likely to be referred to cardiac catheterization (15.4 versus 27.3 percent, $p<0.001$) or coronary bypass surgery (5.9 versus 12.7, $p<0.01$).

The National Heart, Lung, and Blood Institute (NHLBI) PTCA Registry has provided the context for several studies on sex differences in short and long-term

outcomes of PTCA [22, 36, 39]. Table 5 summarizes the findings of these and other studies that have examined the gender issue.

Table 5. Summary of documented sex differences in mortality following PCI

Ref.	Author	Year	Total N	% Female	In-hospital death	
					Males	Females
22	Cowley et al	1978-82	3079	23	0.7	1.8
37	Bell	1979-87	1970	26	2.2	2.9
40	Weintraub	1980-91	10785	26	0.1	0.7
36	Kelsey	1985-86	2136	26	0.3	2.6
37	Bell	1988-90	2101	28	3.1	5.4
41	Malenka	1989-93	12232	33	0.7	1.6
39	Jacobs	1993-94	274	100	-	1.5

As can be seen from the table, women consistently had higher in-hospital mortality following PCI compared to men. However, it should be mentioned that in *all* these studies, women were older at the time of the procedure and had a higher number of comorbidities than men.

Although the evidence is fairly consistent around the short-term outcomes of women being worse than men, data on long-term survival is more equivocal. In Cowley et al's study, follow-up data were available for 2,272 (74%) patients [22]. Mean follow-up was 18 months. Event-free survival, defined as absence of death, MI, and additional revascularization, was higher among women (79.7%) than men (69.0%). In contrast, Kelsey et al showed that the short-term difference in mortality among males and females was maintained up to 3 years and in fact

diverged at four years. The frequency of all other events, namely, non-fatal MI, CABG and repeat PTCA remained similar in both sexes. [36]

In a follow-up study on the same cohorts, Bell et al reported long-term outcomes on patients who had successful procedures [38]. A mean follow-up of 5.5 years (range 6 months to 14 years) was available on 2203 males and 824 females. There was no significant difference in survival at 10 years between males and females after adjusting for baseline variables.

4.3 Diabetes

The studies of independent predictors of short and long-term mortality (Tables 2 and 3) suggest that diabetes may be associated with mortality more in the long-term [2,38,40] than in the short-term [8].

On September 21, 1995 a Clinical Alert was released on diabetics treated with angioplasty [43]. On September 13th 1995 the Data and Safety Monitoring Board had met to review the available 5-year follow-up data from the NHLBI BARI study. The BARI trial enrolled 1829 patients with multi-vessel coronary artery disease who were undergoing a first revascularization procedure. The average age of the patients was 61 years, 27 percent were women and 28 (512) percent had diabetes. Seventy-six percent of the diabetics were on insulin or oral hypoglycemic agents. Patients were randomly assigned to CABG or PTCA. The

primary end-point was mortality after 5 years. At the time of the review 66 percent of patients had completed follow-up. Patients who were on insulin or oral therapy (N=353) were found to have a significantly lower mortality rate with CABG (19%) than with PTCA (35%). Based on these results, the Alert stated that CABG should be the preferred treatment for patients with diabetes on drug or insulin therapy who have multi-vessel coronary artery disease and require a first coronary revascularization procedure. However, given the very specific nature of the patient population, these results were not considered to be generalizable to other patient populations.

The fact that diabetes is a risk factor for coronary artery disease has been long established. In a sixteen-year follow-up in the Framingham study, diabetics were shown to have increased morbidity and mortality from coronary artery disease [44]. The Framingham study consisted of long-term follow-up of a probability sample of 5,209 residents. A total of 239 patients, 118 men and 121 women, were diabetic at initial examination. During the follow-up, diabetics had three-times the mortality of the general population. In general females with diabetes tended to fare worse than males. In fact, insulin treated diabetic women showed the greatest mortality from coronary heart disease.

In order to explain the findings of the BARI trial, Rozenman and colleagues examined retrospectively coronary angiograms from 55 diabetic and 193 non-diabetic patients who were referred to angiography > 1 month after successful

angioplasty [45]. Patients in the two groups had similar baseline characteristics. However, there was a marked difference in the rate of appearance of new narrowings in the diabetics (22%) compared to the non-diabetics (12%). These researchers had shown, in an earlier study that new narrowings were more likely to appear in angioplastied vessels than in non-angioplastied vessels [46]. In this study they concluded that the combined effect of diabetes mellitus and angioplasty is additive, that is, the risk of new narrowings developing among angioplastied vessels among diabetics was especially high.

Stein et al examined the influence of diabetes on early and late outcome after PTCA among 10,433 patients who underwent elective PTCA between 1980 and 1990 at Emory University and Crawford W. Long hospitals [47]. The patients had no prior PTCA or CABG. Of the patients enrolled, 1133 had diabetes. These patients were further classified as insulin requiring (IR) (352) or non-IR (781). The authors found no significant association between diabetes (including IR diabetes) and in-hospital mortality. This, however, may have been due to the low frequency of death overall. In contrast, and more consistent with findings from other studies, diabetes and in particular IR diabetes was a significant predictor of five-year mortality. Diabetics were also more likely to have a MI and repeat revascularization during the follow-up period.

In summary, all patients, and especially women, with diabetes appear to be at a higher risk for adverse outcomes following PCI. Although there is some

evidence to suggest that PCI may not be the recommended therapy for diabetic patients, the introduction of new therapies such as stents and glycoprotein IIb/IIIa inhibitors is likely to improve outcomes among these patients.

4.4 Lipids

In a recent editorial in the European Heart Journal Dr de Feyter provides a table summarizing the evidence from studies exploring the relationship between lipid and lipoprotein levels and angiographic restenosis [48]. Of the thirteen studies reviewed, four found some association between lipid levels and restenosis (at least in subsets of patients) [49-52] and three found a relationship between lipoprotein and restenosis [52-54]. One of the more recent studies was conducted by Jorgensen et al in 305 patients who underwent angioplasty [55]. The authors found no association between lipoproteins or lipids and luminal loss at follow-up.

In addition, no association between a significant reduction in low-density cholesterol in patients with increased lipids and restenosis after coronary angioplasty was reached in the Lovastatin Restenosis Trial [56]. In both the primary analysis and a subgroup analysis of patients with high baseline cholesterol levels, aggressive treatment with lavostatin for 6 months had no effect on restenosis rates.

Although the data on whether lipid lowering effects post-angioplasty restenosis is equivocal, there is little argument that a long-term strategy of lipid lowering is an effective strategy in retarding the progression of atherosclerosis. For instance, the Scandinavian Simvastatin Survival Study (4S) was the first trial to conclusively demonstrate the association between lowering low-density lipoprotein (LDL) cholesterol levels and significant reduction in mortality and need for revascularization procedures [57]. The study included 4,444 patients, aged between 35 and 70 years, with a history of acute myocardial infarction (MI) or angina. Patients were randomized to either simvastatin or placebo and the median follow-up was for 5.4 years.

While the 4S study was focussed on patients with relatively high levels of cholesterol (the mean total cholesterol level among the 4,444 patients was 261 mg/dL), the Cholesterol and Recurrent Events (CARE) trial focussed on patients with total cholesterol levels between 200 and 210 mg/dL [58]. Four thousand and one hundred and fifty nine (1,459) patients were randomized to treatment with pravastatin or placebo within one to two years of having a MI. Benefits, in terms of reduced mortality and need for revascularization were found among both sexes and in both old (60 - 75 years) and young (24 - 59 years) patients.

Although these RCTs have demonstrated beyond a doubt the efficacy of cholesterol lowering therapy in improving outcomes, the gap between clinical evidence and clinical practice is yet to be bridged. For example, in a study of

physician practices in four acute care hospitals in Canada, the Clinical Quality Improvement Network (CQIN) Investigators found only 8% of 3,304 high risk patients had been prescribed drug therapy and only 22% had been advised to modify their diet [59]. Similarly, in a study by Frolkis et al. of physician compliance with the 1993 National Cholesterol Education Program (NCEP-ATPII) guidelines at a CCU of a university-affiliated teaching hospital in the US, the authors found that an LDL value was obtained only 50% of the time among patients at high risk for coronary heart disease [60].

In summary, the evidence on the impact of lipid lowering on restenosis after angioplasty is inconclusive, however, the benefits of lipid lowering in impeding the overall progression of coronary artery disease has been established. Aggressive treatment is therefore recommended in all patients with established coronary artery disease, of which patients undergoing PCI are a subset [15].

4.5 Hypertension

The primary purpose of treating hypertension, not just in the context of angioplasty, is to prevent other cardiovascular complications that it can give rise to, namely stroke, myocardial infarction, sudden death and heart failure [61].

There have been no studies comparing hypertension treatments among patients who have undergone PCI. The prevalence of hypertension among patients

undergoing PCI is, as expected, fairly high. In an examination of all the major American registry databases on PCI patients, Block et al found that the mean rate of hypertension across all sites was 49% with a range of 42% to 63% [64]. Therefore, among these patients, secondary prevention appears more relevant.

In summary, patients undergoing PCI tend to have high rates of hypertension and are probably under treatment for it. The recommended treatment for secondary prevention of hypertension, especially among patients who have undergone a recent myocardial infarction, is beta-blockers and ACE inhibitors. Diuretics are recommended for primary prevention of hypertension among elderly patients [62].

4.6 Congestive Heart Failure and Shock

There is no doubt that the most ominous of all disease stage and severity signs are the indications of congestive heart failure and cardiogenic shock. Referring back to Tables 2 and 3, congestive heart failure was predictive of both short [8,11,21] and long-term mortality [2,38,40]. Shock, however, played a role only in short-term mortality [3,8,9,11,21] and this is probably due to the fact that patients with shock are unlikely to survive in the long-term.

Heart failure is among the leading causes for hospital admissions in America. Haldeman et al analyzed the National Hospital Discharge Survey (NHDS) data

from 1985 to 1995 and found that the number of hospitalizations with a principal diagnosis of congestive heart failure among patients 35 years and older increased from 577,000 in 1985 to more than 871,000 in 1995 [66]. Higher rates of heart failure were associated with increasing age and with male gender.

Among patients undergoing PCI, congestive heart failure has been associated with higher mortality. In a study of 5, 260 PCI patients enrolled in the Duke University database, Anderson et al examined the prognostic value of a history of congestive heart failure in predicting 30-day and 6-month mortality [67]. Patients with heart failure had statistically significantly higher odds of both short and long-term mortality (univariate odds of 9.4 and 21.9, respectively). Heart failure was found to be a significant predictor of 6-month mortality, in addition to ejection fraction, age, and number of diseased vessels, in a multivariable model generated using backward stepwise logistic regression analysis.

When greater than forty percent of the left ventricle is dysfunctional, either due to ischemia or myocardial infarction, the patient is classified as having cardiogenic shock [68]. The use of intra-aortic balloon pumping is highly correlated with the indication of cardiogenic shock. Mortality among these patients, and especially among those with shock complicating myocardial infarctions, is in the region of 60 to 70 percent [69]. The use of PCI has been known to be therapeutic, reducing mortality to the region of 45% [68,69],

although there is speculation that the lower rates may be a result of selection bias on the part of highly skilled practitioners [69].

Data from the SHOCK trial (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) have shed more light on the impact of emergency revascularization in patients with shock [70]. As part of this trial patients with cardiogenic shock complicating acute myocardial infarction were randomly assigned to either an emergency revascularization (PCI or CABG depending on the cardiac anatomy) or medical therapy. Sixty-four percent of patients in the revascularization group underwent PCI. Although revascularization did not reduce the primary end-point of 30-day mortality, it appeared to reduce mortality at six-months (50.3% in the revascularization arm and 63.1% in the medical therapy arm, p=0.03).

In summary, congestive heart failure and cardiogenic shock are indicators of an increased stage and severity of coronary artery disease and are therefore significant predictors of mortality, both in the short and long-term.

4.7 Behavioural factors

In addition to the clinical factors discussed above, several behavioural factors are considered to be risk factors for coronary artery disease and therefore coronary angioplasty. These include smoking, weight reduction and physical activity. It

is estimated that 28% of Canadian men and 25% of Canadian women are smokers [71]. Smoking appears to be more prevalent among people aged between 18 and 44 years. It is ethically infeasible to conduct a randomized controlled trial to examine the impact of smoking and coronary heart disease, however, several observational studies have documented the increased risk of death among patients who smoke [72,73].

The Life Style Heart Trial by Ornish et al. [74] and the study on the effect of regular exercise and low-fat diet on progression of CAD by Shuler et al. [75] demonstrated that significant weight loss in the intervention groups was associated with improved outcomes.

Although several exercise trials have been conducted on CAD patients, none have had the statistical power to determine whether exercise has a significant impact on cardiac mortality. However, a meta-analysis conducted by O'Connor and colleagues of RCTs of rehabilitation with exercise after MI showed that exercise reduced mortality by approximately 20% - 25% over follow-up of 3 months to 3 years [76].

5. CONCLUSION

There is considerable literature, both in the context of randomized clinical trials and from cohort studies, around risk factors of adverse outcomes associated with

coronary artery disease and specifically with coronary angioplasty. However, multivariable analyses have been effective in bringing into focus some of the more important prognostic factors. As the technologies associated with percutaneous coronary intervention continue to evolve additional analyses will have to be conducted taking these emerging therapies into account.

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CHAPTER 3. OBJECTIVES, HYPOTHESES AND SIGNIFICANCE

1. INTRODUCTION

The main objective of the thesis is to identify predictors of adverse events within one-year following percutaneous coronary intervention (PCI). Predictors of adverse events can be classified into six groups: 1) demographic variables, such as age and sex; 2) disease stage and severity indicators, such as acute myocardial infarction on admission and prior PCI and coronary bypass procedures; 3) comorbidities, such as diabetes and hypertension; 4) cardiac anatomy, such as the presence of proximal LAD lesions or left main disease; 5) procedural factors, such as the insertion of an intra-aortic balloon pump or stents; and 6) post-discharge secondary prevention therapies, such as the use of aspirin and lipid-lowering agents.

The thesis is comprised of two studies. Study I (Chapter 5) examines baseline and procedural factors (categories 1 through 5 mentioned above), while Study II (Chapter 6) is focused on the impact of secondary prevention (category 6). Both studies use data collected as part of the *Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease* (APPROACH) project, a description of which is provided in Chapter 4.

All Alberta residents who underwent PCI between July 1, 1995 and December 31, 1997 are included in Study I. A subset of these patients who were enrolled simultaneously in the *Enhancement of Secondary Prevention in Heart Disease Study* (ESP study) make up the patient population for Study II.

The following is a brief description of the objectives, hypotheses and significance of the two studies.

2. Study 1 (Chapter 5): Predictors of Adverse Events Within One-year Following PCI

2.1 Objectives

The *primary* objective of this study is to develop and validate a statistical model to identify significant predictors of mortality within one-year following the index PCI. The *secondary* objectives include developing similar models for short-term (30-day) mortality and for repeat revascularization procedures (repeat PCI or coronary bypass surgery) within one-year of the index PCI.

2.2 Hypothesis

The time-period of the study straddles the introduction and acceleration in use of stents, a new technology in PCI. The study hypothesis is that traditional risk factors that have been found to be predictors of short-term adverse events in the pre-stenting era will likely be significantly associated with longer-term adverse events in the post-stenting era.

2.3 Significance

Risk stratification of patients for event-free survival after PCI has important implications for discharge planning, follow-up care, and use of secondary prevention strategies. Identification of patients with higher probabilities of adverse events can assist in patient counseling and optimal clinical decision-making. No model has been developed to predict longer-term (one-year) outcomes among PCI patients in the post-stenting era nor have studies examined the issue of repeat revascularization in a population-based setting.

3. Study 2 (Chapter 6): Impact of Secondary Prevention on Adverse Outcomes Within One-year Following PCI

3.1 Objectives

The *primary* objective of this study is to examine the impact of secondary prevention strategies and heightened surveillance on mortality and repeat revascularization within one-year of the index PCI. The *secondary* objectives are to document practice-patterns around the use of specific medications, as well as to describe patient reported health services utilization and drug compliance.

3.2 Hypothesis

The study hypothesis is that the use of established medical therapies and diligent follow-up of patients following their index PCI will be associated with better outcomes. It is also hypothesized that compliance among patients who were closely monitored will be higher than for patients who received regular care.

3.3 Significance

Information on the role of secondary prevention in predicting long-term outcomes is a significant addition to existing literature. Collection of data on

secondary prevention therapies is an expensive and time-consuming process. This study will evaluate the contribution of secondary prevention, above and beyond patient and procedural factors, in preventing adverse events.

CHAPTER 4. A DESCRIPTION OF DATA USED

1. THE APPROACH PROJECT

The *Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease* (APPROACH) project is an ongoing study of all Alberta residents undergoing cardiac catheterization for CAD since January 1995 [1]. This population-based multi-year inception cohort database contains detailed information on socio-demographic characteristics, presence or absence of comorbidities, disease-specific variables, coronary angiography results, post-catheterization referral decisions, records of actual revascularization, and data on outcomes post-revascularization, including survival and quality of life. Patients are followed over time for the evaluation of outcomes such as mortality, subsequent revascularization, cardiac-related quality of life (assessed yearly after catheterization), and long-term costs of care.

There are several advantages to APPROACH's study design. Given that it includes all Alberta patients undergoing cardiac interventions, it allows for population-level analyses. The capture of data starting at the time of cardiac catheterization provides information on a larger spectrum of care than databases that are more cross-sectional and focussed on percutaneous coronary intervention (PCI) or coronary surgery (CABG) procedures. The process and magnitude of data collection has been designed to be conducive to clinical

practice. The computerized system has been streamlined and offers clinicians access to the patient's medical history and immediate feedback on their prognosis.

Presently, APPROACH patients are treated at three sites: the University of Alberta Hospitals and the Royal Alexandra Hospital in Edmonton and the Foothills Hospital in Calgary (before March 31, 1996, patients were also treated at the Holy Cross Hospital in Calgary). Given that these sites are the only ones at which coronary angioplasties are performed in Alberta, the APPROACH database captures all patients who undergo PTCA. Data collection is ongoing and about 7,000 patients are enrolled in the database each year. As of December 1999, over 35000 patients have been enrolled in APPROACH.

The sections corresponding to definition of terms and the PCI data entry form from the APPROACH Project Protocol are attached in Appendix I.

2. THE ESP PROJECT

The Enhancement of Secondary Prevention of Heart Disease Study (ESP study), was a quality improvement program that maximized the use of cardiac medications that have been shown to be effective in secondary prophylaxis of heart disease [3]. Secondary prevention is drug treatment prescribed to prevent a recurrence of a coronary event among patients diagnosed with CAD. The ESP study was designed to intervene in a controlled manner to determine if appropriate prescription of and compliance with a secondary prevention regiment makes a significant difference in patient outcomes and total medical care costs. The existing literature identifies the following drugs as contributors in secondary prevention of CAD: Aspirin or Acetylsalicylic Acid (ASA), β-blockers, lipid-lowering agents and angiotensin-converting enzyme (ACE) inhibitors among patients with low ejection fraction or congestive heart failure. In current medical practice these drugs are not always prescribed when they should have been and 50% of all prescriptions are taken incorrectly.

2.1 Study design

The ESP study recruited patients between April 1996 and June 1998. Patient follow-up continued until December 1999. The patient population was selected

from all cardiac admissions to the Foothills Hospital in Calgary. Patients were screened for inclusion criteria (see below). After obtaining consent, patients were randomized to the usual (non-interventional) or the enhanced (interventional) care study arm according to their attending cardiologist. About 30 cardiologists work at Foothill Hospital, therefore approximately 15 were assigned to each arm. A total of 2,930 patients were enrolled in the ESP study of which 1,417 (48%) were in the intervention arm.

2.2 Inclusion/Exclusion Criteria

Patients living in the Calgary Health region with proven coronary artery disease were eligible for inclusion into the study. Patients with poor English, mental incompetence or terminal illness were excluded. Also, patients who were transferred from out of region hospitals, transplant cases, nursing home patients, deaf or blind and living alone, inaccessible for follow-up and who had not consented were excluded.

2.3 Intervention

Intervention (or enhanced care) included regular follow-up, at one week, one month and every three months following hospital discharge, by nurse

coordinators. During these encounters, medication profiles were reviewed for appropriateness and patient compliance was recorded. Several educational interventions, such as medication classes, medication information on video, and individualized medication counseling sessions were available for patients in the intervention arm. At discharge the intervention arm patients received a summary letter to the patient's physician and pharmacy listing information on the hospital stay, past medical history and drug related problems. Nurse coordinators were accessible to interventional patients to discuss problems or concerns at any point in the follow-up. In contrast, the non-interventional arm patient was asked to mail, fax or e-mail completed questionnaires at the scheduled intervals.

2.4 Data collection

The ESP data collection was conducted at several stages. At enrollment to the study, an *ESP Participant Questionnaire* was completed on each patient. A copy of the same is provided in Appendix II. This questionnaire had several sections. These included demographics; past cardiovascular history and etiology; prior interventions and past medical history. Data on insurance status, physicians, pharmacy, and past diagnostic tests were also collected at this stage.

The sections pertaining to *Course in Hospital, Interventions in Hospital, Non-cardiac Events, Admissions for Adverse Drug Reaction, Current Diagnostic Test,* and *Discharge Diagnosis* (Section VIII - XIII, page 6 - 9) were completed for every hospitalization following enrollment into the study. Therefore, there was potential for multiple records of these data for each patient.

The Discharge Diagnosis (Section XIII, page 9) contained data on the medications that the patient was discharged on. Detailed medication summary, including drug name, dose and frequency was available in the Medication Summary (Section XIV, page 10).

Patients were asked to complete the Follow-up Questionnaire at 1 week, 1 month, and every 3 months following discharge from the hospitalization during which they were enrolled. In the intervention arm, the follow-up was done via telephone calls by nurse coordinators. If for any reason compliance was at risk, the nurse took appropriate action to attempt to rectify the problem. In the usual practice arm, patients were asked to mail, fax or e-mail completed questionnaires at the same scheduled times.

3. REFERENCES

1. Ghali WA, Knudtson ML for the APPROACH Investigators. Overview of 'APPROACH' - The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease. [Under review].
2. The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Study Protocol.
3. The Enhancement of Secondary Prevention in Heart Disease Study (ESP Study) Protocol

APPROACH

The Alberta Provincial Program for

Outcome Assessment in Coronary Heart Disease

Principal Investigator: Dr. M.L.Knudtson

Revised 9/22/00

T. DEFINITION OF TERMS

WORK STATUS: 1 = Full Time, 2 = Part Time, 3 = Unemployed, 4 = Sick Leave, 5 = Retired, 6 = Homemaker

OCCUPATION: Document the most recent occupation. Be as specific as possible in relation to employment - do not state name of employer.

QUALITY OF LIFE: The patient's own estimation of the state of his/her health rated on a scale of 1 -10. (1 = poor & 10 = excellent)

CCS CLASS:

0 No angina.

I Ordinary physical activity, such as walking and clilmbing stairs, does not cause angina. Angina with strenuous, rapid or prolonged exertion.

II Slight limitation of ordinary activity. Angina with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening.

III Marked limitation of activity. Angina with walking one or two blocks or climbing more than one flight of stairs in normal conditions.

IVa Unstable angina, pain resolved with intensified medical therapy, now stable on oral medication. Inability to carry on any physical activity without discomfort - anginal syndrome may be present at rest.

IVb Unstable angina on oral therapy, symptoms improved but angina with minimal provocation.

IVc Symptoms persisting, not manageable on oral therapy, may be hemodynamically unstable, requires coronary care monitoring and parenteral medication.

Atypical Pain: Patient is experiencing atypical symptoms of angina.

OUTCOME DETERMINANTS:

RENAL INSUFFICIENCY: Patient has a history of renal insufficiency diagnosed and/or treated by a physician. Specify if at baseline the patient is on dialysis or the creatinine is >200 umol/l.

CONGESTIVE HEART FAILURE: Patient has a history of congestive heart failure diagnosed and/or treated by a physician. There must be a history of one or more of the following: exertional dyspnea, orthopnea, paroxsymal nocturnal dyspnea (PND), and either cardiac rales, or pulmonary congestion on x-ray. Neither edema nor dyspnea qualifies.

PRIOR INFARCTION: Patient has clear cut history and enzyme documentation, or typical ECG changes.

HYPERTENSION: Patient has a history of hypertension diagnosed and/or treated by a physcian.

HYPERLIPIDEMIA: Patient has a history of hyperlipidemia diagnosed and/or treated by a physician (total cholesterol >5.2mmol/l, or HDL cholesterol <0.8).

DIABETES MELLITUS: Patient has a history of diabetes mellitus diagnosed and/or treated by a physician.

TYPE I: Insulin dependent diabetic - there should be a history of 2 of the following: diabetic ketoacidosis, juvenile onset & insulin use within 2 years of diagnosis (if patient is not obese).

TYPE II (INSULIN): All other diabetics on insulin. Usually secondary onset in overweight patient.

TYPE II (NO INSULIN): All type II diabetics not treated with insulin. May be diet or medication controlled.

SMOKING: A. Patient has smoked cigarettes (cigar or pipes are not included) in the preceding 3 months.

B. Patient has smoked cigarettes (cigar or pipes are not included) in the preceding 3 years.

C. Patient has ever smoked cigarettes (cigar or pipes are not included).

FAMILY HISTORY: First degree relatives (parents, siblings, or children: not grandpartents, uncles , aunts) had diagnosed coronary artery disease [myocardial infarction, angina pectoris or requirement of a revascularization procedure (CABG or PTCA)] before age 60. Unexplained sudden death is considered a manifestation of coronary artery disease. If the patient is adopted or does not know record unknown.

PRIOR LYTIC THERAPY: Patient has received streptokinase, urokinase, APSAC, +/or rtPA within the previous 3 months.

PRIOR PTCA: Any previous PTCA's regardless of location

PRIOR CABG: Any previous CABG's regardless of location

PERIPHERAL VASCULAR DISEASE: Typical symptoms of intermittent claudication or prior corrective surgery.

CO-MORBIDITY FACTORS: The presence of pulmonary, liver and/or GI disease or malignancy if the disease interferes with quality of life and is likely to significantly limit life expectancy.

INDICATIONS:

MYOCARDIAL INFARCTION: (HOSPITAL ADMISSION -> DISCHARGE):

A) Direct PTCA: first line of treatment (within 6 hours).

B) Cardiogenic shock: Systolic BP < 90mmhg for > than 30 minutes not responsive to fluid resucitation alone, felt to be secondary to cardiac dysfunction and associated to signs of hypoperfusion and evidence of pulmonary venous congestion.

C) Persistent or recurrent ischemia <12 hours: symptoms and/or ECG changes thought by the physician to represent myocardial ischemia.

D) Recurrent ischemia > 12 hours: symptoms and/or ECG changes thought by the physician to represent myocardial ischemia.

E) Positive pre-discharge ETT: as diagnosed by a physician as strongly positive. (>2 mm ST depression or fall in BP in stage 1).

F) Non Q infarction:

G) Confirm anatomy: Patient is pain free post infarction. Angiogram to determine further treatment or prognosis.

H) Positive pre discharge ETT: as diagnosed by a physician and is in the strongly positive category.

POST INFARCTION (DISCHARGE -< 6 WEEKS):

A) Angina: mark YES if patient complains of post-infarction angina within 6 weeks of discharge

B) Positive ETT: strongly positive category

C) Asymptomatic - non Q infarction

D) Asymptomatic - Q wave infarction

UNSTABLE ANGINA (with ECG changes):

A) ST depression > 1mm.

B) T wave inversion.

C) Indeterminant ECG

D) No data available

UNSTABLE ANGINA (without ECG changes):

A) Known Coronary Artery Disease

B) No known Coronary Artery Disease.

PRIOR PTCA - (CLINICAL RESTENOSIS) - Clinical restenosis (return of symptoms or objective evidence of ischemia in dilated region) but not qualifying under unstable angina category.

PRIOR CABG - SUSPECT GRAFT PROBLEM - Early return of symptoms or objective evidence of ischemia in bypassed region(s))

STABLE ANGINA:

A) Medical failure: To include; (1) adequate doses of 3 categories of antianginal drugs; (2) patient intolerance to medication; (3) patient unable or unwilling to take medications (includes patients whose job precludes taking medications).

B) Positive ETT - Test called positive for ischemia by physician performing test.

C) Strongly positive ETT - Fall in BP or > 2 mm ST depression in Stage 1 (Bruce).

D) Positive nuclear test:

E) Positive stress echo:

F) Need to know anatomy

SERIOUS ARRYTHMIA: Sustained ventricular tachycardia or prior cardiac arrest/defibrillation/sudden death

SILENT ISCHEMIA:

CONGESTIVE HEART FAILURE: Prior documentation of CHF

PROTOCOL STUDY: Investigation dictated by protocol, not patient's clinical circumstances

ATYPICAL SYMPTOMS - CONFIRM ANATOMY:

EXTENT OF CORONARY ARTERY DISEASE:

This will be scored according to the following index:

1. Disease less than 50%	6. 1 VD (95% Prox LAD)	11. 3 VD (Prox LAD)
2. SVD (50-75%)	7. 2 VD (95% LAD)	12. 3 VD (95% Prox LAD)
3. SVD (95%)	8. 2 VD (95% Prox LAD)	13. LM
4. 2 VD	9. 3 VD	14. Severe LM >75%
5. 2 VD (Both 95%)	10. 3 VD (1 95%)	

PROCEDURE SELECTION FACTORS:

LOWER PROCEDURAL RISK EXPECTED: Although other procedures may be possible, the selected procedure was felt to carry the lowest procedural risk.

MORE COMPLETE REVASCULARIZATION POSSIBLE: The selected procedure will achieve a greater degree of revascularization than other options. In the case of PTCA this may be because of small distal vessel size or distal disease; with CABG this may include total occlusions, or complex diffuse proximal disease.

CULPRIT LESSION KNOWN: Culprit lesion PTCA is expected to stabilize patient and/or render him/her asymptomatic.

PATIENT AN IMA CANDIDATE: Patient is a good candidate for internal mammary artery grafting and better longer term result expected than with PTCA.

PATIENT STAGING POSSIBLE: This applies to PTCA only. Although patient has multivessel disease, the procedure can be staged if necessary to control procedure risk.
SMALL OR DISEASED DISTAL VESSEL: Factors that usually preclude a good surgical result, i.e. factors in favour of PTCA and against CABG.
COMPLEX LESION MORPHOLOGY (USUALLY TYPE "C" LESIONS): Factors that favour CABG over PTCA.
PUBLISHED TRIAL RESULTS: Although other approaches may be possible, it is the interventionalists/surgeons opinion that published trials support this decision.
NUMBER OF DISEASED VESSELS: This should be selected if the number of diseased vessels in the subject case strongly influenced the type of revascularization selected, e.g. PTCA and single vessel disease.
VASCULAR ACCESS PROBLEMS: Problems expected in angioplasty device insertion played a role in selection of CABG.
PREVIOUS SURGERY: Patient has had prior bypass surgery. The risk of repeat surgery favours angioplasty.
PREVIOUS ANGIOPLASTY (RESTENOSIS): Patient is a good candidate for surgery and has had 2 or more previous angioplasties.
AGE: In many cases the younger patients (in anticipation of later disease progression) and older patients (in view of higher procedural risk) are selectively referred for angioplasty. This is not always the case where gains outweight increased risk and where complete revascularization by "arterial revascularization" (IMA or gastroepiploic grafts) is possible in younger patients.
PATIENT PREFERENCE : Patient prefers a specific type of revascularization.
PSYCHOSOCIAL / ECONOMIC: The revascularization procedure is expected to increase the likelihood that the patient can return to a more personally rewarding lifestyle even though there is no other important driving force in the decision.
OTHER: Includes special circumstances where revascularization is felt desirable despite other established reasons for this decision. This may include angiographic but asymptomatic restenosis where PTCA is performed to improve level of coronary flow in anticipation of future need in young people or in those with rapidly progressive disease.

PARSONNET SCORE: (Parsonnet V, Dean D, Bernstein AD: A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation* 1989;79(suppl I):I-3 - I-12.) The surgical groups in the Province are developing a modified risk assessment index that may be used instead.

PROCEDURE DATA:

PTCA: The segments which were dilated will be documented according to the *Heartware* program.
CABG: The vessels grafted and type of graft inserted will be documented. IMA=internal mammary artery, SVG = saphenous vein graft, GE= gastroepiploic.

EQUIPMENT USED (PTCA): Intended to track newer technology use (a) Perfusion balloon; (b) DCA, directional atherectomy; (c) other atherectomy, ie. rotational; (d) Stent; (e) other.

COMPLETE REVASCULARIZATION: Confirm with interventionalist/surgeon that there are no vessels > 1.5 mm diameter left with lesion >70% in proximal or mid portion of main arterial trunk of LAD or dominant RCA or LCX.

ENDARTERECTOMY NEEDED: If endarterectomy done during surgery the vessels will be listed.

Form 3 (PTCA)
DATE OF ANGIOPLASTY: ___ ___ ___ (d/m/y) CINE NUMBER: _____
INTERVENTIONALIST _____
Work Status: _____ (1. Full Time 2. Part Time 3. Unemployed 4. Sick Leave 5. Retired 6. Homemaker) Quality of Life Index (1 - 10) _____
CCS CLASS 0_____ I_____ II_____ III_____ Iva_____ Ivb_____ Ivc_____
ATYPICAL _____
PROCEDURE SCHEDULING DIRECT _____ STAGGED _____ PLANNED _____ PRIORITY EMERGENCY _____ URGENT-IN _____ URGENT-OUT _____ ELECTIVE _____

INDICATION (check ONE)	Y	N	INDICATION (con't)	Y	N	INDICATION (con't)	Y	N
Recurrent Pain/Abrupt Closure Post-PTCA			Asymptomatic-Qwave Inf.			Positive Non Invasive Test		
Myocardial Infarction (In hospital)			Unstable Angina Wth ECG chgs			-Need to know anatomy		
Direct PTCA Candidate			ST depression >1mm			Serious Arryth/Sudden Death		
Cardiogenic Shock			-T wave inversion			Evidence for ischemia		
Recurrent Ischemia (< 12 hours)			-Indeterminant ECG			Other		
Recurrent Ischemia (> 12 hours)			-No data available			Silent Ischemia		
Positive Pre-Discharge Exercise Test			U/A Without ECG changes			LV Dysfunction		
Asymptomatic - Critical Anatomy			-Known CAD			Q-wave Infarction		

INDICATION (check ONE)	Y	N	INDICATION (con't)	Y	N	INDICATION (con't)	Y	N
Post Infarction (Discharge to 6 weeks)			No Known CAD			Inferior/Posterior		
- Angina			Prior PTCA-Clinical Restenosis			Anterioe/Lateral		
-Positive Exercise Test			Prior CABG			LBBB		
Asymptomatic -NON Q wave Infarction			Stable Angina Medical Failure			Uninterpretable ECG		

PROCEDURE SELECTION FACTORS OUTCOME DETERMINANTS-1.

FACTOR	Y	N
High Surgical Risk		
Lesion more suitable to PTCA		
Single Vessel Disease		
Restenosis Lesion		
Lesion or clinical instability		
Medical treatment failure		
Suitable - culprit lesion approach		
Age extremess		
Published Clinical trials		
Occupation Consider.		
Psychosocial Consid.		
Patient Preference		

ITEM	?	Y	N
Renal Insufficiency			
- Dialysis			
- Creatinine > 200 umol/L			
Congestive Heart Failure			
Prior Infarction			
Hypertension			
Hyperlipidemia			
Diabetes Mellitus			
Type I			
Type II (Insulin)			
- Type II (No Insulin)			
Peripheral Vascular Disease			

PROCEDURAL OUTCOMES (con't)

ITEM	Y	N
Complications-NONE		
Complete Revascularization achieved		
- NO by intention		
- NO staging planned /eval		
- NO due to PTCA failure		
Death		
MI - Non Q Wave		
MI Inferior/Posterior		
Anterior/Lateral		
Emergency CABG		
Abrupt Closure		
Angiographic Failure		

OUTCOME DETERMINANTS -2.

ITEM	?	Y	N
Cerebrovascular Disease			
SMOKING- Ever			
In Last Threee Months			
In Last Three Years			
Family History			
Prior Lytic Therapy			
Prior PTCA			
Prior CABG			
Co-morbidity Factors			
- Pulmonary			
- Liver/GI			
- Malignancy			

PROCEDURE DATA

Guiding Caths	#	Directional Atherectomy	#	IVUS	#	Balloons	#	Rotational Atherectomy	#
Perfusion Balloons	#	Stents	#	Other	#	Amount of Dye		CC's	
Ejection Fraction (check one or write %)				< 30%		30-50%		>50%	
Type of Dye (check one)				Nonionic		Ionic		Lowionic	

Enhancement of Secondary Prevention in Heart Disease

Questionnaire

Table of Contents

ESP Participant Questionnaire

DEMOG
Nurse ID# ______
MRNO = FHH: ______

☐ Inpatient ☐ Outpatient
Date: ______ yy/mm/dd

PATKEY ______
ENCNO 1
ENCDT ______
VISITYPE 1
CODERNUM ______
CLERKNUM ______
NURSE ______
PATSTAT ______
MRNO=FH ______

I. Demographics

1. Lastname ______ Initial ___ Firstname ______
   Address ______
   City ______ Province ___ Postal Code ______

   Home Phone ______ Work Phone ______ Best time to call ______
2. Gender: ☐ Female ☐ Male 3. Date of Birth(yy/mm/dd): ______ Month ____
4. Marital Status: ☐ Never Married (single) ☐ Married ☐ Separated ☐ Widowed ☐ Divorced ☐ Common Law
5. Number of Years of Formal Education: ______
6. Ethnic Origin: ☐ White ☐ Hispanic ☐ Black ☐ Asian or Pacific Islander ☐ East Indian ☐ North American Native ☐ Other (specify): ______
7. Smoking Hx: Has the patient ever smoked? ☐ No, never ☐ Yes, in the past ☐ Yes, presently
   How many years? ______
8. Alberta Health Care # (ULI): ______
9. Blue Cross #: ______

STATUS
10. Other Insurance Company: ______ Insurance #: ______
    Status. ☐ Usual Care ☐ Enhanced Care ☐ Baseline ☐ Refusal ☐ Ineligible
12. Primary Cardiologist: ______ Other Cardiologist: ______
13. Contamination? ☐ No ☐ Yes Date: ______ yy/mm/dd
14. Emergency Contact: ______ Relationship: ______
    Phone #: ______
15. Family Physician
    First Name: ______ Last Name: ______
    Address: ______
    City: ______ Province: ______ Postal Code: ______
    Phone #: ______ Fax #: ______ ID: ______
16. Rural Patient's Internist:
    First Name: ______ Last Name: ______
    Address: ______
    City: ______ Province: ______ Postal Code: ______
    Phone #: ______ Fax #: ______ ID: ______

Demographic Note: ______

______

ADDRESS ______
CITY ______
PROV ______
PCODE ______
PHONE ______
DAYPHNE ______
CALLTIME ______
SEX ______
BIRTHDAY ______
B_DAY ______
MARITAL ______
EDLEVEL ______
ETHORIG ______
SMOKHX ______
SMOKYRS ______
ULINUM ______
BLUEX ______
NAMEINS ______
OTHINSNO ______
STATUS ______
INELREA ______
FCARDIOL ______
OTHCARDIC ______
CONTCAR ______
CONTDT ______
CONTACT ______
CONRELAT ______
CONPHONE ______
FAMDOC ______
FDOCAD ______
FDOCCITY ______
FDOCPROV ______
FDOCPC ______
FDOCPHON ______
FDOCFAX ______
FDOCID ______
INTERNAM ______
INTADD ______
INTCITY ______
INTPROV ______
INTPC ______
INTPHON ______
INTFAX ______
INTID ______
DEMCOL ______

II. Pharmacy Information

PHARMAC

1. Pharmacy:_____ ID:_____ PHARMACY_____ PHARMID_____
   Status:_____ PHARSTAT_____
   Address:_____ PHARMADD_____
   City:_____ Province:___ Postal Code:_____ PHARCITY_____
   Phone #:_____ Fax #:_____ PHARPROV_____ PHARPC_____ PHARPHON_____ PHARFAX_____

	No	Yes	
2. Patient allergy history:	☐	☐	ALLERGY_____

If "Yes", please list: 1._____ ALLERG1_____
2._____
3._____
4._____
5._____

III. Participant Enhanced Arm

ENHANCE

Compliance Aids

	No	Yes		No	Yes	
Received a Wallet Card	☐	☐	Received Teaching Sheets	☐	☐	EDWALLET____ EDTEACHS_____
Received Medication Schedule	☐	☐	Received one-on-one training	☐	☐	EDMEDSCH_____
Attended Class	☐	☐	Lipid Clinic	☐	☐	EDTRAIN_____
Cardiac Rehabilitation	☐	☐				EDCLASS_____
						EDLIPIDC_____
						CARDREH_____

Comments:_____ EDCOMM_____

Diagnostic Testing

	No	Yes	
Waiting for Catheterization	☐	☐	WCATHERT
Waiting for CABG	☐	☐	WCABG_____
Waiting for PLASTY	☐	☐	WPLASTY_____

IV. Past Cardiac History

PASTCHX

Cardiovascular History ☐ No ☐ Yes HXMEDK_____
If No, go to Past Diagnostic Tests.

	No	Yes			HXHBP_____
1. Hypertension	☐	☐			HXCAD_____
2. Coronary artery disease	☐	☐			HXANGINA_____
3. Angina	☐	☐			HXMI_____
4. Myocardial infarct	☐	☐			HXLVD_____
5. Left vent. dysfunction	☐		☐ Asymptomatic	☐ Symptomatic	
					PETIOLOG_____
Etiology	☐	☐			
					VALVMR_____

Valvular	No	Yes		No	Yes	
Mitral regurgitation	☐	☐	Tricuspid stenosis:	☐	☐	VALVMS_____
Mitral stenosis	☐	☐	Aortic regurgitation:	☐	☐	VALVTRR_____
Tricuspid regurgitation	☐	☐	Aortic stenosis:	☐	☐	VALVTRS_____
						VALVAOR_____
Other(specify)_____						VALVAOS_____
						HXVALVOT_____

Other Past Cardiac History				
6. Atrial fibrillation	☐ No ☐ Yes	☐ Chronic	☐ Recurrent	☐ Acute
7. Hyperlipidemia	☐ No ☐ Yes			
8. Other (specify)_____				

OTPCHX_____
HYARTFIB_____
HYPLIPID_____
HXOTHER_____

V. Past Diagnostic Tests

PASTDXT

1. Lipid Screen ☐ No ☐ Yes ☐ Unknown Date:_____ yy/mm/dd — PLIPID_____ PLIPIDT_____

Most Recent Lipid Screen	Results	Normal Value	
HDL	_____	Male, 0.9-1.87 Female, 1.01-2.49	PHDL_____
HDL/total cholesterol ratio	_____		PHDLTOT_____
LDL	_____	<3	PLDL_____
Cholesterol	_____	<5	PCHOLES_____
Fasting triglycerides	_____	<2	PFAST_____

2. Most Recent Coronary Angiogram ☐ No ☐ Yes ☐ Unknown Date:_____ yy/mm/dd — PANGIO_____ PANGIODT_____
   Ejection Fraction: _____% ☐ Not calculated — PANGEJEC_____
   Coronary Artery Disease ☐ No ☐ Yes — PCAD_____
   Left Ventricle Dysfunction ☐ Normal ☐ Mild ☐ Moderate ☐ Severe — PLVD_____

3. ECHO ☐ No ☐ Yes ☐ Unknown Date:_____ yy/mm/dd — PECHO_____ PECHODT_____
   LVD: ☐ Normal ☐ Mild/Moderate ☐ Moderate ☐ Moderate/Severe ☐ Severe ☐ Unknown — PECHOLVD_____

	Normal	Mild	Moderate	Severe	Unknown	
Aortic Stenosis:	☐	☐	☐	☐	☐	PECHOAS_____
Aortic Regurgitation:	☐	☐	☐	☐	☐	PECHOAR_____
Mitral Stenosis:	☐	☐	☐	☐	☐	PECHOMS_____
Mitral Regurgitation:	☐	☐	☐	☐	☐	PECHOMR_____
Tricuspid Stenosis:	☐	☐	☐	☐	☐	PECHOTS_____
Tricuspid Regurgitation:	☐	☐	☐	☐	☐	PECHOTR_____

Treadmill ☐ No ☐ Yes ☐ Unknown Date:_____ yy/mm/dd — PTREAD_____ PTREADT_____
☐ Negative ☐ Positive ☐ Suggestive — PTREADRE_____

5. MUGA ☐ No ☐ Yes ☐ Unknown Date:_____ yy/mm/dd — PMUGA_____ PMUGADT_____
   Ejection Fraction: _____% ☐ Not calculated — PMUGAEF_____
   LVD: ☐ Normal ☐ Mild ☐ Mild/Moderate ☐ Moderate ☐ Moderate/Severe ☐ Severe — PMUGLVD_____

6. Perfusion Scan ☐ No ☐ Yes ☐ Unknown Dipy: ☐ No ☐ Yes Date:_____ yy/mm/dd — PPSCAN_____ PDIPY_____ PSCANDT_____
   ☐ Normal ☐ Reversible ☐ Irreversible ☐ Not Dx — PSRESULT_____

VI. Prior Interventions

1. History of prior interventions ☐ No ☐ Yes ☐ Unknown — PINTERV_____

	No	Yes	Date yy/mm/dd		No	Yes	Date yy/mm/dd
PTCA:	☐	☐	_____	Stent:	☐	☐	_____
Pacemaker:	☐	☐	_____	Valve Repair:	☐	☐	_____
CABG:	☐	☐	_____	Cardioversion:	☐	☐	_____

PPTCA_____ PPTCADT_____ PPACEMAK_____ PPACDT_____ PCABG_____ PCABGDT_____ PSTENT_____ PSTENTDT_____ PVALVER_____ PVALVDT_____ PCARD_____ PCARDT_____

VII. Past Medical History

PASTMHX

n-Cardiac History	☐ No	☐ Yes	☐ Unknown	PCARDHX_____
Neurological:	☐ No	☐ TIA	☐ Stroke	PNEURO_____
2. Respiratory:	☐ No	☐ Asthma	☐ COPD	PRESP_____
3. Gastrointestinal:				
Ulcer:	☐ No	☐ Active	☐ Resolved	PCASTULC_____
Other:_____				
4. Urological:				
Renal Insufficiency:	☐ No	☐ Active	☐ Resolved	PURORFIN_____
Renal Artery Stenosis:	☐ No	☐ Active	☐ Resolved	PURORARTS_____
5. Endocrinology:				
Diabetes:	☐ No	☐ Yes		PENDOC_____
Other:_____				
6. Autoimmune:				
Arthritis:	☐ No	☐ Active	☐ Resolved	PARTH_____
Other:_____				
7. Hematology:				
Bleeding Disorder:	☐ No	☐ Active	☐ Resolved	PHEMAT_____
Other:_____				
Cancer:				
Cancer Status:	☐ No	☐ Yes, Type:_____		PCANCERT_____
	☐ Active	☐ Resolved	☐ Metastatic	PCANTYPE_____
8. Other: 1._____				OTHMHX1_____
2._____				
3._____				
4._____				
5._____				

Any PMHX Comments:

_____

_____

_____

_____

_____

VIII. Course in Hospital

COURSE

1) Other Hospital Admission Date (if different from FHH):_____ yy/mm/dd — HOSETDT_____

b) Transferred from another hospital: — HOSPTRAN_____
Hospital name_____

2. Admission to FHH Date:_____ yy/mm/dd — HTRASPDT_____

3. Patient Admission Status:
☐ Cardiac, if yes then proceed ☐ Non-Cardiac, if yes go to next page ☐ Adverse drug reaction — HOSTATUS_____

4. Angina ☐ No ☐ Stable ☐ Unstable — HOSANGIN_____
5. Arrhythmia ☐ No ☐ Yes — HARRH_____
Atrial Fibrillation ☐ New Onset ☐ Post-Operation ☐ Recurrent ☐ Chronic — HOSATFIB_____
Other_____ — OTHARRH_____

6. MI	☐ No	☐ Suspect MI	☐ Yes	HOSMI_____
	No Q Wave	Q Wave	Non-Q Wave	
Anterior	☐	☐	☐	MIANT_____
Inferior	☐	☐	☐	MIINF_____
Posterior	☐	☐	☐	MIPOS_____
Septal	☐	☐	☐	MISEP_____
Right Vent.	☐	☐		MIRV_____
Other:_____				MIOTH_____

7. CHF ☐ No ☐ Yes — HOSCHF
Etiology ☐ Arrhythmia ☐ Valve Disease — HCHFETIO_____
Other:_____ — HCHFOT_____
CHF status: ☐ Resolved ☐ Ongoing — HOSCHFS_____

LV Dysfunction: ☐ No ☐ Asymptomatic ☐ Symptomatic — HOSLVD_____

	No	Yes	
9. Chest Pain NYD	☐	☐	HOSCP_____
Hypertension	☐	☐	HOSPBP_____
CVA	☐	☐	HOSPCVA_____
Endocarditis	☐	☐	HOSPENDO_____
10. Waiting for Catheterization:	☐	☐	HCATHERT
Waiting for CABG:	☐	☐	HCABG_____
Waiting for PLASTY:	☐	☐	HPLASTY_____
Other(specify)_____			HOSPOTH_____
			HINTER_____
			CPTCA_____

IX. Interventions in Hospital

CPTCADT_____

INHOSP

CSTENT_____

1. Interventions while in hospital: ☐ No ☐ Yes

	No	Yes	Date yy/mm/dd		No	Yes	Date yy/mm/dd
PTCA:	☐	☐	_____	Stent:	☐	☐	_____
Pacemaker:	☐	☐	_____	Valve Repair:	☐	☐	_____
CABG:	☐	☐	_____	Cardioversion:	☐	☐	_____

CSTENTDT_____
CPACEMAK_____
CPACDT_____
CVALVER_____
CCVALVDT_____
CCABG_____
CCABGDT_____
CCARD_____
CCARDT_____

X. Non-Cardiac Events

NONCHOS

Non Cardiac Events: ☐ No ☐ Yes — NONCHOSP____

Neurological: ☐ No ☐ TIA ☐ Stroke — CNEURO____

Comments:_____

2. Respiratory: ☐ No ☐ Asthma ☐ COPD — CRESP____

Comments:_____ — CRESPCO____

3. Gastrointestinal:

Ulcer: ☐ No ☐ Active ☐ Resolved — CCASTULC____

Other:_____

Comments:_____

4. Urological:

Renal Insufficiency: ☐ No ☐ Active ☐ Resolved — CURORFIN____

Renal Artery Stenosis: ☐ No ☐ Active ☐ Resolved — CUROARTS____

Comments:_____

5. Endocrinology:

Diabetes: ☐ No ☐ Yes — CENDOC____

Other:_____

Comments:_____

6. Autoimmune:

Arthritis: ☐ No ☐ Active ☐ Resolved — CARTH____

Other:_____

Comments:_____

7. Hematology:

Bleeding Disorder: ☐ No ☐ Active ☐ Resolved — CHEMAT____

Other:_____

Comments:_____

8. Cancer:

Cancer Status: ☐ No ☐ Yes, Type:_____ — CANCERT____

☐ Active ☐ Resolved ☐ Metastatic ☐ Terminal — CANTYPE____

Comments:_____ — NCECOM____

9. Other:_____

XI. Admission for Adverse Drug Reaction

ADVRX

1. Adverse Drug Reactions: ☐ No ☐ Yes — ADRHOSP____

If "Yes", please list: 1._____ — ADR1____

2._____

3._____

4._____

XII. Current Diagnostic Test

CTEST

1. Lipid Screen ☐ No ☐ Yes Date:_____ yy/mm/dd — CLIPID_____ CLIPIDT_____

pid Screen	Results	Normal Value	
HDL	_____	Male, 0.9-1.87 Female, 1.01-2.49	CHDL_____
HDL/Total Cholesterol Ratio	_____		CHDLTOT_____
LDL	_____	<3	CLDL_____
Cholesterol	_____	<4.5	CCHOLES_____
Fasting Triglycerides	_____	<2	CFAST_____

Comments_____ CLIPIDC_____

2. Coronary Angiography ☐ No ☐ Yes Date:_____ yy/mm/dd — CANGIO_____ CANGIODT_____

Ejection Fraction: _____% ☐ Not calculated — CEJECT_____
Coronary Artery Disease ☐ No ☐ Yes — CCAD_____
LVD ☐ Normal ☐ Mild ☐ Moderate ☐ Severe — CLVD_____
Comments_____ CANGC_____

3. ECHO ☐ No ☐ Yes Date:_____ yy/mm/dd — CECHO_____ CECHODT_____

LVD: ☐ Normal ☐ Mild/Moderate ☐ Moderate ☐ Moderate/Severe ☐ Severe — CECHOLVD_____

	Normal	Mild	Moderate	Severe	
Aortic Stenosis:	☐	☐	☐	☐	CECHOAS_____
Aortic Regurgitation:	☐	☐	☐	☐	CECHOAR_____
Mitral Stenosis:	☐	☐	☐	☐	CECHOMS_____
Mitral Regurgitation:	☐	☐	☐	☐	CECHOMR_____
Tricuspid Stenosis:	☐	☐	☐	☐	CECHOTS_____
Tricuspic Regurgitation:	☐	☐	☐	☐	CECHOTR_____

Comments_____ CECHOC_____

4. Treadmill ☐ No ☐ Yes Date:_____ yy/mm/dd — CTREAD_____ CTREADDT_____

☐ Negative ☐ Positive ☐ Suggestive — CTREADRE_____
Comments_____ CTREC_____

5. MUGA ☐ No ☐ Yes Date:_____ — CMUGA_____ CMUGADT_____

Ejection Fraction _____% Not calculated ☐ — CMUGAEF_____
LVD: ☐ Normal ☐ Mild ☐ Mild/Moderate ☐ Moderate ☐ Moderate/Severe ☐ Severe — CMUGLVD_____
Comments:_____ CMUGAC_____

6. Perfussion Scan ☐ No ☐ Yes Dipy: ☐ No ☐ Yes Date:_____ yy/mm/dd — CPSCAN_____ CDIPY_____

☐ Normal ☐ Reversible ☐ Irreversible ☐ Not Dx
Comments:_____

7. ECG ☐ No, go to 8 ☐ Yes Date:_____ — CSCANDT_____ CSRESULT_____

☐ Normal ☐ MI ☐ Unstable Angina ☐ Atrial Fibrillation ☐ Non-Diagnostic — CPSC_____
Comments:_____ CECG_____

8. Enzyme ☐ No ☐ Yes Date:_____ yy/mm/dd — CECGDT_____ CECGR_____ CECGC_____

Peak CK:_____
CKMB:_____
Ratio MBI:_____
Comments:_____ CENZ_____ CENZDT_____ CPEAK_____ CCKMB_____ CENZRAT_____ CENZC_____

XIII. Discharge Diagnosis

DISCDX

Discharge Date: _____ yy/mm/dd

Medical Records: ☐ Complete ☐ Incomplete

Filled Out By: _____ Entered By _____

DISCHDT_____
MECREC_____
CODERNUM_____
CLERKNUM_____

1. Discharge
   ☐ Home ☐ Rehabilitation ☐ Long Term Care ☐ Other Institution ☐ Died in hospital

DISCHTO_____
FHLOS_____

2. Discharge Diagnosis

Ischemia:	☐ No	☐ Presumed	☐ Proven	DISCHDXI_____
M.I.:	☐ No	☐ Presumed	☐ Proven	DISCXMI_____
LV Dysfunction:	☐ No	☐ Presumed	☐ Proven	DISCDXLV_____
	☐ Asymptomatic	☐ Symptomatic		DISCDXLD_____
Atrial Fibrillation: ☐ No	☐ Acute	☐ Chronic	☐ Converted ☐ Recurrent	DISCDXAF_____
Valve Disease:	☐ No	☐ Yes		DISCDXVD_____
Hypertension:	☐ No	☐ Yes		DISCDXBP_____
Hyperlipidemia:	☐ No	☐ Yes		DISCDXLI_____

3. Lab

Need to contact physician for lipid results:	☐ No	☐ Yes	DOCLIPID_____
Patient sent home with lipid requisition:	☐ No	☐ Yes	LIPIDREQ_____

4. Follow-up Status ☐ Active ☐ Inactive, go to reason

FUSTAT_____

Reasons

☐ Lost to Follow Up	☐ Terminal Illness
☐ Withdrawn	☐ 2° Therapy not required
☐ Mental Illness	☐ Deceased

WITHREA_____

DISCDXOT_____

5. Any discharge comments _____

ACE1_____
ACERX_____

Study Medications:

	Don't Know	2°Ind	Waiting for Test	No 2° Ind	R	otR	Ci	Cue
ACE-I	☐	☐	☐	☐	☐		☐	☐
B-Blocker	☐	☐	☐	☐	☐		☐	☐
ASA	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	☐	☐	☐	☐	☐		☐	☐
Warfarin	☐	☐	☐	☐	☐		☐	☐

ACECI_____
ACECUE_____
BBLO1_____
BBLORX_____
BBLOCI_____
BBLOCUE_____

ASA1_____
ASARX_____
ASACI_____
ASACUE_____
LLA1_____
LLARX_____
LLACI_____
LLACUE_____

WARF1_____
WARFRX_____
WARFCI_____
WARFCUE_____

XIV. Medication Summary

[redacted]

MEDSUM
'ory of Non-Compliance: ☐ No ☐ Yes   Drug Allergies: ☐ No ☐ Yes
. es", please list: 1. ____
2. ____
3. ____
4. ____
5. ____

RTYPE	DRUG NAME	CARDIAC	DOSE	UNITS	ROUTE	FREQ	START DATE	STOP DATE

XV. Follow Up

FOLLOWU

Follow Up Date: _____ (yy/mm/dd) Follow Up Type: _____ FUDATE_____ FUPTYPE_____

.. Physician visit since last questionnaire. ☐ No ☐ Yes DOCVIS_____

Family Physician Visits: _____ VISFDOC_____
Cardiologist Visits: _____ VISCARD_____
Rural Internist Visits: _____ VISRURI_____
Other: _____ VISOTH_____

FUHOS_____

2. Hospital admissions since last questionnaire or last discharge from Foothills? ☐ No ☐ Yes

		M.R. Contacted? No	Yes
Hospital #1: _____	Discharge Date: _____	☐	☐
Hospital #2: _____	Discharge Date: _____	☐	☐
Hospital #3: _____	Discharge Date: _____	☐	☐
Hospital #4: _____	Discharge Date: _____	☐	☐
Hospital #5: _____	Discharge Date: _____	☐	☐
Hospital #6 _____	Discharge Date: _____	☐	☐

HOSAD1_____ HOSAD1DT_____ HMRCH1_____ HOSAD2_____ HOSAD2DT_____ HMRCH2_____ HOSAD3_____ HOSAD3DT_____ HMRCH3_____

3. Emergency visits since last discharge or last questionnaire? ☐ No ☐ Yes

		M.R. Contacted? No	Yes
Hospital #1: _____	Visit date: _____	☐	☐
Hospital #2: _____	Visit date: _____	☐	☐
Hospital #3: _____	Visit date: _____	☐	☐

HOSAD4_____ HOSAD4DT_____ HMRCH4_____ HOSAD5_____ HOSAD5DT_____ HMRCH5_____

4. Have you had your lipid levels drawn?
☐ No ☐ Yes ☐ To be Drawn in Near Future ☐ Not Indicated

HOSAD6_____ HOSAD6DT_____ HMRCH6_____

FUEM_____

5. List medications patient or physician has stopped or changed.
Note. If a patient has stopped his/her medication, do not put a stop date in the medication table. Patient is non-compliant.

EMER1_____ EMER1DT_____ EMRCH1_____

Nurse's Comments: 1. _____
2. _____
3. _____
4. _____

EMER2_____ EMER2DT_____ EMRCH2_____ EMER3_____ EMER3DT_____ EMRCH3_____

6. List Forget Medications, Forget Frequency and Reason.

Nurses Comments: 1. _____
2. _____
3. _____
4. _____

LIPIDCH_____ FCOMM1_____

XVI. Medication Changes

EXCHANG

ACE-I: ☐ No R ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____ yy/mm/dd
Stopped By: ☐ Patient ☐ Doctor ☐ Other
Number of Times not Taken(days/week): _____
Number of Doses Missed per Week:_____

AFUTXST_____
ACDTYPE_____
ARX_____
AFUTXSDT_____
AFUTXSBY_____
AFUTXDWK_____
AFUTMIWK_____

Reasons:	No	Yes	
Medication Was Too Expensive	☐	☐	AREAEXP_____
Patient Felt Better and stopped	☐	☐	AREAFBET_____
Experienced Unpleasant Side Effects	☐	☐	AREASE_____
Prescription Finished and not Refilled	☐	☐	AREAPF_____
Misunderstanding	☐	☐	AREAMI_____
Forgot	☐	☐	AREAFORG_____
Other:_____			AOTH_____

Intervention Action Taken:	No	Yes	
GP Notified	☐	☐	ACTGP_____
Cardiologist/Internist Notified	☐	☐	ACTCARD_____
Community Pharmacist Notified	☐	☐	ACTPHAR_____
Staff Pharmacist Notified	☐	☐	ACTSTPH_____
Other Notified _____	☐	☐	ACTOTH_____
Further Education Via Phone	☐	☐	ACTEDPH_____
Dosette	☐	☐	ACTDOSET_____
Med Schedule Altered	☐	☐	ACTMSCH_____
Dose Change Suggested	☐	☐	ACTDC_____
Medication Change Suggested	☐	☐	ACTMC_____
Comments: _____			ACTCOMM_____

BFUTXST_____
BCDTYPE_____
BRX_____
BFUTXDT_____
BFUTXBY_____
BFUTDWK_____
BFUTMIWK_____

ß-Blocker: ☐ No R ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____ yy/mm/dd
Stopped By: ☐ Patient ☐ Doctor ☐ Other
Number of Times not Taken(days/week): _____
Number of Doses Missed per Week:_____

Reasons	No	Yes	
Medication Was Too Expensive	☐	☐	BREAEXP_____
Patient Felt Better and stopped	☐	☐	BREAFBET_____
Experienced Unpleasant Side Effects	☐	☐	BREASE_____
Prescription Finished and not Refilled	☐	☐	BREAPF_____
Misunderstanding	☐	☐	BREAMI_____
Forgot	☐	☐	BREAFORG_____
Other:_____			BOTH_____

Intervention Action Taken:	No	Yes	
GP Notified	☐	☐	BCTGP_____
Cardiologist/Internist Notified	☐	☐	BCTCARD_____
Community Pharmacist Notified	☐	☐	BCTPHAR_____
Staff Pharmacist Notified	☐	☐	BCTSTPH_____
Other Notified _____	☐	☐	BCTOTH_____
Further Education Via Phone	☐	☐	BCTEDPH_____
Dosette	☐	☐	BCTDOSET_____
Med Schedule Altered	☐	☐	BCTMSCH_____
Dose Change Suggested	☐	☐	BCTDC_____
Medication Change Suggested	☐	☐	BEDMC_____
Comments: _____			BCOMM_____

RXCHANG cont.

ASA: ☐ No R ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____
Stopped By: ☐ Patient ☐ Doctor ☐ Other yy/mm/dd
Number of Times not Taken(days/week):_____
Number of Doses Missed per Week:_____

Reasons:	No	Yes
Medication Was Too Expensive	☐	☐
Patient Felt Better and stopped	☐	☐
Experienced Unpleasant Side Effects	☐	☐
Prescription Finished and not Refilled	☐	☐
Misunderstanding	☐	☐
Forgot	☐	☐
Other:_____		

Intervention Action Taken:	No	Yes
GP Notified	☐	☐
Cardiologist/Internist Notified	☐	☐
Community Pharmacist Notified	☐	☐
Staff Pharmacist Notified	☐	☐
Other Notified _____	☐	☐
Further Education Via Phone	☐	☐
Dosette	☐	☐
Med Schedule Altered	☐	☐
Dose Change Suggested	☐	☐
Medication Change Suggested	☐	☐

Comments:_____

ASAFUTXS_____
ASACDTX_____
ASARX_NC_____
ASAFUTDT_____
ASAFUTBY_____
ASAFUTWK_____
ASAFUMWK_____

ASREAEXP_____
ASREAFB_____
ASREASE_____
ASREAPF_____
ASREAMI_____
ASREAFOR_____
ASAOTH_____

AACTGP_____
AACTCARD_____
AACTPHAR_____
AACTSTPH_____
AACTOTH_____
AACTEDPH_____
AACTDOSE_____
AACTMSCH_____
AACTDC_____
AACTMC_____
ASACOMM_____

'' A ☐ No R ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____
Stopped By: ☐ Patient ☐ Doctor ☐ Other yy/mm/dd
Number of Times not Taken(days/week):_____
Number of Doses Missed per Week:_____

Reasons:	No	Yes
Medication Was Too Expensive	☐	☐
Patient Felt Better and stopped	☐	☐
Experienced Unpleasant Side Effects	☐	☐
Prescription Finished and not Refilled	☐	☐
Misunderstanding	☐	☐
Forgot	☐	☐
Other:_____		

Intervention Action Taken:	No	Yes
GP Notified	☐	☐
Cardiologist/Internist Notified	☐	☐
Community Pharmacist Notified	☐	☐
Staff Pharmacist Notified	☐	☐
Other Notified _____	☐	☐
Further Education Via Phone	☐	☐
Dosette	☐	☐
Med Schedule Altered	☐	☐
Dose Change Suggested	☐	☐
Medication Change Suggested	☐	☐

mments:_____

LFUTXS_____
LCDTX_____
LRX_____
LFUTDT_____
LFUTBY_____
LFUTWK_____
LFUMWK_____

LSREAEXP_____
LSREAFB_____
LSREASE_____
LSREAPF_____
LSREAMI_____
LSREAFOR_____
LLAOTH_____

LACTGP_____
LACTCAR_____
LACTPHA_____
LACTSTP_____
LACTOTH_____
LACTEDPH_____
LACTDOSE_____
LACTMSCH_____
LACTDC_____
LACTMC_____
LLACOMM_____

EXCHANG cont.

Warfarin: ☐ No R ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____
Stopped By: ☐ Patient ☐ Doctor ☐ Other yy/mm/dd
Number of Times not Taken(days/week):_____
Number of Doses Missed per Week:_____

WFUTXS_____
WCDTX_____
WRX_____
WFUTDT_____
WFUTBY_____
AFUTWK_____
AFUMWK_____

Reasons:	No	Yes	
Medication Was Too Expensive	☐	☐	WSREAEXP_____
Patient Felt Better and stopped	☐	☐	WSREAFB_____
Experienced Unpleasant Side Effects	☐	☐	WSREASE_____
Prescription Finished and not Refilled	☐	☐	WSREAPF_____
Misunderstanding	☐	☐	WSREAMI_____
Forgot	☐	☐	WSREAFOR_____
Other:_____			WAROTH_____

Intervention Action Taken:	No	Yes	
GP Notified	☐	☐	WACTGP_____
Cardiologist/Internist Notified	☐	☐	WACTCAR_____
Community Pharmacist Notified	☐	☐	WACTPHAR_____
Staff Pharmacist Notified	☐	☐	WACTSTPH_____
Other Notified _____	☐	☐	WACTOTH_____
Further Education Via Phone	☐	☐	WACTEDPH_____
Dosette	☐	☐	WACTDOSE_____
Med Schedule Altered	☐	☐	WACTMSCH_____
Dose Change Suggested	☐	☐	WACTDC_____
Medication Change Suggested	☐	☐	WACTMC_____
Comments:_____			WARCOMM_____

Other cardiac drug 1: ☐ No ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____
Stopped By: ☐ Patient ☐ Doctor ☐ Other yy/mm/dd
Number of Times not Taken(days/week):_____
Number of Doses Missed per Week:_____

C1FUTXS_____
C1CDTX_____
C1RX_____
C1FUTDT_____
C1FUTXS_____
C1FUTWK_____
C1FUMWK_____

Reasons:	No	Yes	
Medication Was Too Expensive	☐	☐	C1SREAEX_____
Patient Felt Better and stopped	☐	☐	C1SREAFB_____
Experienced Unpleasant Side Effects	☐	☐	C1SREASE_____
Prescription Finished and not Refilled	☐	☐	C1SREAPF_____
Misunderstanding	☐	☐	C1SREAMI_____
Forgot	☐	☐	C1SREAFO_____
Other:_____			C1OTH_____

Intervention Action Taken:	No	Yes	
GP Notified	☐	☐	C1ACTGP_____
Cardiologist/Internist Notified	☐	☐	C1ACTCAR_____
Community Pharmacist Notified	☐	☐	C1ACTPHA_____
Staff Pharmacist Notified	☐	☐	C1ACTSTP_____
Other Notified _____	☐	☐	C1ACTOTH_____
Further Education Via Phone	☐	☐	C1ACTEDP_____
Dosette	☐	☐	C1ACTDOS_____
Med Schedule Altered	☐	☐	C1ACTMSC_____
Dose Change Suggested	☐	☐	C1ACTDC_____
Medication Change Suggested	☐	☐	C1ACTDMC_____
Comments:_____			C1COMM_____

EXCHANG cont.

Other cardiac drug 2: ☐ No ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____
Stopped By: ☐ Patient ☐ Doctor ☐ Other yy/mm/dd
Number of Times not Taken(days/week): _____
Number of Doses Missed per Week:_____

C2FUTXS_____
C2CDTX_____
C2RX_____
C2FUTDT_____
C2FUTXS_____
C2FUTWK_____
C2FUMWK_____

Reasons:	No	Yes	
Medication Was Too Expensive	☐	☐	C2SREAEX_____
Patient Felt Better and stopped	☐	☐	C2SREAFB_____
Experienced Unpleasant Side Effects	☐	☐	C2SREASE_____
Prescription Finished and not Refilled	☐	☐	C2SREAPF_____
Misunderstanding	☐	☐	C2SREAMI_____
Forgot	☐	☐	C2SREAFO_____
Other:_____			C2OTH_____

Intervention Action Taken:	No	Yes	
GP Notified	☐	☐	C2ACTGP_____
Cardiologist/Internist Notified	☐	☐	C2ACTCAR_____
Community Pharmacist Notified	☐	☐	C2ACTPHA_____
Staff Pharmacist Notified	☐	☐	C2ACTSTP_____
Other Notified _____	☐	☐	C2ACTOTH_____
Further Education Via Phone	☐	☐	C2ACTEDP_____
Dosette	☐	☐	C2ACTDOS_____
Med Schedule Altered	☐	☐	C2ACTMSC_____
Dose Change Suggested	☐	☐	C2ACTDC_____
Medication Change Suggested	☐	☐	C2ACTMC_____
Comments: _____			C2COMM_____

Other cardiac drug 3: ☐ No ☐ Compliance ☐ Non-Compliance
Type: ☐ 1° ☐ 2° Stopped: ☐ No ☐ Yes Date:_____
Stopped By: ☐ Patient ☐ Doctor ☐ Other yy/mm/dd
Number of Times not Taken(days/week): _____
Number of Doses Missed per Week:_____

C3FUTXS_____
C3CDTX_____
C3RX_____
C3FUTDT_____
C3FUTXS_____
C3FUTWK_____
C3FUMWK_____

Reasons:	No	Yes	
Medication Was Too Expensive	☐	☐	C3SREAEX_____
Patient Felt Better and stopped	☐	☐	C3SREAFB_____
Experienced Unpleasant Side Effects	☐	☐	C3SREASE_____
Prescription Finished and not Refilled	☐	☐	C3SREAPF_____
Misunderstanding	☐	☐	C3SREAMI_____
Forgot	☐	☐	C3SREAFO_____
Other:_____			C3OTH_____

Intervention Action Taken:	No	Yes	
GP Notified	☐	☐	C3ACTGP_____
Cardiologist/Internist Notified	☐	☐	C3ACTCAR_____
Community Pharmacist Notified	☐	☐	C3ACTPHA_____
Staff Pharmacist Notified	☐	☐	C3ACTSTP_____
Other Notified _____	☐	☐	C3ACTOTH_____
Further Education Via Phone	☐	☐	C3ACTEDP_____
Dosette	☐	☐	C3ACTDOS_____
Med Schedule Altered	☐	☐	C3ACTMSC_____
Dose Change Suggested	☐	☐	C3ACTDC_____
Medication Change Suggested	☐	☐	C3ACTMC_____
Comments: _____			C3COMM_____

EXCHANG cont.

Study Medications:

	Don't Know	2°ind	Waiting for Test	No 2° ind	R	otR	Ci	Cue
ACE-I	☐	☐	☐	☐	☐		☐	☐
B-Blocker	☐	☐	☐	☐	☐		☐	☐
ASA	☐	☐	☐	☐	☐	☐	☐	☐
A	☐	☐	☐	☐	☐		☐	☐
warfarin	☐	☐	☐	☐	☐		☐	☐

ACE1_____
ACERX_____
ACECI_____
ACECUE_____

BBLO1_____
BBLORX_____
BBLOCI_____
BBLOCUE_____

ASA1_____
ASARX_____
ASACI_____
ASACUE_____

LLA1_____
LLARX_____
LLACI_____
LLACUE_____

WARF1_____
WARFRX_____
WARFCI_____
WARFCUE_____

The Following Questions Only Pertain to Enhanced Care Patients

1. Are you attending a Cardiac Rehab Program
   ☐ No ☐ Yes ☐ Waiting — CARDREH_____

2. Change ESP Study Medication Schedule on Hand?
   ☐ No ☐ Yes — EDMEDSCH_____

3. Still Have Wallet Card?
   ☐ No ☐ Yes — EDWALLET_____

CHAPTER 5: IDENTIFYING PREDICTORS OF ADVERSE EVENTS WITHIN ONE-YEAR FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

1. INTRODUCTION

One of the major contributions of the Framingham Heart Study, a cohort study of 5,209 residents of Framingham to understand the development of cardiovascular disease, was to establish several "risk factors" associated with heart disease [1]. Unlike other chronic diseases, where one risk factor is predominant [for example, smoking in the case of lung cancer], coronary artery disease (CAD) risk appears to be a complex function of personal, behavioral, and physiological patient attributes. In all, 246 risk factors associated with CAD have been identified over the last 40 years [2]. Although this figure may appear remarkable, it is comforting to note that a subset of factors has been acknowledged repeatedly and further research has established causal relationships. Over the last few decades, sophisticated multiple regression modeling techniques have replaced long-standing stratified analyses in examining the effect of each factor within the context of other risk factors.

Treatment of CAD usually involves one or more of the following approaches: medical therapy, percutaneous coronary intervention (PCI) or coronary bypass

surgery. Since its introduction in the late 1970s, PCI has become one of the most popular treatments for CAD. Several prior studies (described in detail in Chapter 2) have reported the results of multivariate analyses to identify risk factors associated with in-hospital adverse events following PCI [3-9]. However, most of these studies were conducted before the introduction of stents in PCI [3-7] and the more recent studies, which include stents, have examined only short-term (30-day) mortality [8-9]. In addition, no prediction model has been developed to address one of the major limitations of PCI: the need for repeat revascularization procedures in the months following the procedure.

The objective of this study was to address this gap in the current literature and to provide population-level data on baseline predictors of adverse events within one-year following PCI in the post-stenting era. Specifically, the aim was to use registry data collected as part of the Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease (APPROACH) study to develop and validate prediction models for three outcomes: 1) mortality within one-year of the index procedure; 2) mortality within 30 days of the procedure; and 3) repeat procedures (i.e. PCI or bypass surgery) within one-year of the procedure.

2. METHODS

Given below is a summary of the steps taken to analyze the data for this study. The following sections describe each step in greater detail.

2.1 SELECTION OF PATIENT POPULATION

2.2 MERGE BETWEEN CARDIAC CATHETERIZATION DATA AND PCI DATA: Merged medical history data collected at the time of PCI with that collected at the time of cardiac catheterization (if the catheterization occurred within 60 days of the PCI procedure) to ensure completeness of data.

2.3 MERGE BETWEEN CLINICAL DATA AND ADMINISTRATIVE DATA TO IMPROVE DATA CAPTURE: Merged clinical data from the APPROACH database with administrative data corresponding to the index PCI to improve completeness of data capture. Restricted the patient population to those patients for whom both APPROACH and administrative data were available.

2.4 DEFINITION OF OUTCOMES OF INTEREST

2.5 DESCRIPTION OF INDEPENDENT (PREDICTOR) VARIABLES: Described coding and issues related to variables considered for inclusion in the study.

2.6 CREATION OF DEVELOPMENT AND VALIDATION DATASETS: Split the dataset into two parts: one for developing the models and the second for validating them.

2.7 STATISTICAL ANALYSES: Conducted statistical analyses which included the following: 1) Kaplan-Meier analyses to document the timing of adverse events; 2) Univariate analyses using chi-square tests for categorical variables and logistic regression analyses for continuous and dichotomous variables; and 3) Multivariable analyses using backward step-wise logistic regression. Examined models' discriminatory power and goodness of fit using the c-index and the Hosmer-Lemeshow goodness of fit test.

2.1 SELECTION OF PATIENT POPULATION

Alberta residents undergoing PCI between July 1, 1995 and December 31, 1997 and enrolled in the APPROACH study were included in the present study. The APPROACH study has been described previously [10]. A description is also provided in Chapter 4. Briefly, the APPROACH initiative is an ongoing study of all Alberta residents undergoing cardiac catheterization for CAD since 1994. This population-based multi-year inception cohort database contains detailed information on socio-demographic characteristics, presence or absence of comorbidities, disease-specific variables, coronary angiography results, post-catheterization referral decisions, records of actual revascularization, and data on outcomes post-revascularization, including survival and quality of life. Patients are followed over time for the evaluation of outcomes such as mortality,

subsequent revascularization, cardiac-related quality of life (assessed yearly after catheterization), and long-term costs of care.

Cardiac catheterization and PCI are performed at three sites: the University of Alberta Hospitals (UAH) and the Royal Alexandra Hospital (RAH) in Edmonton and the Foothills Hospital (FH) in Calgary. Before March 31, 1996, patients could have undergone cardiac procedures at the Holy Cross Hospital (HCH) in Calgary. The APPROACH database captures data on all cardiac catheterizations and PCIs in the province. Data collection is ongoing and about 7,000 patients are enrolled in the database each year.

2.2 Merge between Cardiac Catheterization and PCI data

Clinical data in APPROACH are collected at various stages: when the patient undergoes initial cardiac catheterization and at each subsequent cardiac procedure. In the event of the cardiac catheterization and PCI being in quick succession, clinical data, especially those pertaining to comorbidities, are likely to be recorded at the catheterization stage and ignored (as there is no change in status) at the PCI stage. In order to obtain the most complete clinical data, catheterization and PCI data on comorbidities were merged if the catheterization had occurred less than or equal to 60 days prior to the PCI. If the catheterization had occurred more than 60 days previously, only PCI data were used.

2.3 MERGING CLINICAL AND ADMINISTRATIVE DATA TO IMPROVE DATA CAPTURE

One of the problems encountered as part of an on-going clinical registry system, as opposed to a short-term protocol driven clinical trial, is missing data. Although there has been a temporal improvement in the level of data capture in the APPROACH project, the frequency of missing data has varied across data collection sites. As the 'non-random' nature of the missing data violates the primary assumption for imputation, investigators on the APPROACH project devised an alternative method: enhancing the clinical data in APPROACH with administrative data. The model using the 'enhanced' data (clinical + administrative data) performed the best in predicting one-year mortality, compared to two other models, one in which all cases with missing data were excluded, and the second, in which a missing value was assumed to indicate an absence of the risk factor [11]. A similar exercise, of merging clinical data on PCI procedures from the APPROACH study with administrative data corresponding to the PCI procedures from the hospitals, was undertaken for this study. The following is a brief description of the three hospital administrative databases and a detailed report on the methodology used in merging the administrative and the APPROACH databases.

2.3.1 Description of administrative data

Administrative data on all PCI procedures were acquired from the Calgary Region Health Authority (CRHA), University of Alberta Hospital (UAH) and the Royal Alexander Hospital (RAH). The CRHA file consisted of the discharge records of all hospitalizations during which a PCI procedure was performed in the Calgary Region between 13th June 1994 and 30th March 1998. The file contained 7999 records. The file included the following variables: chart number, admit date, discharge date, site (hospital), a unique personal health number (PHN), sixteen diagnosis fields and ten procedure fields.

Administrative data from RAH consisted of 1966 records corresponding to PCIs performed between December 16th 1994 and March 31st 1998. The dataset included information on the PHN, chart number, admit date, discharge date, procedure date, sixteen diagnosis fields and eighteen procedure fields.

Two files, one consisting of in-hospital records and the other of day-procedures were obtained from UAH. On merging these files there were a total of 1768 records of procedures performed between December 22nd 1994 and March 31st 1998. In addition to the unique PHN number, the UAH file included chart number, admit date, discharge date, procedure date and as many as 29 diagnosis codes and 20 procedure codes.

2.3.2 Process of Merging APPROACH and Administrative data

In order to optimize efficiency and accuracy, the three hospital administrative databases were concatenated and the resulting composite administrative data file was merged with the APPROACH data.

Of the 7,999 CRHA records, 729 (9%) were from out of province patients [postal code starting with letter other than "T"]. These were deleted. Forty-nine patients with missing postal codes were retained for the merge.

Of the 1,966 RAH records, 499 (25%) had the same chart number, admit date, and discharge date. These were considered duplicate records and removed. An additional 22 records (1%) had the same chart number and admission date, but a different discharge date. These may have been patients seen first in an outpatient setting and then admitted to hospital. The record with the longer length of stay [inpatient record] was retained for the merge.

The UAH file consisted of 1261 inpatient records and 507 outpatient records. There were 7 (0.4%) records with the same chart number and admit date and different discharge date. As in RAH's case the record with the longer length of stay, corresponding to the inpatient admission was retained.

On concatenation, there were 10476 (7270+1445+1761) records in the administrative file and it contained the following variables: PHN, chart number, hospital, admit date, discharge date, 29 diagnosis fields and 18 procedure fields.

Figure 1. Administrative data and APPROACH data Merge Process

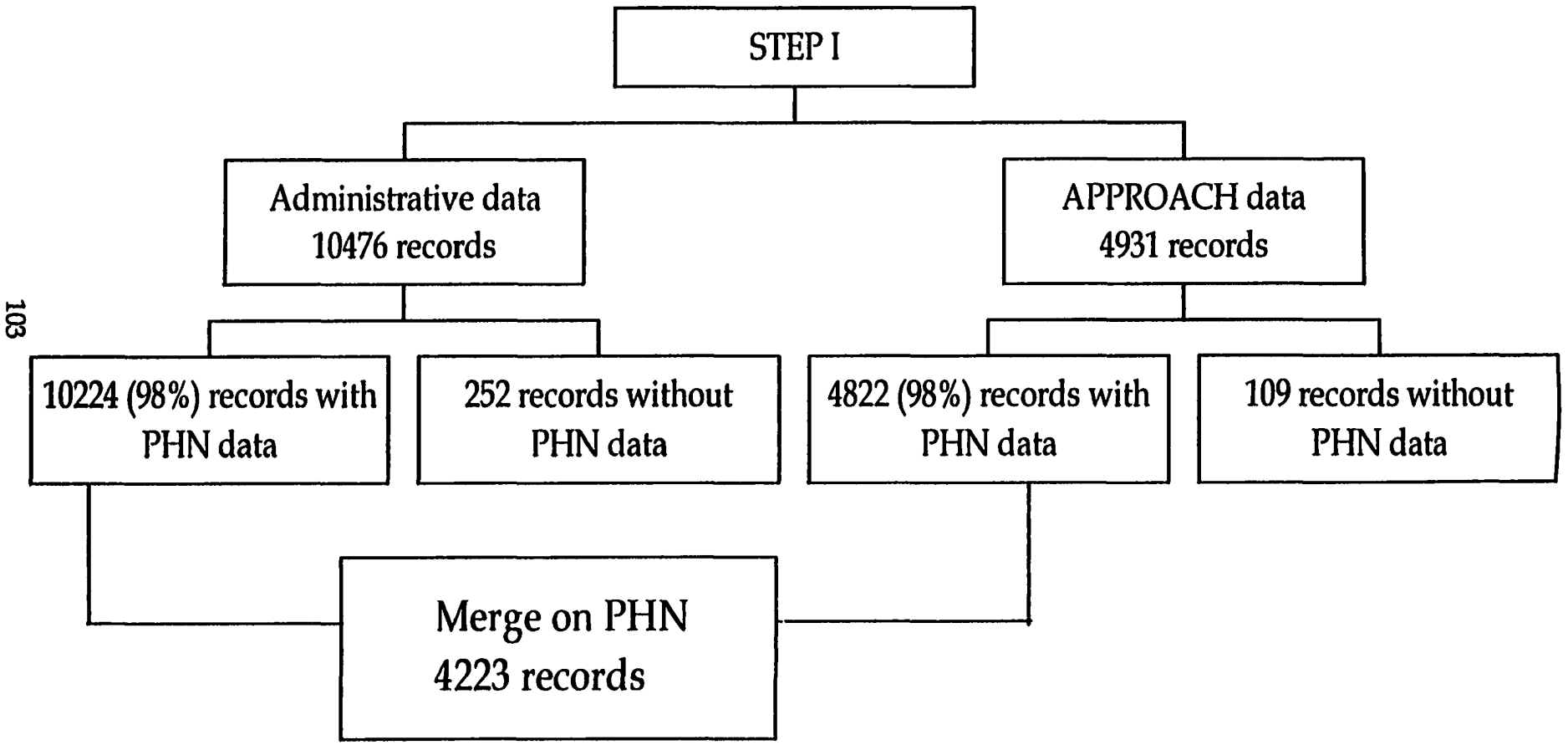
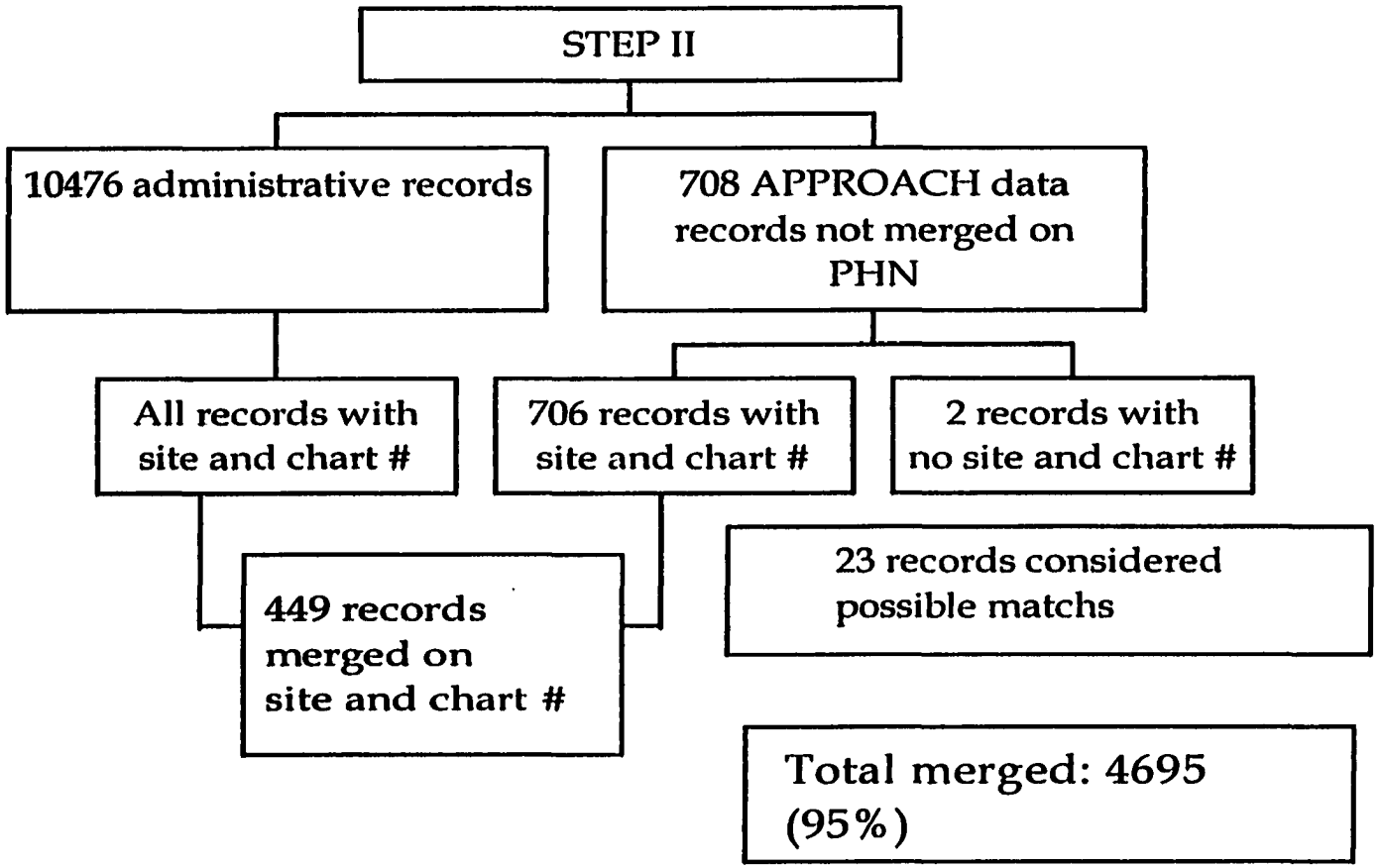


Figure 1. Administrative data and APPROACH data Merge Process



These data were merged with the APPROACH database in the following steps (a pictorial representation of the merge process is provided in Figure 1):

1. The 10476 administrative data records were split into two files based on whether the PHN was available. Ten thousand and two hundred and twenty-four (98%) of the records had PHN numbers and 252 records did not.

2. The APPROACH database was split in a similar manner based on the presence or absence of PHN data. Of the 4931 records, 4822 (98%) had PHN data and 109 records did not.

3. The 10224 administrative records were merged with the 4822 APPROACH records on PHN. It is important to note that there are several reasons for the discrepancy in the number of records in the administrative file and the APPROACH file. First, the time-periods for the administrative records are longer than the APPROACH time-period (June 1994 to March 1998 for the administrative records and July 1995 to December 1997 for APPROACH). Second, the APPROACH file consisted of only the first procedure a patient had undergone during the study time period, whereas the administrative file contained records of all procedures (including repeat procedures) during the specified time-periods.

4. An additional check of whether the PCI procedure date (from APPROACH) was between the admission and discharge date (from the administrative data)

was undertaken to ensure that the correct admissions were being merged. There were 4229 successful merges, however, 6 were duplicate admissions at different hospitals. For example, consider a scenario in which a patient was admitted to a community hospital, and then transferred to Foothills Hospital where the procedure was performed, and then was either transferred back to the community hospital or discharged home. For payment purposes, both hospitals had a record of this patient having a PCI. The six records corresponding to the transferring hospital were deleted. Therefore a total of 4223 (86%) records were considered successfully merged on PHN.

5. The records that did not merge on PHN were then merged using hospital and chart number. Of the 708 APPROACH records that did not merge, 2 did not have chart number. Of the 706 records, 449 records were successfully merged with the administrative data on hospital and chart number.

6. Of the 259 non-merges, 23 were considered *possible* merges because they merged on PHN, however, the PCI date was one-two days off. These were retained for further analyses.

Therefore, a total of 4,695 (95%) of the APPROACH cases between July 1, 1995 and December 31st 1997 were successfully merged with administrative data. The distribution of key factors such as age, sex and important risk factors among the 236 cases (5%) that did not merge was carefully examined.

A risk factor was deemed present if it appeared in either the APPROACH or the administrative database. The crosswalk between the ICD-9-CM codes [12] used in the administrative database and the clinical variables found in APPROACH was the one used by Norris et al [11] which was based on the schemes developed by Deyo et al [13] and Charlson et al [14]. A description of this crosswalk is provided in Appendix I.

2.4 Definition of Outcomes of Interest

The outcome measures of interest were the following: 1) mortality within 30 days of index procedure; 2) mortality within one-year of index procedure; and 3) repeat revascularization, i.e., bypass surgery or repeat PCI within one-year of procedure.

Data on repeat revascularization procedures (PCI and CABG) are collected as part of the APPROACH project. One-year mortality, including date and cause (coded using ICD-9 definitions) [12] of death are obtained routinely from vital statistics at Statistics Canada. All cause deaths were included as outcomes. There were several reasons for this decision. First, the validity of the cause of death data from death certificates or medical records has been shown to be questionable and potentially biasing [15]. And second, even if the cause of death recorded was not cardiac-related, it is possible that for some patients, cardiac

problems contributed to their mortality. Appendix II provides a list of causes stated on the death certificates. There were 75 (43%) deaths that occurred within the hospitalization during which the PCI was performed and these can safely be considered to be cardiac-related. Sixty-five out-of-hospital deaths (37%) had a cardiac cause listed on the death certificate. An additional twelve deaths (7%) had causes that could be considered to have been aggravated by the presence of coronary artery disease, these include diabetes and hypertensive renal disease. There were 17 (10%) deaths, which appear to have been non-cardiac related.

Initially, a composite outcome was considered consisting of the following: an admission for myocardial infarction, a repeat revascularization or death within one-year. However, the composite analysis was not pursued for the following reasons. First, repeat myocardial infarction ((re)-MI) rates could only be determined by examining whether a patient had been admitted to any provincial hospital with a diagnosis of MI following his/her index PCI. This would require linking the APPROACH database with Alberta Health's database on all discharges in the province. However, the Alberta Health data were not available and therefore analyses around this outcome had to be abandoned.

Second, the combination of mortality and repeat revascularization into a single composite outcome was found to be inappropriate because the relationship between some of the predictors and the two outcomes was diametrically opposite, thereby biasing the results towards the null. This is best illustrated

with an example. Figure 2a shows the relationship between patient age and mortality. As expected, higher age groups are associated with higher mortality. In Figure 2b, the relationship between age and repeat procedure rates is depicted. This relationship appears more complex, with patients over the age of 69 years having an inverse association with the likelihood of repeat revascularization. With a composite outcome, defined as repeat revascularization or mortality, these opposing associations would be lost and the relationship would be biased towards the null.

Figure 2a. Mortality by Age Category

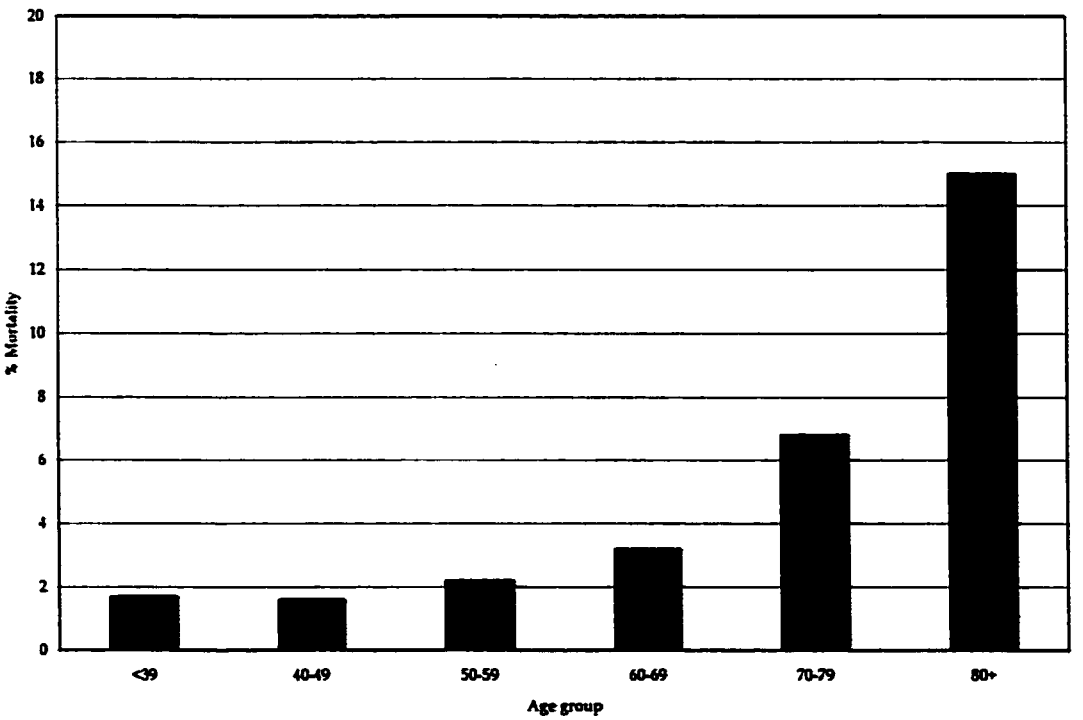
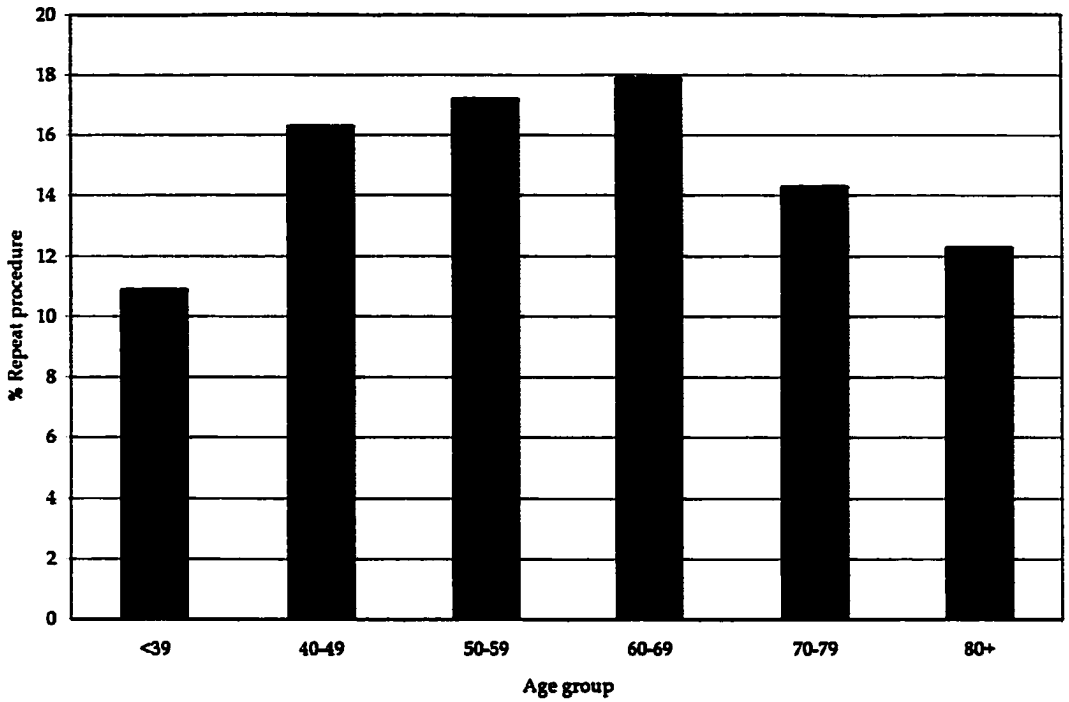


Figure 2b. Repeat Procedure Rate by Age Category



2.5 DESCRIPTION OF INDEPENDENT (PREDICTOR) VARIABLES

Table 1 provides a list of all the predictor variables considered in the analyses. Age was coded in years and captured at the time of the PCI. Sex was coded as an indicator variable with males being coded as 0 and females as 1.

All the heart disease stage and severity measures, other than CCS class, as well all the comorbidities were dichotomous variables with 1 indicating the presence of the condition. CCS class was a categorical variable with eight categories indicating progressive levels of angina.

Table 1. List of predictor variables considered in predicting one-year mortality

Demographics
Age
Sex
Heart disease Stage and Severity Measures
AMI on admission
Congestive heart failure
Prior MI
Prior PTCA
Prior CABG
Cardiogenic shock
NYHA class
CCS class
Comorbidities
Cerebrovascular disease
Pulmonary disease
Renal disease
Diabetes Type I
Diabetes Type II
Dialysis
Lipids
Hypertension
Liver/GI disease
Malignancy
PVD
Family history of CAD
Current smoker
Past smoker
Prior thrombolytic therapy
Left Ventricular Ejection Fraction
Cardiac Anatomy
Lesions >70% stenosis
Graft
Proximal LAD
Left Main disease
Procedural variables
IABP
Direct PCI
Emergent PCI
Stents
Complete revascularization

AMI = acute myocardial infarction; MI = myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Graft; NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; PVD = Peripheral vascular disease; CAD = Coronary Artery Disease; IABP = intro-aortic balloon pump; PCI = Percutaneous Coronary Intervention.

As part of APPROACH, data on prior PTCA and prior CABG are routinely collected at the time of catheterization or PCI. These variables were considered key indicators of disease stage and severity and therefore, in order to verify these patient reported data, the APPROACH database was queried to determine whether study patients had undergone (unreported) procedures prior to the index event.

Left ventricular (LV) ejection fraction (EF) was coded as a categorical variable in the APPROACH database: EF >50%, 30-50%, <30% and not done due to a reason. The "not done" category includes patients who were too sick or had kidney disease that prevented them from having a ventriculargram. Data on left ventricular (LV) ejection fraction were missing for 14 percent of cases. The frequency of adverse outcome among the missing cases was between those with 30-50% and >50% EF. It was therefore invalid to impute the missing cases a category. As a result the missing cases were treated and reported as a separate category. This strategy was consistent with that reported by Norris et al [11].

In addition to age, the number of lesions with greater than 70% stenosis was the only other continuous variable.

As part of the APPROACH project, data on patients' coronary anatomy at the time of cardiac catheterization (and PCI) is classified according to a modified Coronary Artery Disease Severity Class Index developed at Duke University [16]. From the Duke Coronary Index, two new variables, one corresponding to

the presence of proximal LAD lesions and the other corresponding to the presence of left main artery disease were created. These were included as indicator variables.

A variable called "direct procedure" was created to indicate patients who were admitted with a diagnosis of acute myocardial infarction and who had cardiac catheterizations on the same day as the PCIs.

2.6 CREATION OF DEVELOPMENT AND VALIDATION DATASETS

Prior to proceeding with the analysis, the study dataset was split into two random portions: the development dataset consisting of two-thirds of the cases and the test dataset consisting of the remaining one-third. The two-third / one-third split was to ensure that both datasets were adequately powered to detect differences that were clinically and statistically significant. For example, if patients without congestive heart failure had a one-year mortality rate of 3%, then in order to detect an odds ratio of 2.5 associated with the presence of congestive heart failure, at an α=0.05 and a power of 0.80, a sample size of 850 would be required [16]. Obviously, everything else being constant, as the odds ratio of interest increases, the required sample size decreases and vice versa. Therefore, in order to detect an odds of 2, the required sample size would be 1600. The development set consisting of two-thirds of the patients was

considered to be adequate in size for building the models and the test dataset consisting of the remaining one-third for testing the models.

Baseline demographic, clinical characteristics, and crude outcomes of the study patients, overall, and within each dataset were analyzed to ensure that the random split had resulted in a similar distribution of risk factors and outcomes across the two datasets.

2.7 STATISTICAL ANALYSES

All statistical analyses were conducted using SPSS® statistical software. Data were expressed as percentages for categorical variables and means for continuous variables. Chi-square tests (for categorical variables) and t-tests (for continuous variables) were used to detect statistically significant differences in baseline and outcome data the following groups: 1) patients for whom administrative data were available compared to those for whom no administrative data was available (and were subsequently excluded from further analyses); and 2) between patients assigned to the development dataset with those assigned to the test database.

2.7.1 Kaplan-Meier Analyses

As mentioned before, data on whether and *when* an adverse event occurred were available. Current literature indicates that adverse events following PCI are likely to occur within the first few months of the procedure [17-20]. Kaplan-Meier survival curves were generated to examine the temporal trends associated with repeat revascularization and mortality during the year following the PCI. Kaplan-Meier curves are a plot of the survival probabilities, or the probability that a patient will survive past a specified time [21]. Given that the study was focussed on events occurring within one-year of the index PCI, survival time was right-censored at 365 days. Mortality data were obtained from vital statistics registry and therefore were complete for all patients in the study and there was no censoring due to loss to follow-up. With respect to repeat revascularization, however, there was potential for under-representation to the extent that Alberta residents left the province to have additional cardiac procedures. Using data from the one-year follow-up survey that is conducted as part of the APPROACH project, this figure was estimated to be less than 263 patients (5.6%). These include patients who could not be contacted either because they had died or because they had changed addresses within the province.

2.7.2 Univariate analyses

Categorical variables were analyzed using chi-square tests and examinations were made to determine whether categories could be further collapsed. For dichotomous variables, logistic regression analysis was used to obtain univariate odds ratios and their 95% confidence intervals. As the purpose of the univariate analyses were to identify variables for inclusion into the multivariable models, no adjustments were made to account for multiple comparisons at this stage.

2.7.3 Logistic regression

Logistic regression is the most suitable modeling technique when the dependent variable is dichotomous (such as one-year mortality: yes/no). In logistic regression, the dependent variable is the natural log of the odds of an event.

$$\ln O_i = \ln[\frac{p_i}{1-p_i}] = b_0 + \sum_j b_j X_{ij}$$

Where ln O_i = log of odds of an event for the ith case; p_i = probability of an event; X_{ij} are patient and disease characteristics (for the ith case) specified in the analysis; b_0 is a constant and b_j are parameters corresponding to the X variables estimated using maximum likelihood methods.

From an estimate of ln O_i, the predicted probability of an event can be calculated using the following equation:

$$P(outcome \mid X_1,\ldots,X_j) = \frac{\exp(\beta_0 + \sum_{i=1}^{j} \beta_i X_i)}{1 + \exp(\beta_0 + \sum_{i=1}^{j} \beta_i X_i)}$$

When X_i is continuous, β_i is equal to the increase in the log-odds of the dependent variable resulting from a one-unit increase in the independent variable X_i. However, a more intuitive and easier interpretation (especially when X_i is dichotomous) is that e^{β_1} is the odds ratio. For example, if in a univariate logistic regression analysis examining the association between female sex and one-year mortality, the β associated with female sex was 0.9, this would imply that females were 2.5 times more likely to die by one-year compared to males ($e^{0.9} = 2.46$).

2.7.4 Measuring model discrimination using the c-statistic

The logistic regression equation yields a predicted probability, between 0 and 1, of an event (in this case mortality) for each individual patient in the study. However, the actual outcome takes a value of 1 or 0. Therefore, a direct comparison of predicted and observed outcome for each patient does not provide any useful information.

One of the more widely used measures of model discrimination is the c-statistic (or concordance index), which is equal to the area under the receiver operating characteristic (ROC) curve [22]. The ROC was developed in the field of signal detection theory and has been found to be a useful technique in assessing the accuracy of diagnostic systems [23]. It is a plot of the true-positive rate (sensitivity) versus the false positive rate (1-specificity) at a number of decision thresholds. In the current study, in the case of mortality, sensitivity and specificity are calculated using each value of the predicted probability of death (calculated by the logistic regression model) as the cutoff. As an example, consider the predicted probability of death of 0.7 as the cutoff value, then the following table could be generated:

	Dead	Alive
Dead Based on a predicted probability of death $\geq$ 0.7	A	B
Alive Based on a predicted probability of death < 0.7	C	D

And the sensitivity could be calculated as A/(A+C) and the specificity as D/(B+D). These calculations could be repeated for all predicted probabilities of death, resulting in a continuous set of data points, which could then be plotted to generate the ROC curve.

The area under the ROC curve is a measure of the diagnostic accuracy of the prediction rule. If the rule is no better than chance, then the area under the curve will be close to 0.5, alternatively if the rule is perfect, the area would be equal to 1. In general, areas over 0.7 are considered to have merit.

A more intuitively appealing definition of the c-statistic is as follows: among all possible patient pairs such that one patient has the outcome of interest and the other does not, the c-statistic is equal to the proportion of pairs in which the predicted probability of having the outcome is higher for the patient who had the outcome. Therefore, if the predicted probability of outcome were higher for all patients who had the outcome, the c-statistic would take the maximum value of 1. On the other hand, a c-statistic of 0.5 implies that the model had no ability to discriminate between patients who did and did not have the outcome [22].

2.7.5 Measuring model calibration using the Hosmer-Lemeshow test statistic

Hosmer and Lemeshow have developed a goodness of fit statistic to compare the observed to the expected outcomes based on the prediction model [24]. To calculate the Hosmer-Lemeshow goodness of fit statistic the data are divided into deciles based on the predicted probability of outcome. Within each of the deciles, deviations between the observed and expected number of outcomes are

measured using a statistic similar to the $\chi 2$. These deviations are then summed over the 10 groups and the result is compared to a test to a $\chi 2$ distribution with 8 degrees of freedom. A large p-value associated with the test statistic indicates that the observed deviations from the model predictions are consistent with chance deviations that would occur if the model was correct.

The popularity of this test is driven by the visual presentation of the data. The observed outcome rate for the deciles is plotted against the expected outcome rate (as calculated by the prediction model). A line of perfect correlation is generally depicted on the graph and the closer the 10 points (of observed vs. expected rates) are to this line the better.

Several limitations of this test have been documented in the literature [25]. Among them is the dependence of the test statistic on how the deciles have been defined which have been shown to be different across different statistical packages. The test is also sensitive to sample size, i.e., it is likely to be non-significant, thereby indicating a better fit, in studies that are under-powered to detect differences across the risk strata. In larger studies, even small deviations between observed and expected rates could result in the model being rejected [22].

2.7.6 Multivariable analyses

Multivariable analyses were conducted using backward elimination [22]. All variables found to be significant (at a specified level) in the univariate setting were retained for multivariable analyses. Variables in the multivariable model that were not statistically significantly associated with the outcome were dropped in a systematic fashion starting with the least significant. At each step, the "reduced" model (without a particular variable) was compared to the "full" model (with the variable) using the likelihood ratio test. All variables that were statistically significant at $p<0.10$ were retained in the final model. The final model's discriminating ability and overall goodness-of-fit was evaluated using the c-statistic (equal to the area under the ROC curve) [22] and the Hosmer-Lemeshow $\chi 2$ test, respectively [23].

The prediction model developed on two-thirds of the dataset was validated on the remaining one-third cases. A predicted probability of adverse event for each patient was calculated using the regression coefficients from the prediction model. Observed versus expected event rates were evaluated by deciles of risk. Again, the overall performance of the model was assessed using the c-statistic and the Hosmer-Lemeshow chi-square test.

3. RESULTS

The results are presented in a sequence consistent with the methodology section and a summary is provided below. The sections that follow provide detailed information on each set of results.

3.1 STUDY SAMPLE SELECTION

3.2 MERGE BETWEEN CARDIAC CATHETERIZATION AND PCI DATA: Results of the merge between data collected at the time of PCI with data collected at the time of cardiac catheterization (if it occurred within 60 days of the PCI) are presented

3.3 MERGE BETWEEN CLINICAL AND ADMINISTRATIVE DATA TO IMPROVE CAPTURE: Results of the merge between APPROACH data and administrative data are provided in two sections. The first section deals with the comparison of characteristics of patients who had administrative data to those patients for whom no administrative data were available (and were therefore excluded from further analyses). The second set of results highlight the "value added" or the increase in data completeness resulting from the merge of the clinical and administrative datasets.

3.4 DESCRIPTIVE DATA ON STUDY POPULATION: Descriptive data, namely age distribution, the result of verifying patient reported data on prior

procedures, the distribution of ejection fraction and the temporal trend in the deployment of stents are presented.

3.5 KAPLAN-MEIER ANALYSES: Results of the Kaplan-Meier analyses of survival free of adverse events within one year are presented.

3.6 COMPARISON OF DEVELOPMENT DATASET AND TEST DATASET - EFFECTIVENESS OF RANDOM SAMPLING: Comparisons of characteristics between patients selected into the development dataset and those in the test dataset are presented to verify effectiveness of random sampling.

3.7 MODEL 1 - MORTALITY WITHIN ONE-YEAR FOLLOWING PCI: Data on the development and validation of the one-year mortality model are described. These include measuring univariate associations based on chi-square and logistic regression analysis for categorical variables and only logistic regression for dichotomous variables. Univariate analyses were followed by multivariable analyses using backward stepwise logistic regression. Statistics to assess model performance, i.e., the c-statistic and the Hosmer-Lemeshow statistic are presented. Observed versus expected rates calculated in the test dataset using the model developed in the development dataset are presented.

3.8 MODEL 2 - MORTALITY WITHIN 30-DAYS FOLLOWING PCI: Data on the development and validation of the 30-day mortality model are presented. Again, univariate analyses were followed by multivariable analyses using backward stepwise logistic regression.

3.9 MODEL 3 - REPEAT REVASCULARIZATION WITHIN ONE-YEAR FOLLOWING PCI: Data on the development of the model measuring repeat procedures within one-year of PCI are presented. The model was developed using only those patients who survived to the first repeat procedure, i.e., patients who died in-hospital and who died without undergoing a repeat procedure were excluded. Following the validation of this model, a sensitivity analysis assuming all patients who died had undergone a repeat procedure was conducted and the effect of this assumption on associations between predictor and outcome variables was examined.

3.1 STUDY SAMPLE SELECTION

Between July 1, 1995 and December 31, 1997, 6290 PCI procedures were recorded in the APPROACH database. The number of patients, or in other words, the number of first procedures during this time-period was 5,353. Approximately 8% (422) of the patients were not Alberta residents and were excluded from the

study population. Therefore, the final study sample consisted of 4,931 Alberta residents undergoing their first PCI during the study time-period.

3.2 Merge between Cardiac catheterization and PCI data

Table 2 presents the results of the merge between the cardiac catheterization data and the PCI data. As mentioned earlier, data on comorbidities collected at the time of PCI and at the time of cardiac catheterization were merged if the catheterization had taken place within 60 days of the index PCI. Therefore, if a comorbidity was present at either time, it was considered to be present for the final analyses. Ninety percent (4431) of study patients had undergone a cardiac catheterization within sixty days prior to the PCI. As the data show, the capture of information on comorbid disease was fairly complete at the time of the PCI. A few exceptions were the underreporting of family history of CAD (36.6% at PCI and 43.3% at catheterization) and hypertension (37.8% at PCI and 43.3% at catheterization).

Table 2. Frequency of comorbidities recorded at the time of cardiac catheterization and at PCI. Merged rates for subset of patients with cardiac catheterization within 60 days and overall rates in the study sample are presented in columns 3 and 4.

Variable	Cath. data	PCI data	Cath. & PCI	Final rates in study sample
Sample size	4431	4431	4431	4931
Cerebrovascular disease	3.4	3.8	3.9	3.8
Renal disease	1.0	0.6	1.2	1.1
Dialysis	0.5	0.2	0.6	0.6
Diabetes Type 1	0.6	0.3	0.7	0.7
Diabetes Type 2	13.9	11.7	14.8	14.5
Family history	43.3	36.6	48.3	46.3
Congestive heart failure	5.6	6.5	6.8	6.6
Hyperlipidemia	38.1	40.5	43.2	42.0
Hypertension	43.3	37.8	47.7	46.5
Liver/Gastrointestinal disease	2.1	2.8	3.0	2.7
Prior thrombolytic therapy	18.9	21.5	22.2	20.6
Malignancy	2.6	3.1	3.2	2.9
Peripheral vascular disease	4.8	5.3	5.5	5.3
Prior CABG	6.4	6.3	6.7	6.5
Prior PTCA	13.5	11.0	14.8	14.6
Prior infarction	40.7	45.1	47.6	45.8
COPD	4.3	5.4	5.5	5.1

Cath = Cardiac Catheterization; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; PTCA = Percutaneous Transluminal Coronary Angioplasty; COPD = Chronic Obstructive Pulmonary Disease.

3.3.1 Comparison of Patients with and without administrative data

Administrative data corresponding to five percent (236) of study patients was not available. Table 3 offers a comparison of baseline characteristics between patients with and without administrative data. The frequencies of comorbidities shown in the table are based on APPROACH data for both the merged and non-merged groups.

Patients without administrative data did not differ significantly from those with administrative data in terms of age and sex. The only statistically significant difference between the two groups was in rates of hyperlipidemia (42.3% in patients with administrative data versus 34.7 % in patients without) and malignancy (3% and 0% respectively). Nearly half (47.5% or 112) patients without administrative data were from UAH, RAH accounted for 25.8% or 61 patients. Only the 4,695 patients with administrative data were retained for further analyses.

Table 3. Comparison of baseline characteristics (based on APPROACH data) of patients with and without administrative data.

Variable	Patients with both APPROACH and Administrative data	Patients with APPROACH data only	p-value
Sample size	4695	236	
Age (years)	61.6	61.3	0.69
Female	25.9	24.6	0.70
Cerebrovascular disease	3.9	2.1	0.22
Congestive heart failure	6.6	6.8	0.90
Pulmonary disease	5.2	3.4	0.29
Renal disease	14.4	13.3	1.00
Dialysis	0.6	0.8	0.65
Diabetes Type I	0.7	1.3	0.23
Diabetes Type II	14.4	16.1	0.45
Hyperlipidemia	42.3	34.7	0.02
Hypertension	46.6	44.1	0.46
Prior CABG	6.5	5.1	0.50
Prior PTCA	14.7	11.0	0.13
Prior Infarction	46.3	35.2	<0.01
Liver/GI disease	2.8	1.3	0.22
Malignancy	3.0	0.0	<0.01
PVD	5.3	4.7	0.77
Prior lytic. therapy	20.8	16.9	0.16
Hospitals			<0.01
FH	50.8	19.9	
HCH	8.4	6.8	
RAH	19.1	25.8	
UAH	21.7	47.5	

CABG = Coronary Artery Bypass Graft; PTCA = Percutaneous Transluminal Coronary Angioplasty; GI = gastro-intestinal; PVD = Peripheral vascular disease; lytic = thrombolytic; FMC = Foothill Hospital; HCH = Holy Cross Hospital; RAH = Royal Alexander Hospital; UAH = University of Alberta Hospital.

3.3.2 Increase in data completeness as a result of merge between APPROACH and Administrative data

As the data presented in Table 4 demonstrate, merging the APPROACH data with the administrative data made capture of comorbid illness more complete. The most significant contribution of administrative data was in the coding of prior infarction (46.3% in APPROACH versus 65.0% in APPROACH + Administrative data); hyperlipidemia (42.3% and 51.5%, respectively); hypertension (46.6% and 53.7%, respectively); and congestive heart failure (6.6% and 12.8%, respectively).

Table 4. Additional information captured by merging APPROACH data with Administrative data.

Variable	APPROACH data	APPROACH + Administrative data
Sample size	4695	4695
Cerebrovascular disease	3.9	4.8
Renal disease	1.1	2.2
Diabetes Type 1	0.7	1.9
Diabetes Type 2	14.4	16.4
Dialysis	0.6	1.2
Congestive heart failure	6.6	12.8
Hyperlipidemia	42.3	51.5
Hypertension	46.6	53.7
Liver/Gastrointestinal disease	2.8	4.2
Malignancy	3.0	3.6
Peripheral vascular disease	5.3	5.6
Prior CABG	6.5	7.0
Prior infarction	46.3	65.0
Prior PTCA	14.7	16.4
Pulmonary disease	5.2	9.2
Smoking		
Previous	27.4	31.7
Current	21.5	25.8

CABG = Coronary Artery Bypass Surgery; PTCA = Percutaneous Transluminal Coronary Angioplasty

3.4.1 Verifying accuracy of patient reported prior procedures

The results of verifying patient reported data on prior procedures by examining APPROACH data prior to July 1, 1995 are presented in Table 5. The rates of prior CABG and prior PTCA based on the merge between APPROACH and administrative data were quite similar to the rates of procedures on retrospectively verifying APPROACH data. Only an additional 0.6% prior CABG cases and 0.3% prior PTCA cases were identified on retrospective review. The final variables used in the analyses were the composite of patient reported and retrospective review (i.e. prior CABG rate of 7.6 and prior PTCA rate of 16.7).

Table 5. Verifying data on prior procedures

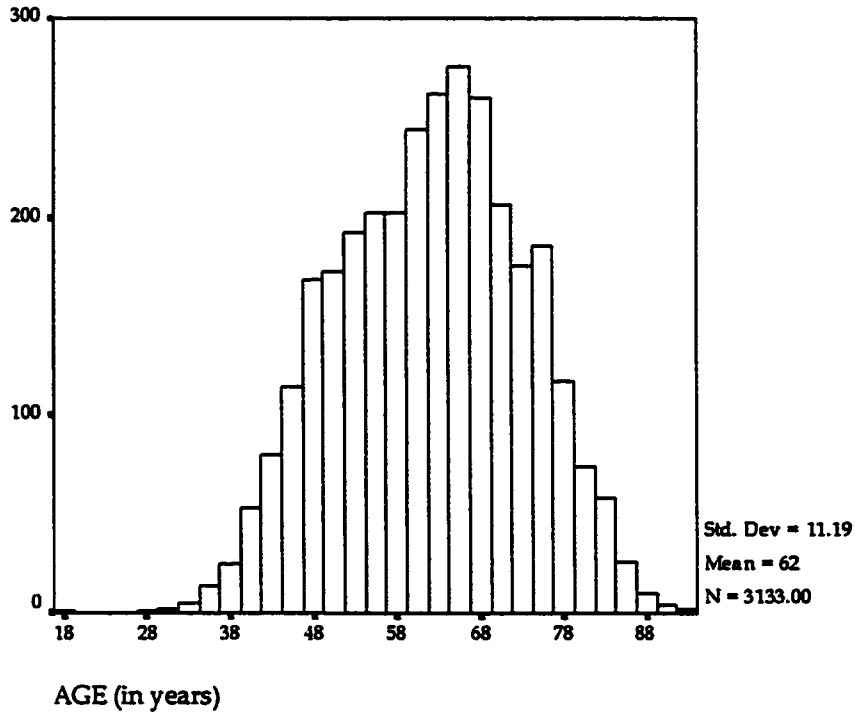
Data	Prior CABG (%)	Prior PTCA (%)
APPROACH	6.5	14.7
Administrative data	2.7	9.6
APPROACH + Admin	7.0	16.4
After checking APPROACH data for prior events	7.6	16.7

3.4.2 Age distribution of study patients

The mean age of the study population at the time of PCI was 61.6 years (Figure 3) and the median was 62.3 years, indicating a non-skewed, and fairly normal

distribution. Only 2.5% patients were under 40 years of age and 4.1% over 80-years of age.

Figure 3. Age Distribution

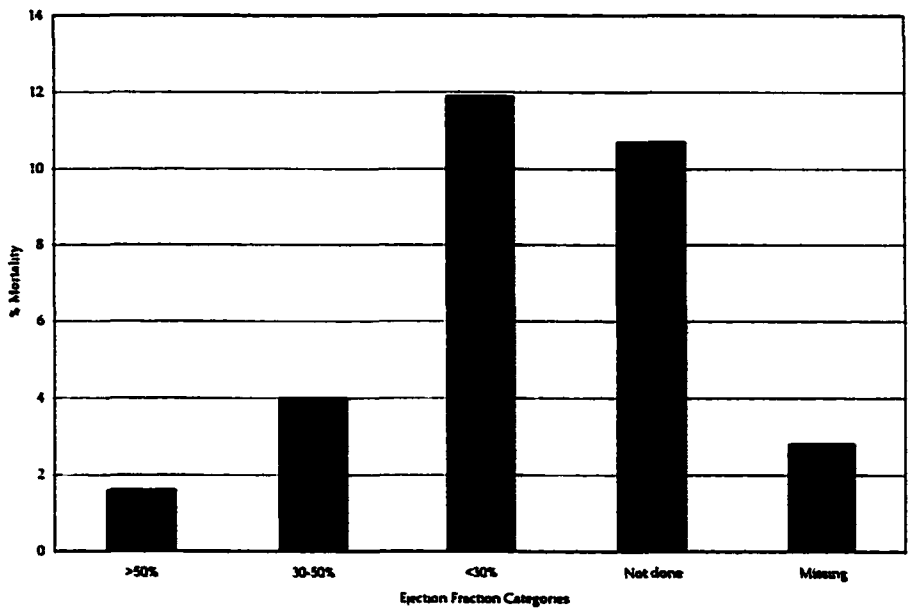


3.4.3 Relationship between ejection fraction and one-year mortality

As mentioned in the methods section, ejection fraction was missing for 706 patients (14%). The distribution of mortality by ejection fraction category is presented in Figure 4. Given that ejection fraction was collected as a categorical variable, and that the 3.3% mortality rate among patients with missing ejection fraction was in between the mortality rates for patients with > 50% ejection

fraction (1.5%) and with 30-50% ejection fraction (4.3%), it was impossible to re-categorize the patients with missing ejection fraction. Therefore, patients with missing ejection fraction were retained in the analyses as a separate category.

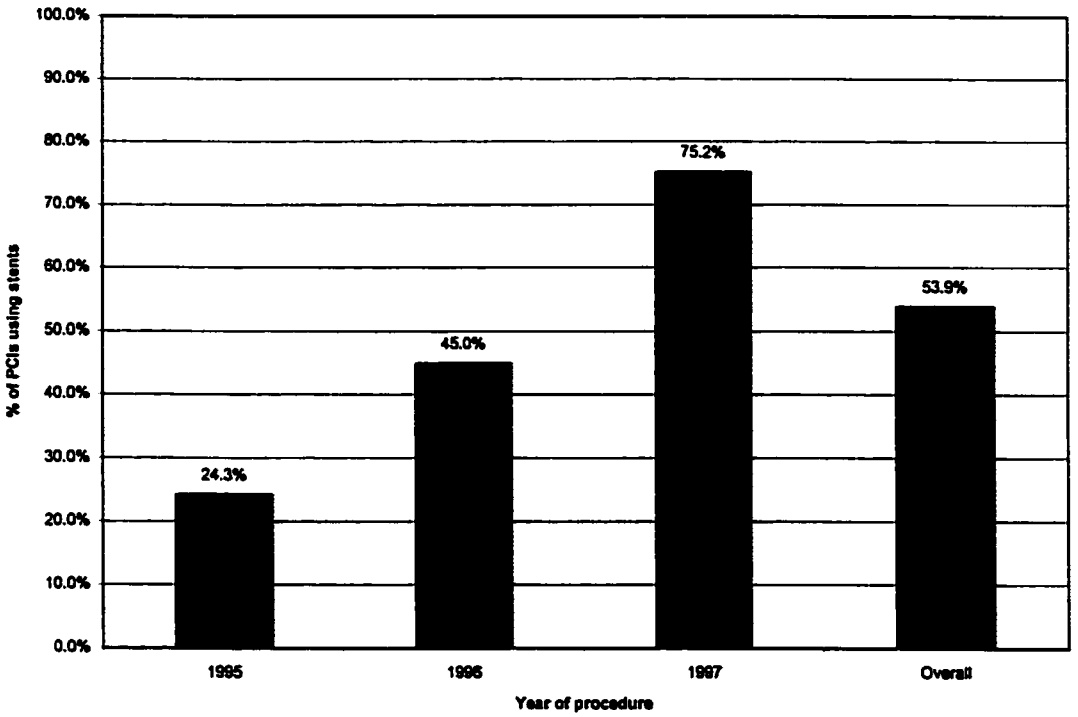
Figure 4. Distribution of Mortality by Ejection Fraction Category



3.4.4 Deployment of stents

The rate of stent use in PCI increased dramatically over this time period from 24% of PCIs in 1995 to 75% PCIs involving stents in 1997 (Figure 5). Of the four sites, over the course of the study's time-period, Foothills Hospital had the highest stent utilization rate (68%), followed by Royal Alexander Hospital (48%) and University of Alberta Hospital (45%).

Figure 5. Deployment of stents by year of procedure and for overall study time-period



3.5 KAPLAN-MEIER ANALYSES OF SURVIVAL FREE OF ADVERSE EVENTS

Kaplan-Meier analyses were conducted to determine the timing and incidence of the outcomes of interest. Survival curves, free of adverse events are presented in Figure 6, Panels A-D. Repeat PCI was the most frequent event (12.6%) followed by CABG (3.7%). Approximately half of the one-year mortality (3.7%) was accounted for in the first 30-days after the procedure (1.9%). All curves show a gradual decline with no obvious plateaus. It should be reiterated that although the capture of one-year mortality is complete for all patients in the study, there is potential for under-representing the number of repeat procedures due to patients undergoing cardiac procedures out-of-province (see discussion around this issue in the Methods section).

Figure 6A. Kaplan-Meier Analyses: Survival Free of Repeat PCI

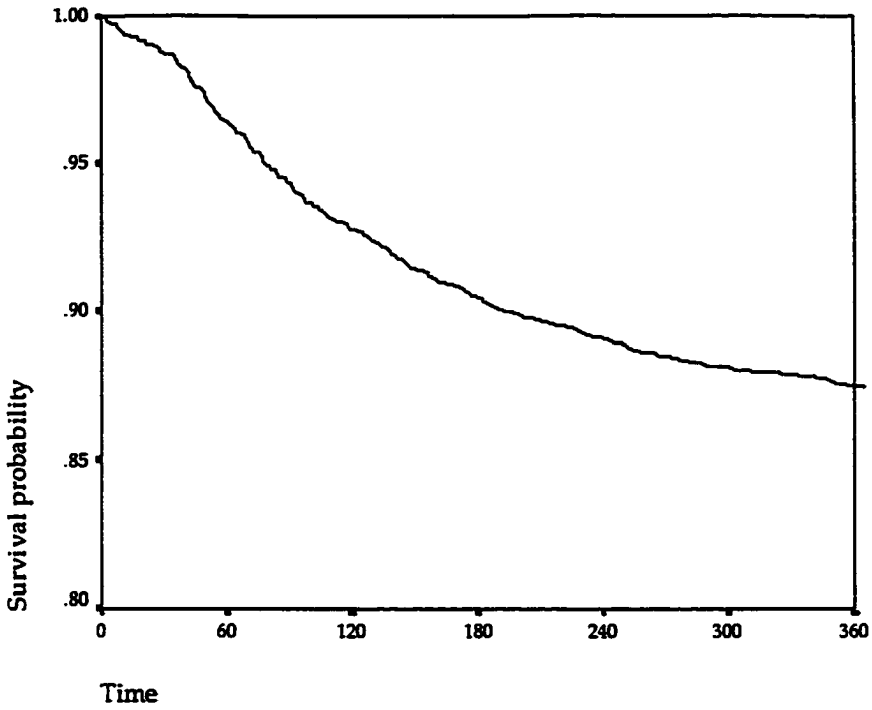


Figure 6B. Kaplan-Meier Analyses: Survival Free of coronary artery bypass surgery

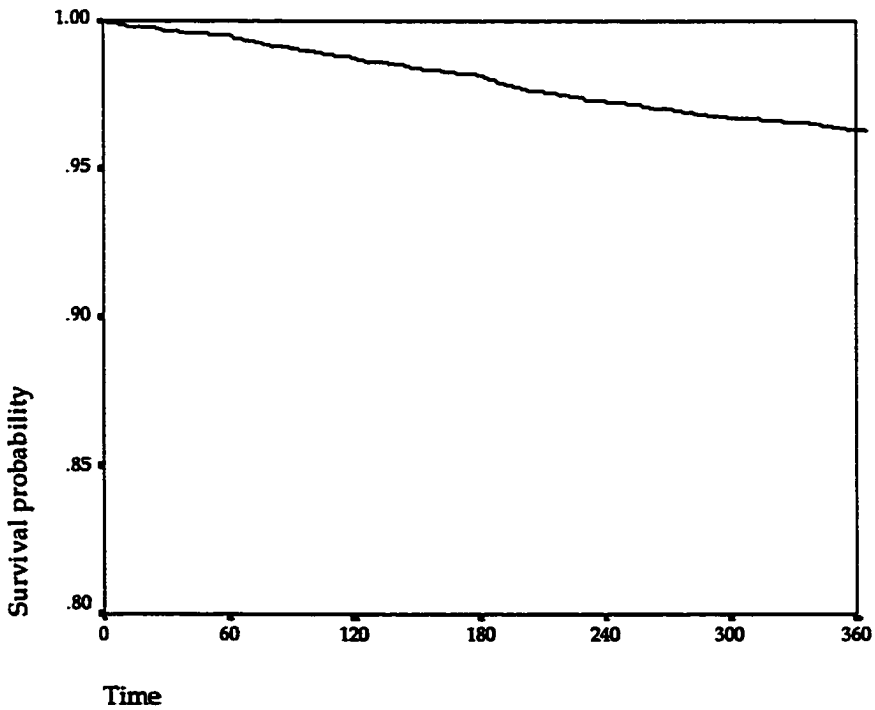


Figure 6C. Kaplan-Meier Analyses: All-cause mortality

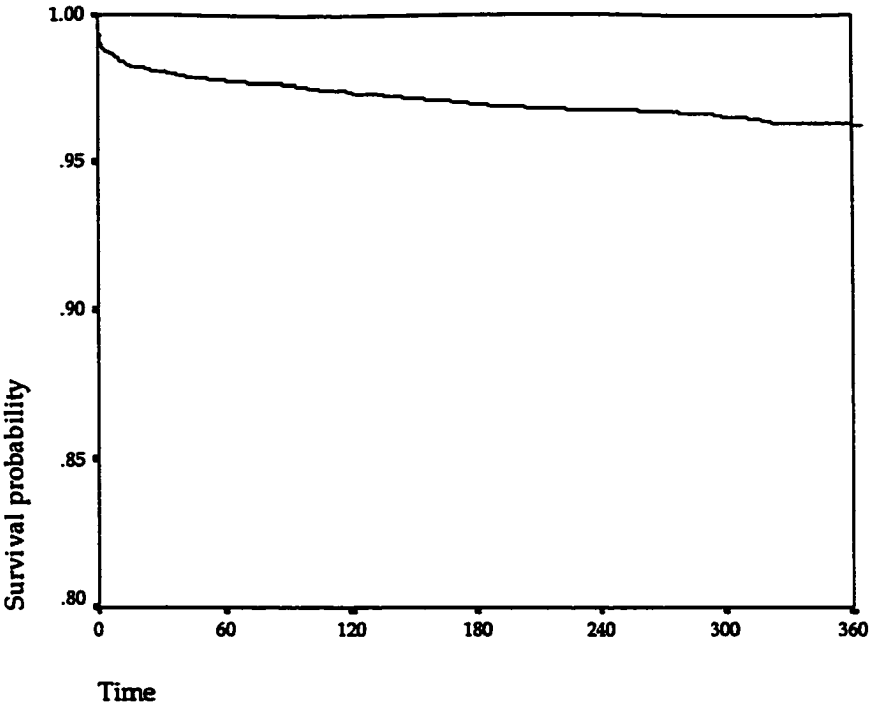
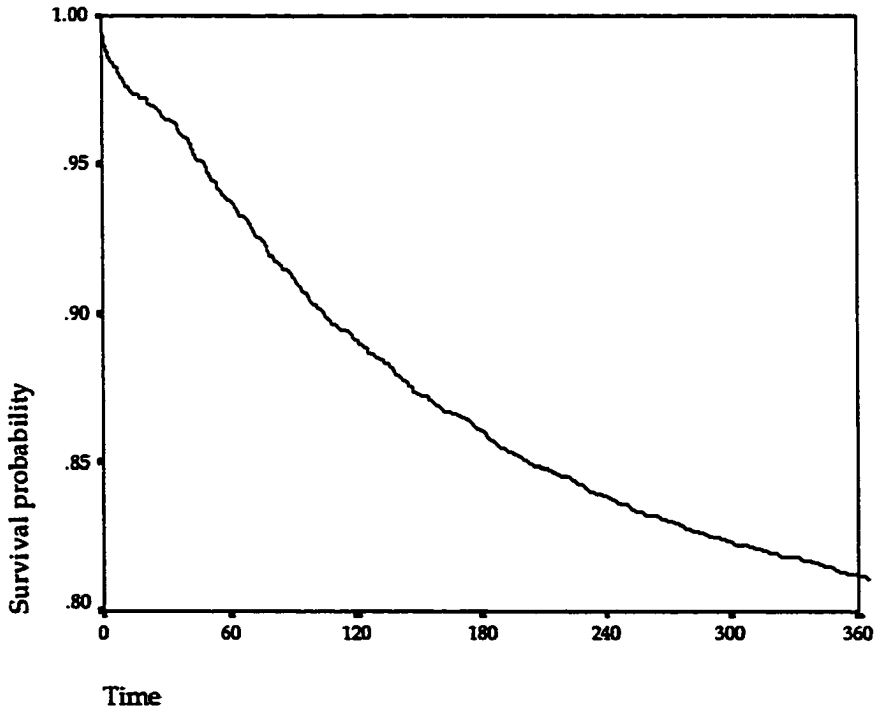


Figure 6D. Kaplan-Meier Analyses - Survival Free of Repeat PCI; CABG or Death



3.6 COMPARISON OF DEVELOPMENT DATASET WITH THE TEST DATASET: EFFECTIVENESS OF RANDOM SAMPLING

Before proceeding with the univariate and multivariate analysis, the dataset was randomly split into two parts – the development dataset consisting of two-thirds of the original data and the test dataset consisting of the remaining one-third. Table 6 provides data on baseline characteristics and outcomes for the total as well as the two subsets. The random split was successful, in the sense that there were no significant differences, other than in the percentage of patients with a repeat PCI, between the two subsets (which also appears to have driven the difference in the combined outcome of any repeat procedure).

Table 6. Comparison of Baseline Characteristics across development and test data sets. All numbers, other than those corresponding to age denote percentages.

Variable	Overall	Development set	Test set	p-value
Sample size	4695	3133	1562	
Demographics				
Age (mean, years)	61.6	61.5	61.6	0.90
Females	25.9	25.5	26.6	0.40
Heart disease Stage and Severity Measures				
CHF	12.8	12.7	13.0	0.78
Prior MI	65.0	66.0	63.1	0.05
Prior PTCA	16.7	16.9	16.5	0.80
Prior CABG	7.6	7.9	7.0	0.29
Comorbidities				
CVD	4.8	4.5	5.3	0.22
COPD	9.2	9.3	9.0	0.79
Renal disease	2.2	2.0	2.4	0.46
Dialysis	1.2	1.2	1.1	0.89
Diabetes Type I	1.9	1.9	1.8	0.82
Diabetes Type II	16.4	16.8	15.6	0.32
Hyperlipidemia	51.5	51.1	52.5	0.37
Hypertension	53.7	53.8	53.6	0.90
Liver/GI disease	4.2	4.0	4.7	0.28
Malignancy	3.6	3.6	3.6	0.93
PVD	5.6	5.3	6.3	0.16
Ejection Fraction				0.43
Not done	14.4	14.1	14.9	
<30%	2.9	2.8	3.0	
30-50%	17.1	17.8	15.8	
>50%	52.1	51.5	53.2	
Missing	13.6	13.8	13.1	
Outcomes				
Repeat PTCA	12.6	11.9	14.0	0.05
Repeat CABG	3.7	3.6	4.0	0.46
Any repeat proc.	15.5	14.7	17.2	0.02
Death w/in 30 d	1.9	2.2	1.4	0.09
Death w/in 1 y	3.7	3.9	3.4	0.42

CHF = Congestive heart failure, MI = myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Surgery; CVD = Cerebrovascular disease; COPD = Chronic Obstructive Pulmonary disease; GI = Gastro-intestinal; PVD = peripheral vascular disease; proc. = procedure.

3.7 MODEL 1: MORTALITY WITHIN ONE-YEAR FOLLOWING PCI

The first logistic regression model developed was to predict one-year all-cause mortality following PCI. The outcome includes both in-hospital and out-of hospital mortality at one-year. All study patients were included in these analyses. One-year mortality rate among the 3,133 patients in the development dataset was 3.9 percent (123 patients) and among the 1,562 patients in the test dataset it was 3.4 percent (53 patients).

3.7.1 Univariate analyses

3.7.1.1 Treatment of categorical variables

Chi-square tests were used to determine whether categorical variables could be collapsed further. As mentioned before, LV ejection fraction was classified into five categories: >50%; 30-50%; <30%, not done and missing. Table 7A shows the mortality rate by each category for the development set. One-year mortality rates by ejection fraction category appear very different and the $\chi 2$ statistic comparing observed and expected rates across the categories was statistically significant ($p<0.01$).

Table 7B shows death rates by PCI procedure priority, which was categorized, into four classes: emergent; urgent; urgent – scheduled; and elective. Unlike

mortality rates by ejection fraction category, the rates of one-year mortality were not very different among patients who underwent urgent, urgent-scheduled, or elective procedures. A chi-square test confirmed their similarity ($p = 0.44$). This variable was therefore dichotomized, one indicating that the procedure was emergent and zero for all other priority categories.

Only 43 patients (1%) had a NYHA classification of 2 or more and therefore these categories were collapsed (Table 7C). Ten percent (299) patients had no NYHA class coded. A chi-square test of one-year mortality rates revealed the missing group to be similar to patients with NYHA class 1 ($p = 0.63$) and therefore they were recategorized as such.

The Canadian Cardiovascular Society Class (Table 7D) is classified into eight categories: 0 - No Angina; 1 - Ordinary physical activity, such as walking and climbing stairs, does not cause angina; angina with strenuous, rapid or prolonged exertion. 2 - Slight limitation of ordinary activity; angina with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. 3 - Marked limitation of activity; angina with walking one or two blocks or climbing more than one flight of stairs in normal conditions. 4a - Unstable angina, pain resolved with intensified medical therapy, now stable on oral medication. Inability to carry on any physical activity without discomfort - anginal syndrome may be present at rest. 4b - Unstable angina on

oral therapy, symptoms improved but angina with minimal provocation. 4c - Symptoms persisting, not manageable on oral therapy, may be hemodynamically unstable, requires coronary care monitoring and parenteral medication. Atypical Pain: Patient is experiencing atypical symptoms of angina. There were only 10 patients (0.3%) coded as "Atypical" and these were categorized with patients who were coded as CCS class 1. Based on clinician input, the variable was not collapsed further.

Table 7A. One-year mortality rate by left ventricular ejection fraction categories

Ejection Fraction	Frequency	Mortality rate
>50%	51.5	1.4
30-50%	17.8	3.9
<30%	2.8	13.6
Not done	14.1	11.3
Missing	13.8	3.9

$\chi 2 = 114.0$, df = 4, $p<0.01$

Table 7B. One-year mortality rates by priority of PCI procedure

Priority	Frequency	Mortality rate
Emergent	12.0	14.6
Urgent	54.0	2.7
Urgent - Scheduled	9.2	1.4
Elective	24.8	2.4

$\chi 2 = 130.8$, df = 3, $p<0.01$

Table 7C. One-year mortality rates by NYHA classification category

NYHA Class	Frequency	Mortality rate
1	89.1	3.7
2	0.8	7.7
3	0.2	0.0
4	0.4	72.7
Missing	9.5	3.0

$\chi 2 = 140.0$, df = 4, $p<0.01$

Table 7D. One-year mortality rates by CCS classification category

CCS Class	Frequency	Mortality rate
1	1.9	1.7
2	8.9	1.8
3	16.9	2.3
4a	29.2	3.1
4b	11.3	2.5
4c	11.9	9.9
Atypical	0.3	0.0
Not done	19.6	5.0

$\chi 2 = 49.8$, df = 7, $p<0.01$

3.7.1.2 Results of univariate analyses

The number of patients, their one-year mortality rates, and the univariate associations (based on logistic regression analyses) between demographic, stage and severity measures, comorbidities, coronary anatomy and function, and

procedure related factors and one-year mortality for the development dataset are presented in Tables 8 A-E.

Increasing age (Table 8A) was linearly associated with increased risk of death (OR = 1.07 for each additional year). However, a more relevant comparison may be in ten-year increments. For example, a sixty-year old patient was twice as likely to die (OR = 2.19) compared to a fifty-year old patient. Sex was also a significant predictor. Females had higher mortality rates (5.9%) compared to men (3.3%). Among heart disease stage and severity measures, the variable most associated with one-year mortality was cardiogenic shock (OR = 46.6; 95% CI, 23.17, 93.75). However, very few patients had cardiogenic shock in this patient population (1.1%) therefore resulting in very large confidence intervals. Acute myocardial infarction on admission, congestive heart failure, prior myocardial infarction, NYHA class greater the 1 and CCS class were all significantly associated with worse outcome. Patients who had undergone a PCI prior to their index PCI were less likely to die by one year (2.1% versus 4.3%). Prior CABG did not have any impact on one-year mortality.

Table 8A. Univariate associations between patient demographic data and stage and severity measures and one-year mortality using logistic regression analysis (N=3133)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Demographics					
Age	-	-	1.07	1.05-1.09	<0.01
Sex					
Male	74.5	3.3	1.00	Ref.	
Female	25.5	5.9	1.86	1.28-2.70	<0.01
Heart disease Stage and Severity Measures					
AMI on admission					
No	58.0	2.8	1.00	Ref.	
Yes	42.0	5.5	2.07	1.44-2.99	<0.01
Congestive heart failure					
No	87.3	2.4	1.00	Ref.	
Yes	12.7	14.1	6.52	4.42-9.46	<0.01
Prior MI					
No	34.0	2.2	1.00	Ref.	
Yes	66.0	4.8	2.30	1.45-3.64	<0.01
Prior PTCA					
No	83.1	4.3	1.00	Ref.	
Yes	16.9	2.1	0.47	0.25-0.89	0.02
Prior CABG					
No	92.1	3.9	1.00	Ref.	
Yes	7.9	4.4	1.15	0.61-2.16	0.67
Cardiogenic shock					
No	98.9	3.3	1.00	Ref.	
Yes	1.1	61.1	46.64	23.17-93.75	<0.01
NYHA class					
I	98.6	3.7	1.00	Ref.	
II, III, IV	1.4	23.3	7.98	3.84-16.60	<0.01
CCS class*					<0.01
1	2.2	1.4	1.00	Ref.	
2	8.9	1.8	1.24	0.14-10.70	
3	16.9	2.3	1.57	0.20-12.20	
4a	29.2	3.1	2.13	0.29-15.82	
4b	11.3	2.5	1.77	0.22-14.12	
4c	11.9	9.9	7.47	1.01-55.06	
Not done	19.6	5.0	3.59	0.49-26.56	

OR = Odds ratio; CI = Confidence interval; AMI = acute myocardial infarction; MI = myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Graft; NYHA = New York Heart Association; CCS = Canadian cardiovascular society; * = See definitions on page 45.

Table 8B. Univariate associations between patient comorbidities and one-year mortality using logistic regression analysis (N=3133)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Cerebrovascular disease					
No	95.5	3.6	1.00	Ref.	
Yes	4.5	10.6	3.18	1.80-5.61	<0.01
Pulmonary disease					
No	90.7	3.5	1.00	Ref.	
Yes	9.3	8.2	2.48	1.56-3.94	<0.01
Renal disease					
No	98.0	3.5	1.00	Ref.	
Yes	2.0	23.4	8.39	4.56-15.44	<0.01
Dialysis					
No	98.8	3.7	1.00	Ref.	
Yes	1.2	24.3	8.41	3.88-18.23	<0.01
Diabetes Type I					
No	98.1	3.8	1.00	Ref.	
Yes	1.9	10.0	2.81	1.18-6.66	0.02
Diabetes Type II					
No	83.2	3.5	1.00	Ref.	
Yes	16.8	6.3	1.88	1.24-2.83	<0.01
Lipids					
No	48.9	5.9	1.00	Ref.	
Yes	51.1	2.0	0.33	0.22-0.49	<0.01
Hypertension					
No	46.2	3.9	1.00	Ref.	
Yes	53.8	4.0	1.03	0.72-1.48	0.88
Liver/Gastrointestinal disease					
No	96.0	3.8	1.00	Ref.	
Yes	4.0	7.2	1.97	0.97-3.98	0.06
Malignancy					
No	96.4	3.8	1.00	Ref.	
Yes	3.6	8.0	2.23	1.10-9.52	0.03
Peripheral Vascular Disease					
No	94.7	3.6	1.00	Ref.	
Yes	5.3	10.3	3.10	1.81-5.31	<0.01
Family history of coronary artery disease					
No	52.9	4.6	1.00	Ref.	
Yes	47.1	3.1	0.66	0.46-0.96	0.03
Current smoker					
No	74.7	4.2	1.00	Ref.	
Yes	25.3	3.0	0.71	0.45-1.11	0.14
Past smoker					
No	68.5	4.2	1.00	Ref.	
Yes	31.5	3.2	0.76	0.50-1.14	0.18

Table 8B. Univariate associations between patient comorbidities and one-year mortality using logistic regression analysis (N=3133)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Sample size	3133				
Prior thrombolytic therapy					
No	78.9	3.9	1.00	Ref.	
Yes	21.1	3.9	1.00	0.64-1.56	0.99

Table 8C. Associations between left ventricular ejection fraction and one-year mortality using logistic regression analysis (N=3133)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Ejection Fraction					<0.01
>50%	51.5	1.4	1.00	Ref.	
30-50%	17.8	3.9	2.97	1.63-5.41	<0.01
<30%	2.8	13.6	11.42	5.45-23.93	<0.01
Not done	14.1	11.3	9.22	5.52-15.41	<0.01
Missing	13.8	3.9	2.96	1.56-5.62	<0.01

Table 8D. Associations between coronary anatomy and one-year mortality using logistic regression analysis (N=3133)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
# Lesions >70% stenosis			1.21	1.09-1.34	<0.01
Graft					
No	93.4	4.0	1.00	Ref.	
Yes	6.6	2.9	0.72	0.31-1.65	0.43
Proximal LAD					
No	76.4	3.3	1.00	Ref.	
Yes	23.6	6.0	1.86	1.27-2.71	<0.01
Left Main disease					
No	97.5	3.5	1.00	Ref.	
Yes	2.5	19.5	6.60	3.64-11.98	<0.01

Table 8E. Associations between procedural factors and one-year mortality using logistic regression analysis (N=3133)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Intra-aortic balloon pump					
No	99.3	3.6	1.00	Ref.	
Yes	0.7	47.8	24.54	10.60-56.81	<0.01
Direct procedure					
No	90.9	3.0	1.00	Ref.	
Yes	9.1	13.0	4.80	3.19-7.20	<0.01
Emergency procedure					
No	88.0	2.5	1.00	Ref.	
Yes	12.0	14.6	6.77	4.66-9.84	<0.01
Stents					
No	46.4	4.1	1.00	Ref.	
Yes	53.6	3.8	0.90	0.63-1.30	0.59
Complete revascularization					
No	56.7	5.3	1.00	Ref.	
Yes	43.3	2.1	0.39	0.26-0.60	<0.01
In-hospital cardiac complications					
No	95.1	3.3	1.00	Ref.	
Yes	4.9	15.7	5.41	3.35-8.75	<0.01

The data confirm that the presence of comorbid disease increases the risk of adverse events (Table 8B). Renal disease, dialysis, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes (both Type I and II) and malignancy were all associated with higher mortality at one-year. The presence of hyperlipidemia and a family history of coronary artery disease were associated with lower mortality rates. Smoking status, either past or present, had no impact on one-year mortality; neither did the prior use of thrombolytic therapy.

In terms of coronary anatomy and left ventricular function (Table 8C, D), ejection fraction was a strong predictor of one-year mortality, as was the number of lesions with > 70% stenosis measured prior to PCI. Forty-three percent of the patients (1334) had only one lesion with > 70% stenosis; 28% had two; 14% had 3 and 13% had 4 or more lesions with > 70% stenosis. The mean and median number of lesions with > 70% stenosis was 2. The presence of grafts had no impact on one-year mortality. This is consistent with the finding of prior CABG not being a predictor. Stenoses in the proximal LAD and left main artery were associated with increased risk of mortality at one-year.

In general, procedural factors (Table 8E) were highly predictive of one-year mortality. The insertion of an intra-aortic balloon pump, whether the patient underwent direct procedure and whether the procedure was classified as an emergency were all associated with higher mortality rates at one year. As shown before, during the study time period stents were used in a majority of the PCI procedures (53.6%); however they had no significant impact on long-term mortality. In hospital cardiac complications occurred in 4.9% cases and expectedly were associated with higher one-year mortality.

3.7.2 Multivariable analyses

All variables that were associated with one-year mortality at a significance level of $p < 0.10$ in univariate analyses were included in the multivariable analysis. The only notable variable described in Tables 8 A-E that was not included in the

multivariable model was in-hospital cardiac complications. The intention of the modeling was to identify significant baseline and procedural predictors of one-year mortality. Post-procedure cardiac complications are likely to be highly correlated with in-hospital mortality and were therefore not included in the multivariable model. Table 9 describes the complete multivariable model used to predict one-year mortality, i.e. the starting model that included all variables found to be significant univariate predictors..

Table 9. Complete multivariate model to predict one-year mortality, i.e. including all variables significant in univariate analyses (N=3133)

Variable	Beta	OR	Lower 95% CI	Upper 95% CI	p-value
Demographics					
Age	0.06	1.06	1.03	1.08	<0.01
Female	0.31	1.36	0.86	2.14	0.19
Disease Stage and Severity					
AMI on admission	-0.14	0.87	0.48	1.56	0.63
CHF	0.30	1.35	0.79	2.29	0.27
Cardiogenic shock	1.67	5.32	1.79	15.81	<0.01
Previous MI	0.27	1.31	0.69	2.48	0.41
Prior PTCA	-0.41	0.66	0.33	1.35	0.26
NYHA2+	0.44	1.56	0.53	4.60	0.42
CCS class*					0.16
1	1.00				
2	-0.23	0.80	0.08	7.56	0.84
3	-0.06	0.94	0.11	7.96	0.95
4a	-0.12	0.88	0.11	7.20	0.91
4b	-1.01	0.36	0.04	3.32	0.37
4c	-0.94	0.39	0.04	3.37	0.39
Not done	-0.02	0.98	0.12	8.02	0.98

Table 9. Continued

Variable	Beta	OR	Lower 95% CI	Upper 95% CI	p-value
Comorbidities					
CEVD	0.34	1.41	0.67	2.98	0.37
COPD	0.52	1.68	0.95	8.98	0.08
Renal disease	0.47	1.61	0.63	4.10	0.32
Dialysis	1.71	5.54	1.66	18.54	<0.01
Diabetes Type I	0.55	1.74	0.51	5.91	0.37
Diabetes Type II	0.20	1.23	0.72	2.08	0.45
Lipids	-0.69	0.50	0.31	0.82	<0.01
Liver/GI disease	0.36	1.44	0.63	3.28	0.39
Malignancy	0.87	2.40	1.04	5.55	0.04
PVD	0.59	1.80	0.90	3.60	0.10
Family history of CAD	0.31	1.36	0.86	2.14	0.18
Coronary Anatomy and LV Function					
Ejection Fraction					<0.01
>50%	1.00				
30-50%	0.71	2.03	1.06	3.87	0.03
<30%	1.45	4.28	1.65	11.06	<0.01
Not done	1.34	3.83	2.07	7.09	<0.01
Missing	0.80	2.22	1.09	4.53	0.03
Lesions > 70% stenosis	-0.21	0.81	0.69	0.95	0.01
Proximal LAD	0.69	1.95	1.21	3.15	<0.01
Left main disease	1.90	6.68	2.70	16.57	<0.01
Procedural factors					
IABP	1.48	4.40	1.27	15.29	0.02
Direct procedure	0.18	1.19	0.57	2.52	0.64
Emergency procedure	1.46	4.32	2.27	8.21	<0.01
Complete revasc.	-0.78	0.46	0.28	0.76	<0.01
Constant	-7.64				<0.01

MI = Acute Myocardial Infarction; CHF = Congestive heart failure; MI = Myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; * see definitions on page 45 CEVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; CAD = coronary artery disease; LV = left ventricular; IABP = intra-aortic balloon pump; revasc. = revascularization

It is useful to compare the associations between independent variables and one-year mortality in the univariate and multivariable settings. In general there was a downward shift in the odds ratios which is consistent with the effect being

shared across multiple variables measuring differing levels of severity of the same underlying disease (for example congestive heart failure and NYHA class greater than 2). However, the direction of the association (positive or negative) remained consistent. The notable exceptions were acute myocardial infarction on admission (which was not statistically significant) and the number of lesions with greater than 70% stenosis. The odds ratio associated with the number of lesions with > 70% stenosis went from 1.2 (95% CI, 1.09, 1.34) in the univariate context (Table 8D) to 0.81 (0.69, 0.95) in the multivariable context (Table 9). The multivariable result is counterintuitive. Higher number of lesions with> 70% stenoses are indicative of more diffuse disease and therefore should be associated with worse outcomes. One possible explanation for the findings is that the higher risk is accounted for by the proximal LAD and left main disease variables included in the model.

Tables 10 provides a summary of the modeling process. Variables in the complete model (Table 9) that were not statistically significantly associated with the outcome were dropped sequentially, starting with the least significant. In each row of the table, the -2 log likelihood value corresponds to the model run after the variable was dropped. The likelihood ratio test statistic, equal to the difference in the -2 log likelihood values corresponding to the models with and without a particular variable, and its p-value are also presented.

Direct procedure, acute myocardial infarction on admission, prior myocardial infarction, NYHA class greater than 2, diabetes type I and II, liver/gastro-intestinal disease, cerebrovascular disease, prior PTCA, renal disease, family history of CAD, CCS class and female sex had no significant impact on one-year mortality.

Plausible interactions, such as age and sex, and age and hyperlipidemia, were explored and were found to be non-significant and were therefore not included in the model.

Table 10. Model building process using backward stepwise logistic regression

Variable	-2Log Likelihood	Likelihood ratio test statistic	df	p-value
Constant	1036.825			
Complete model (Table 9)	710.825	325.996	36	<0.01
Direct procedure	711.045	0.22	1	0.64
AMI on admission	711.222	0.18	1	0.67
Prior MI	711.693	0.47	1	0.49
NYHA2+	712.267	0.57	1	0.45
Diabetes Type II	712.901	0.63	1	0.43
Liver/GI disease	713.543	0.64	1	0.42
CEVD	714.541	1.00	1	0.32
Prior PTCA	715.484	0.94	1	0.33
Renal disease	716.611	1.13	1	0.29
Diabetes Type I	717.607	1.10	1	0.32
Family history of CAD	719.602	1.99	1	0.16
CCS class	729.544	9.94	6	0.13
Female	731.314	1.77	1	0.18

AMI = Acute myocardial infarction; MI = myocardial infarction; NYHA = New York Heart Association; GI = Gastro-intestinal; CEVD = Cerebrovascular disease; PTCA = Percutaneous Transluminal Coronary Angioplasty; CAD = Coronary Artery Disease; CCS = Canadian Cardiovascular Society; df = degrees of freedom.

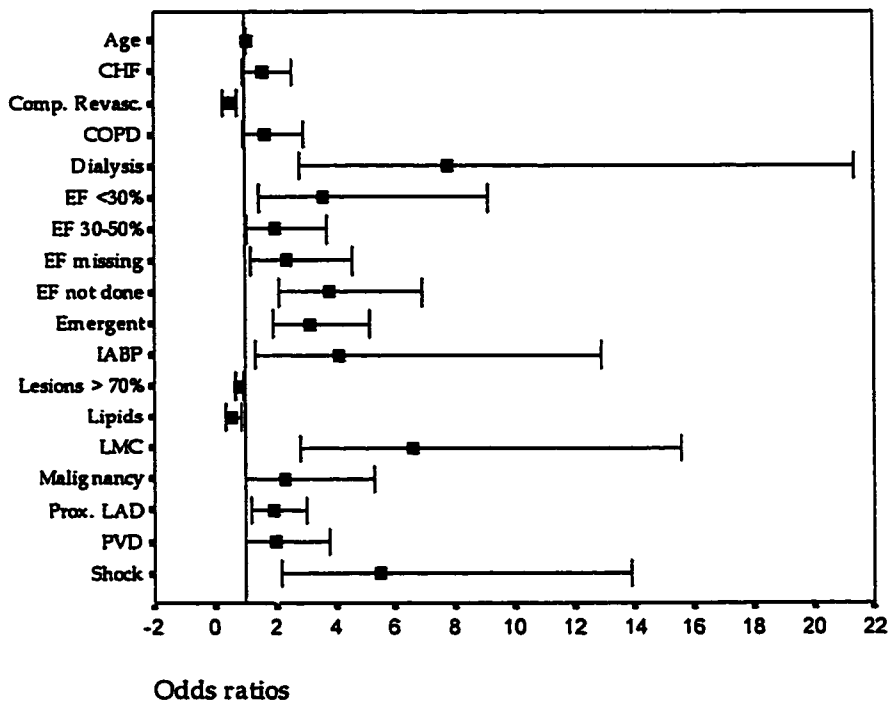
The final multivariate model to predict one-year mortality following PCI is provided in Table 11 and Figure 7. The most significant predictors of one-year mortality were, dialysis, left main disease, cardiogenic shock, insertion of an intra-aortic balloon pump, left ventricular ejection fraction, emergency procedure, and malignancy. Other factors such as age, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, and proximal LAD lesions were also associated with higher mortality. Hyperlipidemia, the number of lesions with greater than 70% stenosis and complete revascularization were associated with lower mortality. Comparing the final model to the complete model containing all univariate predictors [Table 9] resulted in a non-significant likelihood ratio [$\chi 2$ LR [18 df] = 20.5, $p > 0.25$] indicating that the variables that were dropped did not significantly add to the prediction model.

Table 11. Final multivariate model to predict one-year mortality

Variable	OR	Lower CI	Upper CI	p-value
Age	1.05	1.03	1.08	<0.01
CHF	1.55	0.94	2.56	0.08
COPD	1.67	0.95	2.92	0.07
Dialysis	7.74	2.81	21.34	<0.01
Hyperlipidemia	0.53	0.33	0.84	<0.01
Malignancy	2.31	1.02	5.26	0.05
PVD	1.95	1.00	3.80	0.05
Cardiogenic Shock	5.49	2.17	13.88	<0.01
Ejection Fraction				<0.01
>50%	1.00			
30-50%	1.98	1.05	3.75	0.04
<30%	3.60	1.42	9.11	<0.01
Not done	3.79	2.08	6.92	<0.01
Missing	2.33	1.18	4.57	0.01
Lesions > 70%	0.80	0.69	0.94	<0.01
Proximal LAD les	1.87	1.18	2.98	0.01
Left Main disease	6.60	2.80	15.57	<0.01
IABP	4.14	1.33	12.90	0.01
Emergent	3.12	1.90	5.14	<0.01
Complete Revasc.	0.45	0.28	0.74	<0.01

OR= odds ratio; CHF = Congestive Heart Failure; COPD = Chronic Obstructive Pulmonary Disease; PVD = Peripheral Vascular Disease; IABP = Intra-aortic balloon pump; Revasc. = revascularization.

Figure 7. Odds Ratios and 95% CI of baseline predictors of one-year mortality



The non-parametric estimate of the area under the ROC curve [Figure 8, left panel] for the development set was 0.87 [95% CI: 0.83, 0.90]. Values of the c-statistic range from 0.5 indicating no discriminatory ability to 1.0 indicating that the model has perfect ability to discriminate between patients who died and did not die. A c-statistic of 0.87 indicates that the one-year mortality model has reasonably good discriminatory power. The Hosmer-Lemeshow goodness of fit was not statistically significant indicating satisfactory fit [χ^2 = 5.20, 8 df, p = 0.74]. The gradient-of-risk, calculated by dividing the expected number of deaths

in highest-risk decile by the expected number of deaths in the lowest risk decile, was 97.2 indicating that the model was effective in spreading out the expected risk of death [26].

The coefficients in the one-year mortality model developed using the "development" dataset were used to calculate predicted probabilities of one-year mortality for each patient in the test dataset.

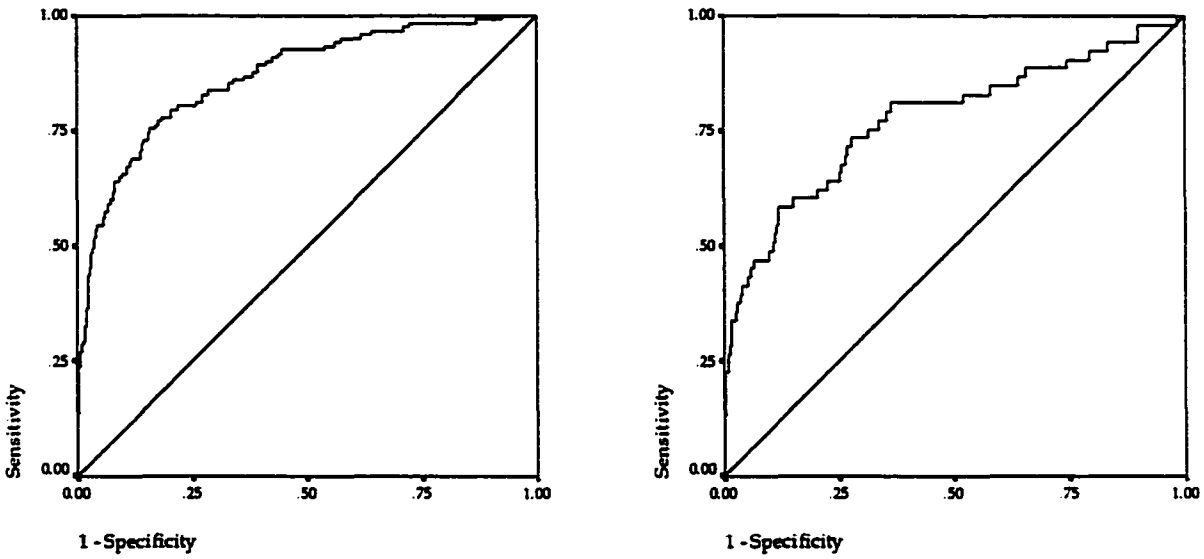
The odds of one-year mortality was calculated as:

exp [- 7.24 + (0.05 * age) + (0.44 * congestive heart failure) + (0.51 * chronic obstructive pulmonary disease) + (2.05 * dialysis) - (0.64 * hyperlipidemia) + (0.84 * malignancy) + (0.67 * peripheral vascular disease) + (1.70 * cardiogenic shock) + (0.68 * ejection fraction 30-50%) + (1.28 * ejection fraction <30%) + (1.33 * ejection fraction not done) + (0.84 * ejection fraction missing) - (0.22 * lesions > 70% stenosis) + (0.63 * proximal lad lesion) + (1.89 * left main disease) + (1.42 * intra-aortic balloon pump) + (1.14 * emergency procedure) - (0.79 * complete revascularization)].

The area under the ROC curve for the test set was 0.78 [95% CI: 0.70, 0.86] - Figure 8, right panel. Observed and expected mortality rates across deciles of risk are presented in Table 12. Figure 9 shows the graphical representation of the observed versus expected mortality rates in the test dataset. Again, the Hosmer-Lemeshow goodness of fit statistic was insignificant (although more significant

compared to the development set) indicating little departure from satisfactory fit [$\chi 2 = 13.53$, 8 df, p=0.09].

Figure 8. ROC Analysis for One-year Mortality model – Left panel: development dataset; Right panel: Test dataset



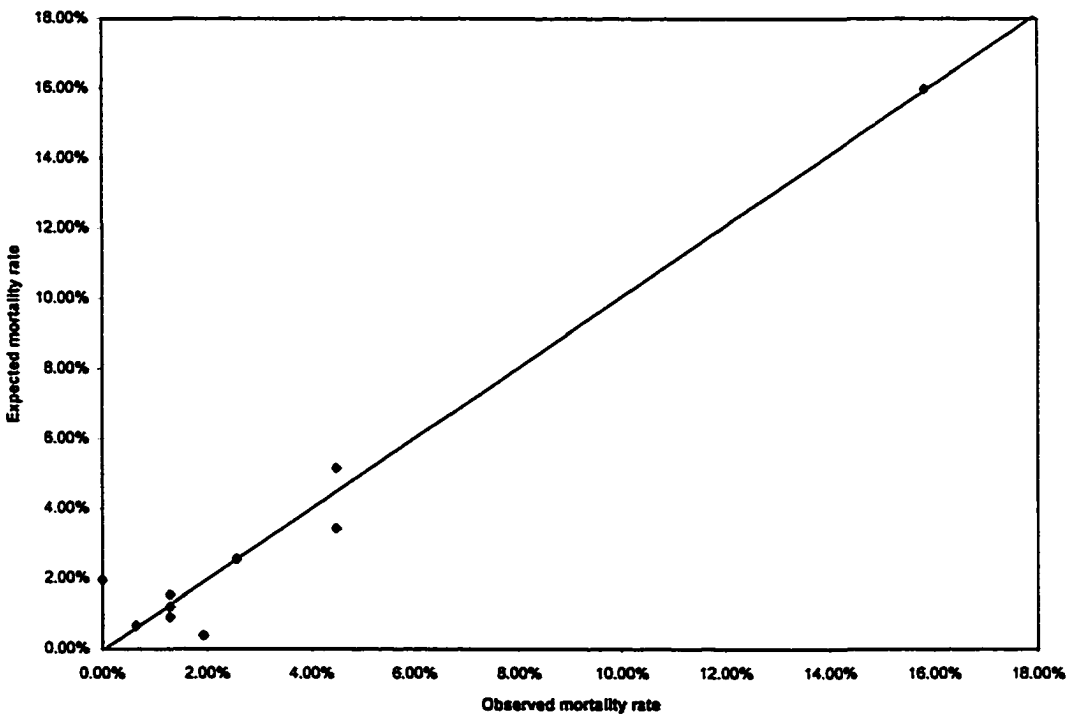
Dataset	Area under the ROC curve	95% Confidence Interval	
		Lower	Upper
Development	0.87	0.83	0.90
Test	0.78	0.70	0.86

Table 12. Observed vs. Expected One-year mortality in the test database

Deciles	Observed Mort Rate (%)	Expected Mort rate (%)
1	1.92	0.39
2	0.64	0.67
3	1.28	0.91
4	1.28	1.20
5	1.28	1.54
6	0.00	1.95
7	2.56	2.55
8	4.49	3.43
9	4.49	5.15
10	15.82	15.98

Hosmer-Lemeshow goodness of fit $\chi 2 = 13.53$, 8 df, $p=0.09$

Figure 9. Observed vs. Expected One-year mortality in the test database



3.8 MODEL 2: MORTALITY WITHIN 30-DAYS OF PCI

A second logistic model was developed to identify predictors of 30-day mortality. Most of the 30-day mortality is accounted for by in-hospital mortality. Among the 3,133 patients in the development dataset, 68 patients (2.2%) died within 30 days of the procedure. Of these 68 patients, 54 (79%) died during the index hospitalization. Only two in-hospital deaths occurred after the 30-day time window. Similarly, in the test dataset, 22 patients (1.4%) died within 30 days. Of these, 18 (82%) occurred within hospital. Only one in-hospital death occurred after 30-days of the procedure.

3.8.1 Univariate analyses

Table 13 A-E lists the univariate associations between demographic, comorbid, and procedural variables and 30-day death in the development dataset. Given that approximately half of the one-year mortality was accounted for by the 30-day mortality, there was considerable overlap in the significant predictors of short and long-term mortality. The association between cardiogenic shock and 30-day mortality was even more dramatic than its association with one-year mortality with more than half the patients with shock dying within 30 days. Most disease stage and severity variables were significantly (and positively,) associated with 30-day mortality. Patients who had undergone a prior PTCA were less likely to have died by 30 days and those who had undergone prior

CABG had no significant difference in mortality compared to those who had not undergone a CABG.

Table 13 A. Univariate associations between demographic data and stage and severity measures and 30-day mortality using logistic regression (N=3133)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Sample size	3133				
Demographics					
Age	-	-	1.06	1.03-1.08	<0.01
Sex					
Male	74.5	1.8	1.00	Ref.	
Female	25.5	3.1	1.72	1.05-2.84	0.03
Heart disease Stage and Severity Measures					
AMI on admission					
No	58.0	0.8	1.00	Ref.	
Yes	42.0	4.0	5.03	2.82-8.96	<0.01
Congestive heart failure					
No	87.3	1.2	1.00	Ref.	
Yes	12.7	9.0	8.40	5.15-13.69	<0.01
Cardiogenic shock					
No	98.9	1.5	1.00	Ref.	
Yes	1.1	58.3	90.85	44.11-187.11	<0.01
Prior MI					
No	34.0	0.8	1.00	Ref.	
Yes	66.0	2.9	3.94	1.88-8.27	<0.01
Prior PTCA					
No	83.1	2.5	1.00	Ref.	
Yes	16.9	0.6	0.22	0.07-0.71	0.01
Prior CABG					
No	92.1	2.1	1.00	Ref.	
Yes	7.9	2.8	1.34	0.61-2.97	0.46
NYHA class					
I	98.6	1.9	1.00	Ref.	
II, III, IV	1.4	23.3	15.84	7.46-33.66	<0.01
CCS class*					
1	2.2	0.0	1.00	Ref.	
2	8.9	0.7			
3	16.9	0.6			
4a	29.2	1.1			
4b	11.3	1.7			
4c	11.9	7.5			
Not done	19.6	3.1			

AMI = Acute Myocardial Infarction; MI = Myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Graft; NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; * See definitions of page 45.

Table 13B. Univariate associations between patient comorbidities and 30-day mortality using logistic regression

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Cerebrovascular disease					
No	95.5	2.0	1.00	Ref.	
Yes	4.5	6.4	3.39	1.65-6.98	<0.01
Pulmonary disease					
No	90.7	2.0	1.00	Ref.	
Yes	9.3	3.8	1.91	0.99-3.69	0.05
Renal disease					
No	98.0	1.9	1.00	Ref.	
Yes	2.0	15.6	9.61	4.67-19.81	<0.01
Dialysis					
No	98.8	2.1	1.00	Ref.	
Yes	1.2	8.1	4.11	1.23-13.74	0.02
Diabetes Type I					
No	98.1	2.2	1.00	Ref.	
Yes	1.9	1.7	0.76	0.10-5.57	0.79
Diabetes Type II					
No	83.2	2.0	1.00	Ref.	
Yes	16.8	3.0	1.55	0.88-2.73	0.13
Lipids					
No	48.9	3.7	1.00	Ref.	
Yes	51.1	0.7	0.18	0.09-0.34	<0.01
Hypertension					
No	46.2	2.3	1.00	Ref.	
Yes	53.8	2.0	0.86	0.53-1.39	0.53
Liver/Gastro-Intestinal disease					
No	96.0	2.1	1.00	Ref.	
Yes	4.0	3.2	1.52	0.54-4.24	0.42
Malignancy					
No	96.4	2.1	1.00	Ref.	
Yes	3.6	3.6	1.71	0.61-4.78	0.31
PVD					
No	94.7	2.0	1.00	Ref.	
Yes	5.3	4.8	2.47	1.16-5.25	0.02
Family history of Coronary artery disease					
No	52.9	2.8	1.00	Ref.	
Yes	47.1	1.4	0.50	0.29-0.73	<0.01
Current smoker					
No	74.7	2.6	1.00	Ref.	
Yes	25.3	0.9	0.33	0.15-0.73	<0.01

Table 13B. Univariate associations between patient comorbidities and 30-day mortality using logistic regression

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Sample size	3133				
Past smoker					
No	68.5	2.6	1.00	Ref.	
Yes	31.5	1.3	0.51	0.28-0.93	0.03
Prior thrombolytic therapy					
No	78.9	2.3	1.00	Ref.	
Yes	21.1	1.7	0.72	0.37-1.38	0.32

Table 13C. Univariate associations between left ventricular ejection fraction and 30-day mortality

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Ejection Fraction					<0.01
>50%	51.5	0.3	1.00	Ref.	
30-50%	17.8	1.1	3.50	1.06-11.51	0.04
<30%	2.8	9.1	32.14	10.28-100.43	<0.01
Not done	14.1	9.3	32.86	12.91-83.66	<0.01
Missing	13.8	1.8	6.05	1.97-18.58	<0.01

Table 13D. Univariate associations between coronary anatomy and 30-day mortality using logistic regression

Variable	% patients	%Outcome	OR	CI (95%)	p-value
# Lesions >70% stenosis			1.48	1.22-1.81	<0.01
Graft					
No	93.4	2.2	1.00	Ref.	
Yes	6.6	1.4	0.65	0.20-2.08	0.47
Proximal LAD					
No	76.4	1.7	1.00	Ref.	
Yes	23.6	3.7	2.18	1.33-3.56	<0.01
Left main disease					
No	97.5	1.8	1.00	Ref.	
Yes	2.5	18.2	12.35	6.52-23.40	<0.01

Table 13E. Univariate associations between procedural factors and 30-day mortality using logistic regression

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Intra-aortic balloon pump					
No	99.3	1.9	1.00	Ref.	
Yes	0.7	43.5	40.48	17.05-96.07	<0.01
Direct procedure					
No	90.9	1.3	1.00	Ref.	
Yes	9.1	11.3	9.92	6.06-16.25	<0.01
Emergent procedure					
No	88.0	0.7	1.00	Ref.	
Yes	12.0	12.8	20.03	11.74-34.16	<0.01
Stents					
No	46.4	2.5	1.00	Ref.	
Yes	53.6	1.9	0.76	0.47-1.24	0.27
Complete revascularization					
No	56.7	3.1	1.00	Ref.	
Yes	43.3	1.0	0.30	0.17-0.56	<0.01
In-hospital cardiac complications					
No	95.1	1.6	1.00	Ref.	
Yes	4.9	12.4	8.48	4.86-14.81	<0.01

In the case of comorbidities, presence of cerebrovascular disease, pulmonary disease, renal disease and peripheral vascular disease was associated with significantly higher 30-day mortality. Diabetes (Type I and II), hypertension, liver/GI disease, and malignancy had no impact on short-term mortality. Patients with hyperlipidemia, family history of CAD and who were current or past smokers were less likely to die by 30-days.

In general, coronary anatomy and function and procedural factors were significant predictors of 30-day mortality. Lower ejection fraction, higher number of lesions with > 70% stenosis, and the presence of stenoses in the

proximal LAD and left main arteries as well as the insertion of an intra aortic balloon pump, direct procedure, emergent procedure, and in-hospital cardiac complications were all associated with higher mortality. As expected complete revascularization was protective of adverse outcome. The implantation of stents had no significant impact on mortality.

3.8.2 Multivariable analyses

All variables found to be significant at the $p< 0.10$ level in univariate analyses were included in the multivariable model. Table 14 presents the complete multivariable model used to predict 30-day mortality. Variables that were not significantly associated with the outcome were dropped in a step-wise fashion. Congestive heart failure, direct procedure, prior myocardial infarction, dialysis, female sex, cerebrovascular disease, NYHA class greater than 2, peripheral vascular disease, number of lesions with > 70% stenosis, age, family history, and prior PTCA were all non-significant predictors of 30-day mortality [Table 15].

Table 14. Complete multivariable model to predict 30-day mortality, i.e. including all predictors found to be significant at the univariate level

Variable	Beta	OR	Lower 95% CI	Upper 95% CI	p-value
Demographics					
Age	0.02	1.02	0.99	1.06	0.15
Female	0.06	1.07	0.53	2.14	0.86
Disease Stage and Severity					
MI on admission	0.84	2.32	0.82	6.57	0.11
CHF	0.03	1.03	0.48	2.24	0.94
Cardiogenic shock	1.53	4.63	1.39	15.44	0.01
Previous MI	-0.09	0.92	0.27	3.13	0.89
Prior PTCA	-0.78	0.46	0.13	1.64	0.23
NYHA 2+	0.49	1.63	0.48	5.50	0.43
Comorbidities					
CEVD	0.35	1.42	0.47	4.31	0.53
COPD	0.65	1.92	0.78	4.73	0.15
Renal disease	0.89	2.44	0.79	7.48	0.12
Dialysis	0.17	1.19	0.16	8.66	0.86
Lipids	-1.28	0.28	0.12	0.64	<0.01
PVD	0.47	1.60	0.55	4.65	0.39
Family history	0.51	1.66	0.82	3.38	0.16
Current smoker	-1.58	0.21	0.07	0.57	<0.01
Past smoker	-0.84	0.43	0.19	1.00	0.05
Coronary Anatomy and LV function					
Ejection Fraction					<0.01
>50%	1.00				
30-50%	0.75	2.11	0.57	7.77	0.26
<30%	1.73	5.65	1.25	25.47	0.02
Not done	2.42	11.22	3.81	33.07	<0.01
Missing	1.71	5.55	1.57	19.55	<0.01
Lesions > 70% stenosis	-0.12	0.88	0.71	1.10	0.27
Proximal LAD	0.90	2.45	1.23	4.91	0.01
Left main disease	2.94	18.84	5.79	61.22	<0.01
Procedure factors					
IABP	1.93	6.86	1.66	28.38	<0.01
Direct procedure	-0.06	0.95	0.37	2.41	<0.01
Emergency procedure	1.70	5.47	2.47	12.11	<0.01
Complete revasc	-1.43	0.24	0.11	0.54	<0.01
Constant	-7.29				<0.01

AMI = Acute Myocardial Infarction; CHF = congestive heart failure; MI = Myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Graft; NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; IABP = intra-aortic balloon pump

Table 15. Model building process using backward stepwise logistic regression

Variable	-2Log Likelihood	Likelihood ratio test statistic	df	p-value
Constant	655.030			
Complete model (Table 14)	326.769	328.61	28	<0.01
CHF	326.775	0.01	1	0.94
Direct procedure	326.789	0.01	1	0.91
Previous MI	326.807	0.02	1	0.90
Dialysis	326.836	0.03	1	0.86
Female	326.876	0.04	1	0.84
CEVD	327.236	0.36	1	0.55
NYHA 2+	327.889	0.65	1	0.42
PVD	328.764	0.88	1	0.35
Lesions > 70%	330.407	1.64	1	0.20
Age	332.477	2.07	1	0.15
Family history of CAD	334.431	2.00	1	0.16
Prior PTCA	336.379	1.95	1	0.16

MI = myocardial infarction; CEVD = cerebrovascular disease; NYHA = New York Heart Association; PVD = peripheral vascular disease; CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty

Table 16 gives the final 30-day mortality model. Left main disease, intra-aortic balloon pump, shock and emergency procedure were the highest contributors to short term mortality. Other factors associated with higher mortality were acute myocardial infarction on admission, chronic obstructive pulmonary disease, renal disease, ejection fraction, and proximal LAD lesions. Current and past smoking, hyperlipidemia and complete revascularization were associated with lower mortality.

Testing the final multivariable model against the full model containing all univariate predictors of 30-day mortality, the $\chi 2$ LR, 12 df = 9.61 $p > 0.25$. The

non-significant likelihood ratio test indicates that the variables that were dropped did not add significantly to the model's predictive power.

Table 16. Final multivariate logistic regression model to predict 30-day mortality

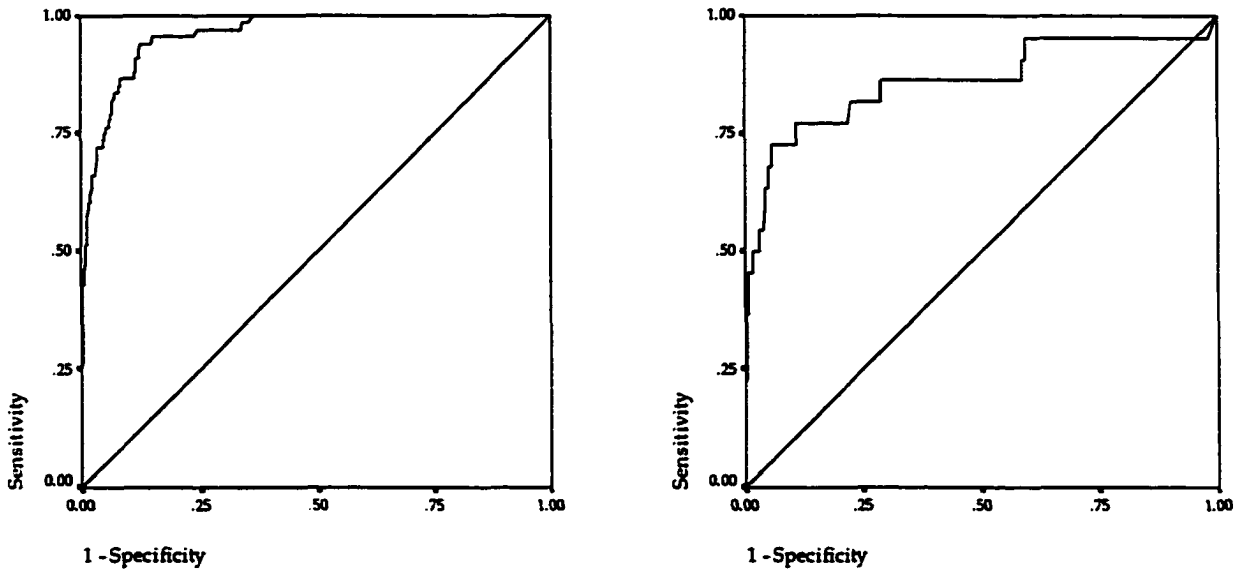
Variable	OR	Lower 95% CI	Upper 95% CI	p-value
AMI on admission	2.69	1.26	5.73	0.01
Cardiogenic shock	4.45	1.70	11.69	<0.01
COPD	2.15	0.94	4.92	0.07
Renal disease	2.69	0.99	7.31	0.05
Hyperlipidemia	0.27	0.12	0.59	<0.01
Current smoker	0.18	0.07	0.46	<0.01
Past smoker	0.42	0.19	0.94	0.04
Ejection Fraction				<0.01
>50%	1.00			
30-50%	2.15	0.59	7.88	0.25
<30%	5.89	1.43	24.19	0.01
Not done	11.47	3.93	33.47	<0.01
Missing	4.81	1.40	16.55	0.01
Proximal LAD	2.21	1.14	4.30	0.02
Left main disease	16.52	5.93	46.01	<0.01
IABP	7.17	1.85	27.85	<0.01
Emergency procedure	4.74	2.35	9.56	<0.01
Complete revasc	0.25	0.12	0.54	<0.01

AMI = acute myocardial infarction; COPD = Chronic Obstructive Pulmonary disease; IABP = intra-aortic balloon pump

The c-statistic of 0.96 (95% CI: 0.94, 0.98) associated with the 30-day mortality model in the development dataset is graphically represented in Figure 11, left panel and that for the test dataset (0.86, 95% CI, 0.76; 0.97) in Figure 11b. The Hosmer-Lemeshow statistic for the development dataset was $\chi 2 = 2.17$, df = 8, p= 0.98 indicating little departure from a perfect fit. The observed versus expected rates of 30-day mortality in the test dataset calculated using the model described

in Table 16 are presented in Table 17. The Hosmer-Lemeshow test statistic was significant (χ^2 = 20.2, 8df, p=0.01) indicating that the model did not fit the data well. This may be due to the infrequency of outcomes in the test dataset.

Figure 11. ROC Analysis for 30-day mortality models. Left panel: development dataset; Right panel: test dataset



Dataset	Area under the ROC curve	95% Confidence Interval	
		Lower	Upper
Development	0.96	0.94	0.98
Test	0.86	0.76	0.97

Table 17. Model Characteristics - Hosmer-Lemeshow goodness of fit test

Group	Observed mortality rate (%)	Expected mortality rate (%)
1	0.65	0.06
2	0.00	0.11
3	0.00	0.18
4	1.27	0.24
5	0.00	0.36
6	0.00	0.50
7	0.65	0.07
8	0.64	1.02
9	0.64	1.92
10	11.59	10.20

Goodness of fit test = 20.2 ($\chi 2$; 8 df; p=0.01)

3.9 MODEL 3. REPEAT PROCEDURE WITHIN ONE-YEAR FOLLOWING PCI

A third and final logistic regression was model developed to identify significant predictors of repeat procedures within one-year following PCI. Only those patients discharged alive from the index hospitalization were eligible for inclusion in these analyses. Also, patients who died within one year without a repeat procedure were excluded from the analyses. This methodology has the potential to bias the results if death consistently preempted repeat revascularization, therefore, sensitivity analyses (described later) were conducted to estimate the impact of this decision. An additional source of bias, mentioned earlier, is the possible under-representation of repeat procedures due to patients undergoing repeat revascularization outside the province of Alberta. Given that the estimate for this under-representation was fairly low (a maximum of 5.6%), no analyses were undertaken to address this bias.

The exclusion of deaths is resulted in a sample size of 3,017 patients in the development dataset, of which 112 (3.7%) had a CABG and 372 (12.3%) had a repeat PCI within one-year. The composite rate of either CABG or repeat PCI among these patients was 15.2 percent (459 patients). In the test dataset 1,516 patients were retained for analysis. Among them 63 patients (4.2%) had a CABG

and 218 (14.4%) had a repeat PCI within a year for a composite rate of 17.7% (269 patients).

There were 67 deaths in the development dataset that occurred after discharge. Of these 60 were among patients who had not undergone a repeat procedure. A sensitivity analysis, assuming all these 60 patients had undergone a repeat procedure was conducted. The impact of this assumption on the associations between predictor variables and the outcome variable is presented subsequently.

3.9.1 Univariate analyses

Univariate associations between baseline variables and the outcome variable in the development dataset are provided in Tables 18 A-E. Unlike the associations between increasing age and both short and long-term mortality, there was no significant relationship between age and repeat procedures. Women were more likely to have repeat procedures than men. Patients with a history of myocardial infarction or congestive heart failure were less likely to have repeat procedures. None of the patients with shock in this population underwent a repeat procedure. Prior PTCA had no impact on the likelihood of repeat revascularization, although prior CABG was positively correlated with repeat procedures within one-year. Unlike the impact on mortality, the presence of comorbid disease did not appear to impact the frequency of repeat procedures.

However, the presence of renal disease and diabetes were associated with higher repeat procedures. The number of lesions with greater than 70 percent stenosis and stenosis in the proximal LAD were positively correlated with adverse outcomes. In contrast, the use of stents and the complete revascularization were protective of repeat procedures among these patients.

Table 17 A. Univariate associations between patient demographic data and stage and severity measures and one-year repeat revascularization using logistic regression (N=3017)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Demographics					
Age			0.99	0.99-1.01	0.57
Sex					
Male	74.9	14.1	1.00	Ref.	
Female	25.1	18.5	1.38	1.11-1.72	<0.01
Heart disease Stage and Severity Measures					
AMI on admission					
No	58.7	16.8	1.00	Ref.	
Yes	41.3	12.9	0.73	0.59-0.90	<0.01
Congestive heart failure					
No	88.6	88.6	1.00	Ref.	
Yes	11.4	14.5	0.94	0.69-1.29	0.71
Cardiogenic shock					
No	99.5	15.3	-	-	-
Yes	0.5	0.0	-	-	
Prior MI					
No	34.6	18.3	1.00	Ref.	
Yes	65.4	13.6	0.70	0.57-0.86	<0.01
Prior PTCA					
No	82.8	15.3	1.00	Ref.	
Yes	17.2	14.6	0.95	0.73-1.24	0.69
Prior CABG					
No	92.1	14.8	1.00	Ref.	
Yes	7.9	20.6	1.50	1.08-2.09	<0.01
NYHA class					
I	98.9	15.2	1.00	Ref.	
II, III, IV	1.1	12.1	0.77	0.27-2.19	0.02
CCS class					0.12
1	2.3	4.4			
2	9.1	15.3	3.91	1.18-13.01	
3	17.2	16.6	4.92	1.32-13.95	
4a	29.5	13.7	3.44	1.06-11.09	
4b	11.4	18.0	4.75	1.45-15.58	
4 c	11.2	14.5	3.68	1.11-12.14	
Not done	19.4	16.2	4.18	1.29-13.56	

AMI = Acute Myocardial Infarction; MI = Myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Graft; NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society

Table 17B. Univariate associations between patient comorbidities and repeat revascularization within one year using logistic regression analysis (N=3017)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Cerebrovascular disease					
No	95.8	15.4	1.00	Ref.	
Yes	4.2	10.3	0.63	0.35-1.13	0.12
Pulmonary disease					
No	91.1	15.1	1.00	Ref.	
Yes	8.9	16.0	1.07	0.76-1.50	0.71
Renal disease					
No	98.4	15.1	1.00	Ref.	
Yes	1.6	24.5	1.83	0.95-3.53	0.07
Diabetes Type I					
No	98.2	15.1	1.00	Ref.	
Yes	1.8	24.1	1.79	0.95-3.37	0.07
Diabetes Type II					
No	83.6	14.7	1.00	Ref.	
Yes	16.4	17.8	1.26	0.97-1.62	0.08
Dialysis					
No	99.1	15.2	1.00	Ref.	
Yes	0.9	21.4	1.53	0.62-3.79	0.36
Lipids					
No	48.0	14.4	1.00	Ref.	
Yes	52.0	15.9	1.12	0.92-1.37	0.25
Hypertension					
No	46.2	15.1	1.00	Ref.	
Yes	53.8	15.3	1.02	0.84-1.25	0.84
Liver/Gastro-intestinal disease					
No	96.2	15.3	1.00	Ref.	
Yes	3.8	13.8	0.89	0.52-1.52	0.66
Malignancy					
No	96.6	15.3	1.00	Ref.	
Yes	3.4	13.6	0.87	0.49-1.55	0.64

Table 17B. Univariate associations between patient comorbidities and repeat revascularization within one year using logistic regression analysis (N=3017)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
PVD					
No	95.1	15.2	1.00	Ref.	
Yes	4.9	14.9	0.97	0.61-1.55	0.90
Family history of CAD					
No	52.5	14.1	1.00	Ref.	
Yes	47.5	16.4	1.19	0.98-1.46	0.08
Current smoker					
No	74.5	15.9	1.00	Ref.	
Yes	25.5	13.3	0.81	0.64-1.03	0.08
Past smoker					
No	68.3	15.5	1.00	Ref.	
Yes	31.7	14.6	0.94	0.75-1.16	0.54
Prior thrombolytic therapy					
No	78.9	15.8	1.00	Ref.	
Yes	21.	13.1	0.80	0.62-1.03	0.09

Table 17C. Univariate associations between left ventricular function and repeat revascularization within one year using logistic regression analysis (N=3017)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
Ejection Fraction					0.69
>50%	52.8	15.8	1.00	Ref.	
30-50%	17.8	13.4	0.83	0.62-1.10	0.18
<30%	2.6	12.8	0.78	0.40-1.54	0.48
Not done	13.0	15.1	0.94	0.69-1.28	0.71
Missing	13.9	15.8	1.00	0.74-1.34	0.99

Table 17D. Univariate associations between cardiac anatomy and repeat revascularization within one year using logistic regression analysis (N=3017)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
# Lesions >70% stenosis			1.21	1.15-1.30	<0.01
Graft					
No	93.3	15.0	1.00	Ref.	
Yes	6.7	18.3	1.27	0.88-1.84	0.20
Proximal LAD					
No	76.9	14.6	1.00	Ref.	
Yes	23.1	17.3	1.23	0.98-1.54	0.08
Left Main disease					
No	97.9	15.0	1.00	Ref.	
Yes	2.1	24.2	1.80	1.00-3.26	0.05

Table 17E. Univariate associations between procedural factors and repeat revascularization within one year using logistic regression analysis (N=3017)

Variable	% patients	%Outcome	OR	CI (95%)	p-value
IABP					
No	99.6	15.2	1.00	Ref.	
Yes	0.4	8.3	0.51	0.07-3.93	0.51
Direct PCI					
No	91.8	15.5	1.00	Ref.	
Yes	8.2	13.0	0.78	0.53-1.15	0.22
Emergent PCI					
No	89.3	18.5	1.00	Ref.	
Yes	10.7	12.4	0.82	0.58-1.15	0.25
Stents					
No	46.3	18.4	1.00	Ref.	
Yes	53.7	11.2	0.63	0.51-0.77	<0.01
Complete revascularization					
No	55.9	23.4	1.00	Ref.	
Yes	44.1	14.6	0.56	0.45-0.69	<0.01
In-hospital cardiac complications					
No	95.7	15.2	1.00	Ref.	
Yes	4.3	14.5	0.94	0.57-1.55	0.82

3.9.2 Multivariable analyses

All variables included in building the multi-variable model to predict repeat procedures within one-year following PCI are presented in Table 18. There was no major shift in odds ratios associated with significant variables from the univariate (Table 17 A-E) to the multivariable context (Table 18). The final model to predict repeat procedures included female sex, prior myocardial infarction on admission, family history of CAD, lesions > 70%, stents and complete revascularization (Table 20). The c-statistic for the model in the development set was 0.639, 95% CI, 0.62, 0.67 (Figure 12, left panel). When the model was imposed on the test dataset the c-statistic was 0.612, 95% CI, 0.57, 0.64. The

Hosmer-Lemeshow goodness of fit statistic, based on observed and expected rates of repeat procedure in the test set (data presented in Table 21) was non-significant ($\chi 2=5.26$, $p=0.73$) indicating that the model fit the data well.

Table 18. Full multivariable model to predict one-year repeat procedures, i.e. including all variables found to be statistically significant in the univariate analyses

Variable	beta	OR	Lower 95%	Upper 95%	p-value
Sex	0.31	1.36	1.09	1.70	<0.01
A MI on admission	-0.05	0.95	0.72	1.26	0.75
Prior MI	-0.41	0.66	0.50	0.87	<0.01
Prior CABG	-0.03	0.97	0.65	1.44	0.87
Renal disease	0.39	1.47	0.74	2.94	0.27
Diabetes Type I	0.44	1.56	0.80	3.04	0.19
Diabetes Type II	0.03	1.03	0.78	1.35	0.83
Family history of CAD	0.23	1.26	1.03	1.54	0.03
Current smoker	-0.11	0.90	0.70	1.15	0.40
Prior lytic therapy	0.04	1.04	0.79	1.38	0.77
Lesions > 70% stenosis	0.17	1.19	1.10	1.29	<0.01
Stent	-0.49	0.61	0.50	0.75	<0.01
Complete revasc.	-0.38	0.69	0.55	0.86	<0.01
Proximal LAD	0.15	1.16	0.91	1.48	0.24
Left main disease	0.17	1.18	0.61	2.31	0.62
Constant	-1.67				

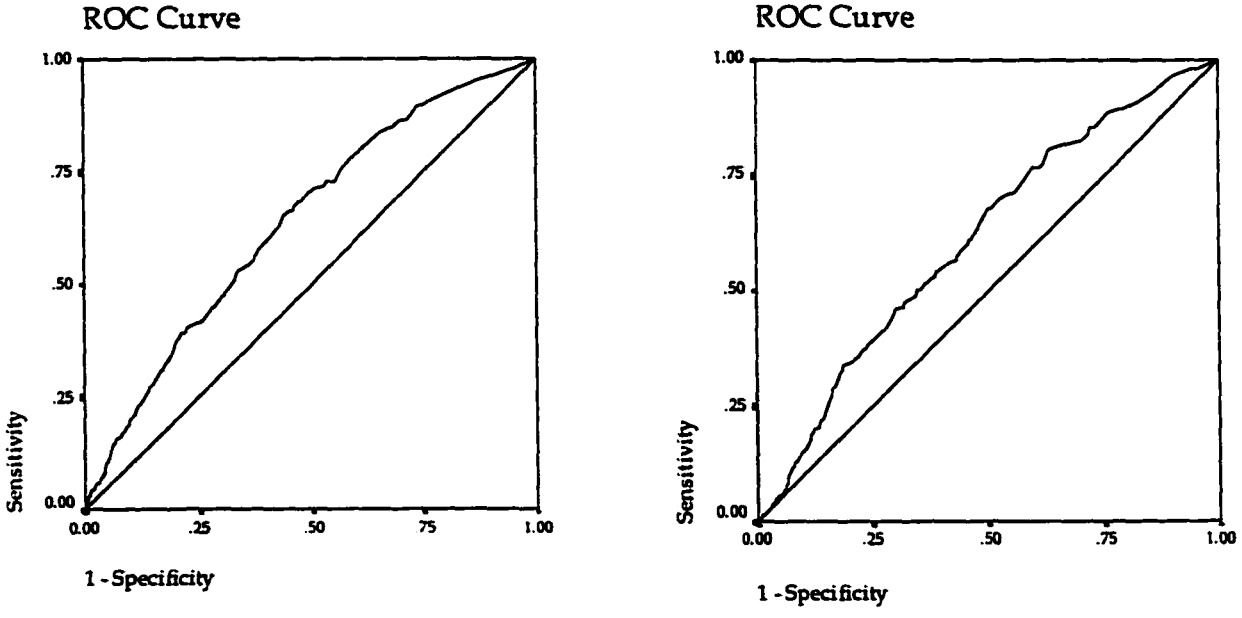
Table 19. Model building process using backward stepwise logistic regression

Variable	-2Log Likelihood	Likelihood ratio test statistic	df	p-value
Constant	2572.895			
Full model (Table 18)	2466.768	106.127	15	<0.01
Prior CABG	2466.795	0.027	1	0.87
Diabetes Type II	2466.838	0.043	1	0.84
Prior Thrombolytic tx	2466.925	0.087	1	0.77
AMI on admission	2466.988	0.063	1	0.80
Left main disease	2467.201	0.214	1	0.64
Current smoker	2467.968	0.766	1	0.38
Renal disease	2469.158	1.190	1	0.28
Proximal LAD	2470.538	1.381	1	0.24
Diabetes Type I	2472.316	1.778	1	0.18

Table 20. Final multivariate model to predict one-year repeat procedures

Variable	beta	OR	Lower 95% CI	Upper 95% CI	p-value
Sex	0.32	1.37	1.10	1.71	<0.01
Prior MI	-0.44	0.65	0.52	0.80	<0.01
Family history of CAD	0.22	1.24	1.02	1.52	0.04
Lesions > 70%	0.19	1.21	1.13	1.30	<0.01
Stent	-0.49	0.62	0.50	0.76	<0.01
Complete revasc.	-0.38	0.69	0.55	0.86	<0.01
Constant	-1.67				<0.01

Figure 12. ROC Analysis for one-year repeat procedures. Left panel: development dataset; Right panel: test dataset



Dataset	Area under the ROC curve	95% Confidence Interval	
		Lower	Upper
Development	0.65	0.62	0.67
Test	0.61	0.57	0.64

Table 21. Model Characteristics HosmerLemeshow goodness of fit test

Group	Observed repeat procedure rate (%)	Expected repeat procedure rate (%)
1	8.9	10.5
2	11.3	12.5
3	12.0	13.7
4	19.1	14.8
5	15.1	16.0
6	15.2	17.5
7	20.4	19.2
8	22.3	20.8
9	26.0	23.2
10	26.1	29.7

Goodness of fit test = 5.26 (χ2; 8 df; p=0.73)

3.9.3 Sensitivity analyses

Univariate associations (based on data in the development dataset) between predictor variables and the outcome (repeat procedures within one-year) after assuming that all patients who died without repeat procedures (N = 60) had undergone repeat revascularization are presented in Table 22. In general, there are no dramatic changes in the associations, however the associations between chronic pulmonary obstructive disease and dialyses achieve statistical significance indicating that the frequency of these factors are likely to have been high among patients who died.

Table 22. Impact of assuming all patients who died post-discharge underwent a repeat procedure on univariate associations (based on logistic regression)

	Removing deaths (Table 17 A-E)		Treating Deaths as Repeat procedures	
Variable	OR	p-value	New OR	p-value
Sample size				
Demographics				
Age	0.99	0.57	1.01	0.24
Female	1.38	<0.01	1.39	<0.01
AMI on admit	0.73	<0.01	0.74	<0.01
CHF	0.94	0.71	1.24	0.13
Cardiogenic shock	-	-	0.70	0.64
Prior MI	0.70	<0.01	0.74	<0.01
Prior PTCA	0.95	0.69	0.90	0.40
Prior CABG	1.50	0.02	1.46	0.02
NYHA class	0.77	0.62	0.69	0.47
CCS class		0.12		0.24
CEVD	0.63	0.12	0.91	0.71
COPD	1.07	0.71	1.52	0.07
Renal disease	1.83	0.07	2.45	<0.01
Diabetes Type I	1.79	0.07	2.08	0.01
Diabetes Type II	1.26	0.08	1.36	0.01
Dialysis	1.53	0.36	2.73	<0.01
Lipids	1.12	0.25	1.03	0.73
Hypertension	1.02	0.84	1.02	0.87
Liver/GI	0.89	0.66	1.04	0.88
Malignancy	0.87	0.64	1.11	0.67
PVD	0.97	0.90	1.27	0.24
Family history of CAD	1.19	0.08	1.12	0.23
Current smoker	0.81	0.08	0.86	0.20
Past smoker	0.94	0.54	0.95	0.62
Prior lytic therapy	0.80	0.09	0.83	0.13
Ejection Fraction				0.91
Lesions > 70%	1.21	<0.01	1.21	<0.01
Graft	1.27	0.20	1.18	0.38
Proximal LAD	1.23	0.08	1.26	0.04
Left main disease	1.80	0.05	2.02	0.01
IABP	0.51	0.51	0.90	0.89
Direct PCI	0.78	0.22	0.87	0.45
Emergent PCI	0.82	0.25	0.93	0.62
Stents	0.63	<0.01	0.68	<0.01
Complete revasc.	0.56	<0.01	0.55	<0.01

4. DISCUSSION

In this population-based cohort study of mortality and repeat procedures within one-year of PCI, 4695 Alberta residents who underwent PCI between July 1, 1995 and December 31, 1997 were included. Models to predict 30-day and one-year mortality, and one-year repeat procedures, were developed on a randomly selected two-third of the study population and validated on the remaining third.

Table 23 provides a summary of the factors found to be significant predictors of the three outcomes of interest and the statistics describing the models' performance in the development and test databases.

As mentioned before, there was considerable overlap between predictors of 30-day mortality and one-year mortality. The presence of cardiogenic shock, chronic obstructive pulmonary disease, renal disease, low ejection fraction, proximal LAD lesions, left main disease, intra-aortic balloon pump and emergency procedure were associated with both short and long-term mortality.

Age, congestive heart failure, malignancy and peripheral vascular disease were associated with one-year mortality, while acute myocardial infarction on admission had more short-term consequences.

Table 23. Summary of significant predictors of 30-day and one-year mortality and repeat procedures within one-year

Variables	One-year mortality model	30-day mortality model	Repeat revascularization model
Demographics			
Age	+		
Female sex			+
Heart disease stage and severity			
AMI on admission		+	
CHF	+		
Cardiogenic shock	+	+	
Prior MI			-
Prior PTCA			
Prior CABG			
NYHA class 2+			
CCS class			
Comorbidities			
CEVD			
COPD	+	+	
Renal disease		+	
Dialysis	+		
Diabetes Type I			
Diabetes Type II			
Hyperlipidemia	-	-	
Hypertension			
Liver/GI disease			
Malignancy	+		
PVD	+		
Family hx of CAD			+
Current smoker		-	
Past smoker		-	
Prior thrombo. Tx			

Table 23. Continued

Variables	One-year mortality model	30-day mortality model	Repeat revascularization model
Coronary anatomy and LV function			
Ejection fraction	+	+	
# lesions>70%	-		+
Graft			
Proximal LAD	+	+	
Left main disease	+	+	
Procedural factors			
IABP	+		
Direct PCI		+	
Emergent PCI	+	+	
Stents			-
Complete revasc	-	-	-
Model performance			
c-statistic (D)	0.87	0.96	0.65
c-statistic (T)	0.78	0.86	0.61
H-L statistic (D)	5.20 p=0.74	2.17 p=0.98	7.13 p=0.52
H-L statistic (T)	13.53 p=0.09	20.2 p=0.01	5.26 p=0.73

CHF = Congestive heart failure; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; IABP = Intra aortic balloon pump; CAD = coronary artery disease; revasc = revascularization; D = development dataset; T = test dataset.

Complete revascularization was protective of both short and long-term mortality. This relationship is intuitive, i.e., the more successful the procedure is in removing the stenoses, the less likely the patient is to die. A relationship that is less intuitive is the inverse association between the presence of hyperlipidemia and 30-day and one-year mortality. A purely speculative hypothesis to explain this finding is that identification of hyperlipidemia implies treatment for it and

therefore patients treated with lipid lowering agents are in fact less like to suffer an adverse event than those not being treated.

The paradoxical positive effects of current and past smoking have been documented before. Barbash, et al showed better outcomes of 17,507 current and 11,117 past smokers compared to 11,975 non-smokers in the GUSTO-1 study [26]. Smokers were younger at the time of presentation than non-smokers which may have accounted, in some part, for their better outcomes, however, even after adjusting age and sex, the odds of 30-day mortality was lower for smokers than non-smokers. The authors hypothesized that the outcomes may be due to lesser extent of coronary disease and better patency (TIMI grade 3 flow) in smokers compared to non-smokers. A possible, though purely speculative, explanation for these results is selection bias. The selection of only the healthiest smokers to undergo revascularization may account for the positive outcomes in this patient population.

As mentioned before, the other surprising finding is that of the number of lesions with greater than 70% stensosis being associated with *lower* long-term mortality. One possible explanation for this finding is that the higher risk associated with severe multi-vessel disease, noted in previous studies [7], was accounted for by the proximal LAD and left main disease variables, and to some extent the cardiogenic shock variable. PCI procedures may have been more successful in addressing lesions in other vessels, thereby showing a positive relationship.

The c-indices associated with the multivariate prediction models developed for 30-day and one-year mortality were high in both the development as well as test datasets reflecting a good ability to discriminate between patients who did and did not die. The non-significant Hosmer-Lemeshow $\chi 2$ goodness-of-fit test statistics, other than for the 30-day model in the test dataset, indicate that the models were well calibrated. The significant Hosmer–Lemeshow statistic for the 30-day model in the test dataset may have been a result of the low frequency of the outcome (22/1516).

Female sex, family history of coronary artery disease, and increasing number of lesions with greater than 70% stenosis were positively associated with repeat revascularization, while, a history of myocardial infarction, use of stents and complete revascularization were associated with lower rates of repeat procedures. The greater need for repeat revascularization among females may be due to physiological factors, such as restenosis in smaller vessels. The opposing influences on the extent of multi-vessel disease and complete revascularization on the need for repeat procedures is fairly intuitive. The negative association between prior myocardial infarction and repeat procedures may be due to the fact that these patients have a higher disease severity and are therefore medically managed.

The c-statistic associated with the repeat model in the development dataset was 0.65 and in the test dataset it was 0.62. There can be several explanations for the

lower c-statistics associated with these models (compared to the mortality models). Unlike mortality which is considered a "hard-endpoint" and can be explained to a large extent by the nature and extent of disease, several exogenous factors may play a role in determining whether a patient undergoes a repeat revascularization procedure. For example, the features of the health care system may effect the utilization of intervention procedures. In fact, several studies comparing practice patterns have found that the United States is a more aggressive user of intervention procedures compared to Canada [27-29]. Other factors that may play a role are patient and physician preferences.

Comparison with other studies. The most recent study in the post-stenting era involving multivariate prediction of in-hospital mortality after PCI is by O'Connor et al from the Northern New England (NNE) Cardiovascular Disease Study Group [8]. In a study of 15,331 PCI procedures performed at six clinical centers between 1994 and 1996, the authors found older age, congestive heart failure, peripheral or cerebrovascular disease, increased creatinine levels, lower ejection fraction, urgent priority, emergent priority, pre-procedure insertion of an intra aortic balloon pump and PCI of a type C lesion, to be associated with an increased risk of in-hospital mortality.

Ellis et al from the Cleveland Clinic (CC) analyzed data on 12,985 consecutive PCI patients between 1993 through 1995 and found the log of patient age in

years, cardiogenic shock, treatment for acute MI, lesion complexity, female sex, and the number of diseased vessels to be correlates of in-hospital death [30].

Both the NNE model and the CC model had good discriminatory powers. The c-index associated with the NNE model was 0.88 and with the CC model was 0.85. Moscucci and colleagues compared the performance of these models on an independent high-risk patient population (N=1,476) who underwent procedures between July 1, 1994 and June 1, 1996 and found the models to be comparable in their ability to predict in-hospital mortality [9]. As part of the study, the authors also developed a separate model fit to the patient population and found the following variables to be significant predictors of in-hospital mortality: emergency procedure, age, female gender, cardiogenic shock, number of diseased vessels, congestive heart failure and creatinine level > 2 mg/dl.

In a classic study of development and validation of a simplified predictive index of major complications in PTCA practice, Kimmel et al used data collected as part of the Registry of the Society for Cardiac Angiography and Interventions [7]. Major complication was defined as a composite of emergent coronary artery bypass surgery, myocardial infarction of death. The model was developed on 10,622 patients in 1992 and validated on 10,030 patients in 1993. The components of the predictive index were aortic valve disease, left main coronary angioplasty, shock, acute myocardial infarction within 24 hours before coronary angioplasty,

multi-vessel disease and unstable angina. The model's c-index in the development data set was 0.71 and in the validation data set was 0.65.

In a study based on population-based registry data on all angioplasties performed in New York in 1991, Hannan et al found female gender, hemodynamic instability, shock and ejection fraction to be significant predictors of in-hospital mortality [3]. The c-index for the model was 0.88, however, no external validation of the model was conducted.

The current study's 30-day mortality model based on the APPROACH data is comparable to previously published models both in terms of the predictors identified and in the model's performance.

The current study's one-year mortality model is the first to be developed (and validated) using population-based data in the post-stenting era. However, Mick et al's study examined long-term (4.1 ± 1.9 years) survival of 5000 patients who underwent coronary angioplasty between 1980 and 1988. Their study found male gender, age, extent of disease, CCS classification, diabetes mellitus, congestive heart failure, hypertension, and previous PTCA to be significant predictors of long-term survival [6]. Several of these predictors (age, congestive heart failure, proximal LAD, and left main disease) were found to be significant in the current study.

There are no studies in the current literature identifying predictors of repeat revascularization within one year of PCI. This is not surprising given the limitations mentioned previously. However, there is considerable evidence to support one of the key findings of the repeat revascularization model, i.e. the association between stent use and the reduced need for repeat revascularization. At least in the context of clinical trials, this relationship is well-documented [31-34].

APPENDIX I

Crosswalk between ICD-9-CM codes and Clinical variables in APPROACH

Variable	ICD-9-CM
Cerebrovascular disease	430-438
Congestive heart failure	428
Pulmonary disease	490-496, 500-505, 5064
Renal disease	584, 582, 583.0-583.7, 585, 586, 588
Diabetes Type 1	250.0-250.9 with 5th digits 1 & 3
Diabetes Type 2	250.0-250.9 with 5th digits 0 & 2
Dialysis	V42.0, V45.1, V56.0, V56.1, V56.8 OR procedure 39.27, 39.42, 39.93-39.95, 54.0
Hyperlipidemia	272.0-272.4
Hypertension	401-405
Prior CABG	V45.81
Prior PTCA	V45.82
Prior infarction	410, 412
Prior thrombolytic therapy	E934.4
Liver/Gastrointestinal disease	456.0-456.21, 572.2-572.8, 571.2, 571.4-571.49, 571.5, 571.6, 531-534
Malignancy	140-172, 174-208
Peripheral vascular disease	441, 443.9, 785.4, V43.4

Appendix II – List of Mortality Causes

Total deaths		176
In-hospital mortality		75
Out-of-hospital mortality		101
ICD-9-CM	Description	N
Cardiac Related		
410	Acute Myocardial Infarction	21
414.0	Coronary artherosclerosis	16
414.8	Other forms of chronic ischemic heart disease	1
414.9	Chronic heart disease unspecified	17
416.0	Chronic pulmonary heart disease	1
427.1	Paroxysmal ventricular tachycardia	1
427.4	Ventricular fibrillation and flutter	1
427.5	Cardiac arrest	2
428.0	Congestive heart failure	1
429.2	Cardiovascular disease unspecified	3
746.4	Congenital insufficiency of aortic valve	1
Cardiac aggravated		
486	Pneumonia, organism unspecified	1
431	Intracerebral hemorrhage	3
436	Acute but ill defined cerebrovascular disease	1
496	Chronic airway obstruction not elsewhere classified	1
250.0	Diabetes mellitus	1
250.6	Diabetes with neurological manifestations	1
403.9	Hypertensive renal disease unspecified	1
434.9	Cerebral artery occlusion, unspecified	1
437.0	Other and ill defined cerebrovascular disease	1
443.9	Peripheral vascular disease unspecified	1
Non-cardiac related		
185	Malignant neoplasm of the prostate	1
389	Hearing loss	1
162.9	Bronchus and lung unspecified	5
199.1	Malignant neoplasm without specification of site	2
202.8	Other lymphonas	1
335.2	Motor neuron disease	1
356.8	Other specified idiopathic peripheral neuropathy	1
557.9	Unspecified vascular insufficiency of intestine	1
812.0	Fracture of hummerus	2
812.9	Fracture of hummerus	1
955.4	Injury to peripheral nerves of shoulder	1
Missing		7

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CHAPTER 6: IMPACT OF SECONDARY PREVENTION ON ADVERSE EVENTS WITHIN ONE-YEAR FOLLOWING PCI

1. INTRODUCTION

Given the progressive nature of coronary artery disease, its treatment cannot be episodic and should incorporate a continuum of care. Agreement with this philosophy has led to the establishment of patient education programs focusing on secondary prevention of CAD at most cardiac care centres in North America. However, a quantitative assessment of the impact of close monitoring to ensure appropriateness and compliance with prescribed medical therapy among patients undergoing percutaneous coronary intervention has not been documented. The Enhancement of Secondary Prevention in Heart Disease Study (ESP study) provided a unique opportunity to examine the association between the use and compliance with secondary prevention strategies and adverse outcomes within one-year following PCI.

This study in an extension of the previous study (Chapter 5) and incorporates factors associated with the post-discharge time-period in the evaluation of outcomes. The study patients (described in detail in the next section) are a subset

of the previous study's patients who were enrolled in the ESP study and for whom secondary prevention data are available.

The current study has several objectives. The first is to compare baseline, clinical, procedural and outcome variables of the subset of patients in the ESP study (from now on referred to as ESP-APPROACH patients) to those patients in the APPROACH database who underwent PCI during a similar time period but were not included in the study (from now on referred to as the non-ESP APPROACH patients). The similarities or differences in these patient populations have implications for the generalizability of the results found in the ESP subset to non-study patients. The second objective is to document prescription patterns, healthcare resource utilization and compliance patterns among ESP patients. And the third, and most important, objective is to examine the effect of secondary prevention therapies, intense surveillance, and compliance on adverse outcomes among study patients.

2. METHODS

A description of the ESP project and data collection is presented in Chapter 4. Briefly, the ESP study, conducted at the Foothills Hospital in Calgary, was a quality improvement program that was designed to determine if appropriate prescription of and compliance with a secondary prevention regiment makes a

significant difference in patient outcomes and total medical care costs [1]. Patients were randomized according to their attending cardiologist into the enhanced care (interventional) arm or the usual care (non-interventional) arm. Approximately 30 cardiologists work at Foothills Hospital and 15 were assigned to each arm. The reason for randomizing cardiologists rather than patients was to prevent "contamination". If a cardiologist was overseeing the care of patients in both treatment arms, it may inadvertently influence his/her usual care practice.

In addition to their usual care, enhanced care patients received follow-up telephone calls from nurse coordinators at one week, one month and every three months following hospital discharge. During these encounters, medication profiles were reviewed for appropriateness and patient compliance was recorded. Several interventions, such as medication classes, medication information on video, and individualized medication counseling sessions were available for patients in the intervention arm. At discharge, the intervention arm patients received a summary letter to the patient's physician and pharmacy listing information on the hospital stay, past medical history and drug related problems. Nurse coordinators were accessible to intervention patients to discuss problems or concerns at any point in the follow-up. In contrast, the non-intervention arm patient was asked to mail, fax or e-mail completed

questionnaires on health services utilization and medication compliance at scheduled intervals.

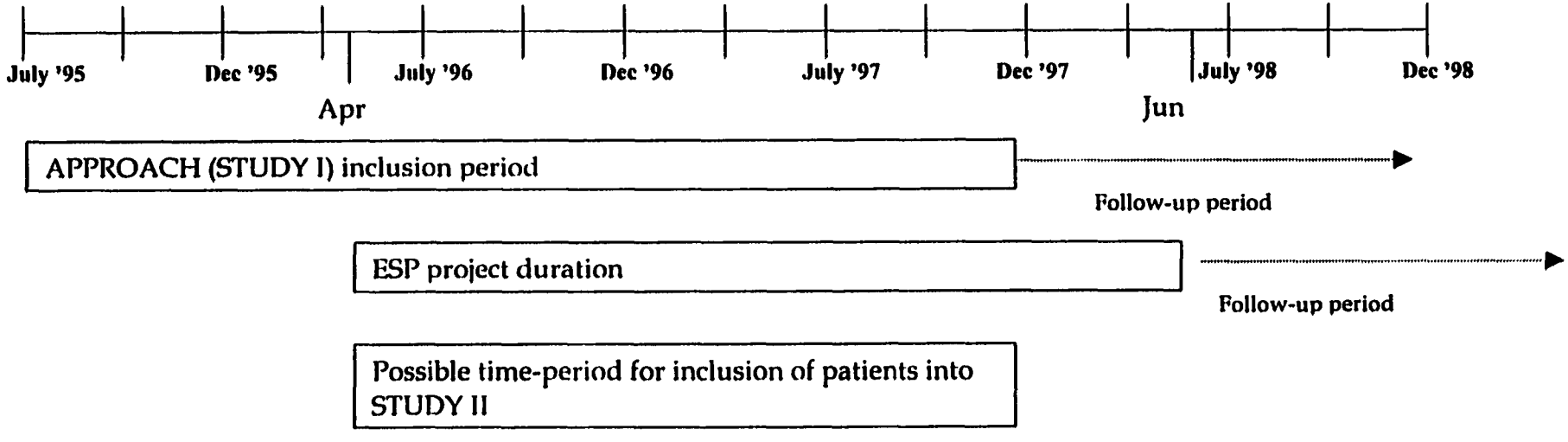
2.1 Patient population: ESP Project

Patients living within the Calgary Region Health Authority boundaries who were admitted to the Foothills Hospital with proven coronary artery disease were eligible for inclusion into the study. Patients with poor English, mental incompetence or terminal illness were excluded, as were patients who were transferred from out of region hospitals, transplant cases, nursing home patients, deaf or blind and living alone, inaccessible for follow-up and who had not consented. Enrollment in the ESP project took place between April 1996 and June 1998. Patients were followed up through December 1999. A total of 2,930 patients were enrolled in the ESP study of whom 1,417 (48%) were in the intervention arm.

2.2 Current Study Population

Figure 1 is a pictorial representation of the overlap between patients enrolled in the APPROACH database (Study I/Chapter 5) and the ESP project. The APPROACH dataset containing data on Alberta residents who underwent PCIs

Figure 1. Time-period for APPROACH and ESP Projects



between July 1, 1995 and December 31, 1997 was merged with the ESP database using the unique patient health insurance number available in both datasets.

In order to satisfy the study objectives, i.e. examine the impact of secondary prevention strategies on future adverse events, it was necessary that the patients' enrollment into ESP coincide with their index PCI in APPROACH. Therefore, patients who were enrolled into the ESP study during the same hospitalization as the index PCI in the APPROACH database, i.e. the ESP study enrollment date fell between the admission date and discharge date of the hospitalization during which the PCI procedure was performed, were included in the current study.

2.3 Outcome of interest

The generally low mortality rate among PCI patients translated into too few deaths in the ESP patient population (8/425) to allow any meaningful statistical analyses. Therefore, the study examined the more frequent outcome of repeat revascularization (that is either repeat PCI or CABG) within one year following the index PCI.

2.4 Comparison of ESP-APPROACH patients to non-ESP APPROACH patients

All demographic, clinical and outcome related data used in the analyses, other than those pertaining to medication and compliance, were from the APPROACH database. Although similar data pertaining to patient demographics and clinical profile were collected as part of the ESP project, APPROACH data were used to maintain consistency with the previous study.

Baseline characteristics and outcomes of the final sample of ESP patients were examined. Chi-square tests (for categorical variables) and t-tests (for continuous variables) were used to compare the baseline characteristics and outcomes of the ESP-APPROACH patients with the non-ESP APPROACH patients (Study 1 patient population) in order to assess their representativeness. As described before, Study 1 included patients who had undergone a PCI between July 1, 1995 and December 31, 1997. In order to control for any temporal changes, a second set of comparisons between patients in the ESP study and non-ESP APPROACH patients who underwent PCI during the exact same time-period as the ESP patients (April 18, 1996 - December 22, 1997) was conducted.

Patients would have to be discharged alive in order to be eligible for inclusion into ESP, therefore patients who died in-hospital were excluded from the comparison (non-ESP APPROACH) groups.

2.5. Kaplan-Meier Analysis

Kaplan-Meier analyses were used to compare survival free of repeat revascularization within one year of PCI between patients enrolled in the ESP project and the rest of the APPROACH patient population. Kaplan-Meier curves are a plot of the survival probabilities, or the probability that a patient will survive past a specified time [2]. Given that the study was focussed on events occurring within one-year of the index PCI, survival time was right-censored at 365 days. The log-rank statistic was used to compare whether the survival curves for the ESP-APPROACH patients and the non-ESP APPROACH patients were statistically equivalent. The log-rank test is a chi-square test that compares observed and expected events over a specified time period.

It should be noted that the limitation of under-representation of repeat procedures due to patients leaving the province to undergo repeat cardiac procedures mentioned in the previous study is applicable to this study as well.

2.5.1 Treatment of deaths

Survival times for patients who died without undergoing a repeat revascularization procedure were censored at the time at which the death occurred. However, death can be assumed to be a non-random event in this

population and could have preempted revascularization. Data were reanalyzed under the assumption that all patients who died would have had a repeat procedure. The date of death was used as the date of the assumed revascularization. This sensitivity analysis was conducted to provide a measure of the lower bound of the difference in survival free of repeat revascularization between ESP-APPROACH patients and non-ESP APPROACH patients.

2.6 Descriptive information on intervention and non-intervention ESP patients

2.6.1 Survival free of repeat revascularization

The ESP patient population was categorized according to intervention and non-intervention status. Baseline characteristics and outcomes between the two arms were examined for statistically significant differences. Kaplan-Meier survival curves, depicting survival free of repeat events, were generated for three sets of patients: ESP patients in the intervention arm; ESP patients in the non-interventional arm; and non-ESP APPROACH patients. Again, log-rank statistics, were used to compare each curve with the other.

There were a total of eight deaths in the ESP study population, of which six occurred among patients who did not have a repeat procedure. The six deaths were evenly divided (three each) in the intervention and non-intervention arm. These patients were censored at the time of death. Due to the low frequency of

deaths, sensitivity analysis assuming that the patients who died had all undergone repeat revascularization was deemed to be unnecessary.

2.6.2 Discharge Medications

The frequencies with which patients in both the intervention arm and the non-intervention arm were discharged on ACE inhibitors, beta-blockers, aspirin, lipid lowering agents and warfarin were calculated and compared using chi-square tests. Bivariate associations between prescription of medications (assuming complete compliance) and the outcome (repeat revascularization within one-year) were analyzed using Cox proportional hazard models. The non-intervention arm could be considered to be representative of usual practice and therefore, the association between discharge medications and repeat revascularization was recalculated using only the non-intervention arm patients.

In addition, preliminary analyses regarding "appropriateness" of medications were conducted. These included the following: 1) examining how many congestive heart failure patients were discharged on ACE Inhibitors; 2) how many hyperlipidemic patients were discharged on lipid-lowering agents; and 3) how many hypertensive patients were discharged on beta-blocker therapy.

2.6.3 Follow-up data

As mentioned previously, as part of the study, patients were asked to complete follow-up questionnaires at one week, one month, and every three months following discharge from the hospitalization during which the enrollment took place. For the intervention arm the questionnaires were completed via telephone calls by nurse coordinators. Non-intervention patients were asked to mail their surveys at regular intervals. Each contact was called an "encounter". The follow-up questionnaires contained questions on overall utilization such as the number of physician visits (family and cardiologist) and hospitalizations as well as data on medication changes and compliance post-discharge (See Appendix II of Chapter 4 for a copy of the questionnaire).

The follow-up questionnaire data were used to calculate the duration of follow-up and the median number of encounters for the intervention and the non-intervention patients. Medians were used in the event that the distribution of encounters was not normally distributed. Mann-Whitney tests were used to compare medians between the two groups.

Given that the period of interest was one year, the same analyses, i.e. median follow-up and encounters, were conducted for encounters that occurred within one-year of enrollment into ESP.

2.6.4 Compliance data

One-year compliance with medication use was calculated for all patients using patient reported data from follow-up questionnaires. Patients were categorized into three groups: 1) those who were not prescribed a particular medication at discharge or at any other point in the follow-up period; 2) patients who had been prescribed a particular medication and had been 100% compliant during the follow-up period; and 3) patients who had been prescribed a particular medication but had been non-compliant at any point during the follow-up period. The definition of non-compliance was therefore extremely stringent and included patients who were non-compliant even once during the follow-up period.

Differences in prescription and compliance rates between intervention arm patients and non-intervention arm patients were examined using chi-square tests and univariate Cox proportional hazard models were used to measure associations between one-year compliance and the outcome of survival free of repeat revascularization within one-year. Interactions between compliance and intervention and their impact on one-year outcomes were also examined.

It should be noted that the compliance data have several limitations. They are patient reported and are therefore subject to recall and reporting biases. The categorization of patients into "compliant" and "non-compliant" groups

(described above) was extremely stringent which may bias the results towards the null.

2.7 Univariate and Multivariable analysis using the Cox Proportional Hazards Model

The Cox proportional hazard model is used to assess the relationship between multiple explanatory variables and survival time. Like Kaplan-Meier analysis, the Cox proportional hazard model allows for censoring.

The measure of effect in the Cox proportional hazard model is the hazard ratio, which is equal to the exponential of the regression coefficient of the variable in the model. The hazard ratio is interpreted in a similar manner to the odds ratio in the context of logistic regression: a hazard ratio of one implies no effect, and that of 0.1 can be interpreted as the treatment arm having one-tenth the hazard of the non-treatment arm.

2.7.1 Proportionality assumption

In the Cox model the hazard at time t is a combination of the baseline hazard function and the exponential of the linear sum of the effects of a collection of predictor variables [3, 4]. The formula is written as follows:

$$h(t, X) = h_0(t)e^{\sum_{i=1}^{p} \beta_i X_i}$$

where $X = (X_1, X_2, X_3, \ldots X_p)$ is the vector of explanatory/predictor variables

As the formula indicates, the baseline hazard is a function of time, however, the exponential expression does not include time. Therefore, the Cox model assumes that the predictor variables are time-independent.

Before running univariate Cox regression models to examine the association between each baseline and procedural variable and repeat revascularization, the proportionality assumption was assessed. There are several methods of examining whether variables are time-independent, however, the most popular approach of graphically examining the log minus log (LML) survival curves was used. If the curves were equidistant for patients with the risk factor and those without it, the variable was considered to have met the proportional hazard assumption.

If the curves were not equidistant, several options were considered. In the case of categorical variables, transformations of the variables, i.e. regrouped categories were examined. Dichotomous variables, which did not meet the proportional hazard assumption due to their very low frequency were considered to be ineligible for inclusion in the Cox proportional hazard model. In the case of variables that were not infrequent and were felt to be particularly relevant to the analyses, a special form of the Cox model for time-dependent

covariates, called the extended Cox model containing a "Heaviside function" was used.

2.7.2 Time-dependent covariates

When the hazard ratio associated with a particular variable was not constant over time, the variable was considered time-dependent. One way to deal with such variables is to include a "Heaviside function" which yields constant hazard ratios for different time intervals [2]. For example, a variable X_1 that appears to behave differently after an initial 30-day period can be modeled as follows:

$$h(t,\ldots) = h_0(t)\exp[\beta_1 X_1 + \beta_2 X_2 + \ldots + \delta X_1 g(t)]$$

where

$$g(t) = \begin{cases} 1 \text{ if } \geq 30 \text{ days} \\ 0 \text{ if } < 30 \text{ days} \end{cases}$$

All variables found to meet the Cox proportional hazard model assumptions and were statistically significant at the $p < 0.20$ level in the univariate analyses were included in a multivariable survival model. Backward stepwise regression technique was used to systematically remove variables that were found to be non-significant in the multivariable context. At each step the reduced model without the variable was compared to the model with the variable using the likelihood ratio test.

3. RESULTS

The merge of the 4,695 patients with PCIs between July 1995 and December 1997 in the APPROACH database and the 2,930 patients enrolled in the ESP study between April 1996 and June 1998 resulted in 857 matches. Of these 857 patients, for 425 (50%) patients, the enrollment date into ESP occurred between the admission date and discharge date of the hospitalization during which they underwent the index PCI procedure. These patients were retained for further analyses.

3.1 ESP-APPROACH Patients compared to Non-ESP APPRAOCH patients

Table 1 provides the baseline characteristics of the ESP study patients and all APPROACH patients (Study 1 patient population). Seventy-five non-ESP APPROACH patients (2%) who died in hospital were excluded from the comparison group as they would not have been eligible for enrollment into the ESP study.

Comparisons of baseline and procedural characteristics of the 425 patients in the study to the 4195 patients in the APPROACH database who were not enrolled in the ESP study reveal some significant differences between the two patient

populations (Table 1). The current study's patients had a higher rate of acute myocardial infarction on admission, and more severe disease as indicated by the increased frequency of prior myocardial infarction and higher CCS classification. Pulmonary disease, hyperlipidemia and malignancy were more prevalent in the ESP study population. These patients were also more likely to have a family history of coronary artery disease, be current smokers, and have received thrombolytic therapy at a prior time. Patients in the ESP study were more likely to have undergone direct or emergent PCI. A significantly higher percentage of the study patients (74% compared to 52%) had PCIs that included stents. This may be due to two factors: 1) these patients underwent procedures in 1996 and 1997 (as opposed to 1995) by which time the frequency of stent use had increased dramatically, and 2) these are all Foothills Hospital Patients which had higher rates of stent use compared to other hospitals that performed PCI in Alberta (See data presented in Chapter 5).

In order to control for temporal changes accounting for the differences between these populations, a second analysis, restricting the non-ESP APPROACH patients to those who underwent PCI during the exact time-period as the ESP-APPROACH patients was conducted. The results of the comparisons between these two groups are presented in Table 1a.

Table 1. Comparison of baseline characteristics between all APPROACH patients and those enrolled in the ESP project.

Variable	APPROACH	ESP	p-value
Sample size	4195	425	
Demographics			
Age	61.5	60.7	0.144
Sex			0.009
Male	74.9	68.9	
Female	25.1	31.1	
AMI on admission	38.6	59.8	<0.001
Congestive heart failure	11.9	13.9	0.241
Prior MI	63.3	76.9	<0.001
Prior PTCA	16.9	17.6	0.684
Prior CABG	7.7	6.8	0.630
NYHA 2+	1.3	0.0	0.013
CCS class			<0.001
1	2.3	1.4	
2	9.3	5.2	
3	17.2	12.7	
4a, b, c	50.5	71.8	
Other	20.8	8.9	
Comorbidities			
Cerebrovascular disease	4.6	5.4	0.398
Pulmonary disease	8.8	12.2	0.027
Renal disease	2.0	0.9	0.186
Diabetes Type I	2.0	0.7	0.085
Diabetes Type II	15.9	19.5	0.062
Dialysis	1.1	0.2	0.320
Hyperlipidemia	51.3	59.8	0.001
Hypertension	53.6	55.1	0.610
Liver/GI disease	4.1	5.2	0.307
Malignancy	3.3	6.1	0.006
PVD	5.4	6.4	0.433
Family history of CAD	45.8	58.8	<0.001
Current smoker	25.4	32.9	0.001
Past smoker	31.7	34.1	0.300
Prior thrombolytic therapy	19.6	32.9	<0.001

Table 1. Continued.

Variable	APPROACH	ESP	p-value
Sample size	4195	425	
Ejection Fraction			<0.001
>50%	51.3	67.3	
30-50%	17.4	16.5	
<30%	2.7	3.1	
Not done	13.8	11.3	
Missing	14.9	1.9	
Graft	6.5	4.7	0.173
Proximal LAD	23.6	23.8	0.905
Left Main disease	1.9	1.9	1.000
Procedural variables			
IABP	0.4	0.7	0.411
Direct PCI	7.4	12.9	<0.001
Emergent PCI	10.3	15.1	0.004
Stents	52.0	73.9	<0.001
Complete revascularization	42.8	44.7	0.472
In-hospital cardiac complications	4.3	7.1	0.014

AMI = acute myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Surgery; NYHA = New York Heart Association; CCS = Canadian cardiovascular society; CAD = Coronary artery disease; IABP = intra-aortic balloon pump; PCI = Percutaneous Coronary Intervention

Table 1a. Comparison of baseline characteristics between APPROACH patients who underwent PCI between April 1996 and December 1997 and those enrolled in the ESP project.

Variable	APPROACH	ESP	p-value
Sample size	2782	425	
Demographics			
Age	61.6	60.7	0.111
Sex			0.006
Male	75.3	68.9	
Female	24.7	31.1	
AMI on admission	38.9	59.8	<0.001
Congestive heart failure	12.4	13.9	0.387
Prior MI	62.7	76.9	<0.001
Prior PTCA	14.1	17.6	0.055
Prior CABG	7.9	6.8	0.496
NYHA 2+	1.0	0.0	0.043
CCS class			<0.001
1	2.7	1.4	
2	8.8	5.2	
3	16.1	12.7	
4a, b, c	49.4	71.8	
Other	23.0	8.9	
Comorbidities			
Cerebrovascular disease	4.3	5.4	0.312
Pulmonary disease	9.0	12.2	0.040
Renal disease	2.0	0.9	0.174
Diabetes Type I	1.7	0.7	0.199
Diabetes Type II	15.8	19.5	0.057
Dialysis	1.3	0.2	0.221
Hyperlipidemia	52.7	59.8	0.007
Hypertension	54.1	55.1	0.715
Liver/GI disease	4.5	5.2	0.531
Malignancy	3.7	6.1	0.023
PVD	5.5	6.4	0.497
Family history of CAD	46.4	58.8	<0.001
Current smoker	24.9	32.9	0.001
Past smoker	30.7	34.1	0.160
Prior thrombolytic therapy	19.9	32.9	<0.001

Table 1a. Continued

Variable	APPROACH	ESP	p-value
Sample size	2782	425	
Ejection Fraction			<0.001
>50%	52.5	67.3	
30-50%	17.0	16.5	
<30%	3.0	3.1	
Not done	13.6	11.3	
Missing	3.9	1.9	
Graft	6.4	4.7	0.195
Proximal LAD	24.2	23.8	0.855
Left Main disease	2.2	1.9	0.857
Procedural variables			
IABP	0.6	0.7	0.732
Direct PCI	8.0	12.9	0.002
Emergent PCI	11.1	15.1	0.022
Stents	63.4	73.9	<0.001
Complete revascularization	44.0	44.7	0.793
In-hospital cardiac complications	4.3	7.1	0.018

AMI = acute myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Surgery; NYHA = New York Heart Association; CCS = Canadian cardiovascular society; CAD = Coronary artery disease; IABP = intra-aortic balloon pump; PCI = Percutaneous Coronary Intervention

Of the 4195 procedures, 2782 (66%) occurred between April 1996 and December 1997. The differences seen between the overall APPROACH population and the ESP study patients were maintained in this subset of patients.

The implications of these findings (i.e. differences in the two patient populations) on the generalizability of the results are discussed in the following sections.

Table 2 shows the frequency of adverse outcomes among these patients. Among ESP-APPROACH patients, less than two percent patients died within one-year of the index PCI and approximately 18 percent underwent a repeat

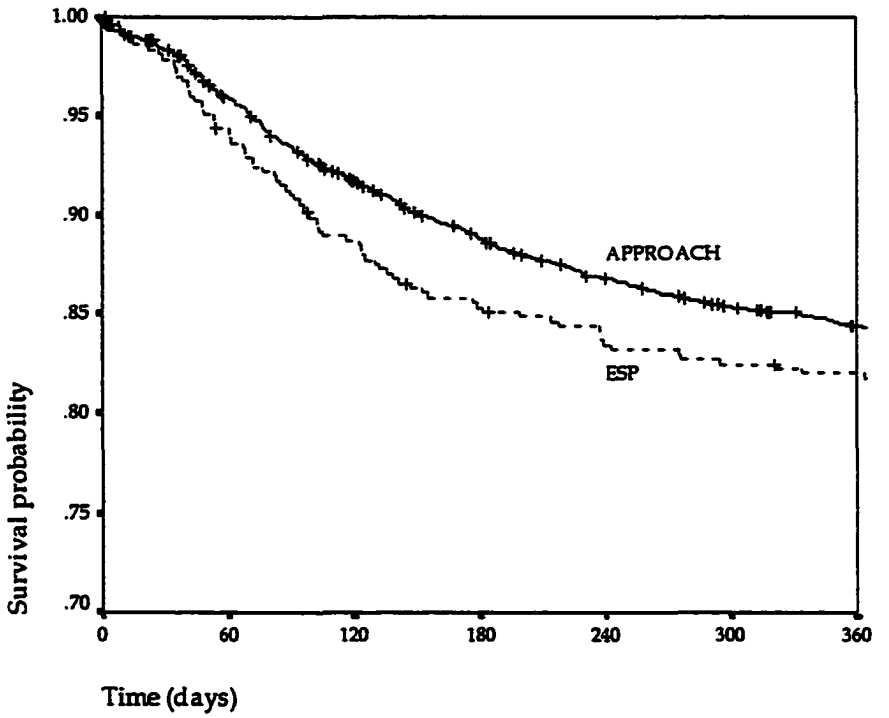
revascularization (either a CABG or a repeat PCI) within one-year of the index PCI. Mortality, at 30 days and one-year, was marginally higher in the APPROACH only population (no statistical difference) compared to the ESP-APPROACH patients. Repeat revascularization rate within one year was higher in the ESP-APPROACH group but not statistically significantly so. This is represented graphically in Figure 2, which is a plot of the Kaplan-Meier curves of survival free of repeat revascularization. The log-rank test statistic comparing the two curves was 2.20 ($p = 0.14$).

Table 2. Comparison of post-discharge outcomes in patients enrolled in APPROACH alone and those enrolled in APPROACH and ESP

Variable	APPROACH	ESP	p-value
Sample size	4195	425	
Death within 30 days	0.4	0.2	1.000
Death within 1 year	2.2	1.9	0.861
Repeat PCI within 1 year	12.6	14.4	0.321
CABG within 1 year	3.6	5.4	0.081
Repeat revasc within 1 yr	15.5	18.1	0.163

PCI = Percutaneous Coronary Intervention; CABG = coronary artery bypass surgery

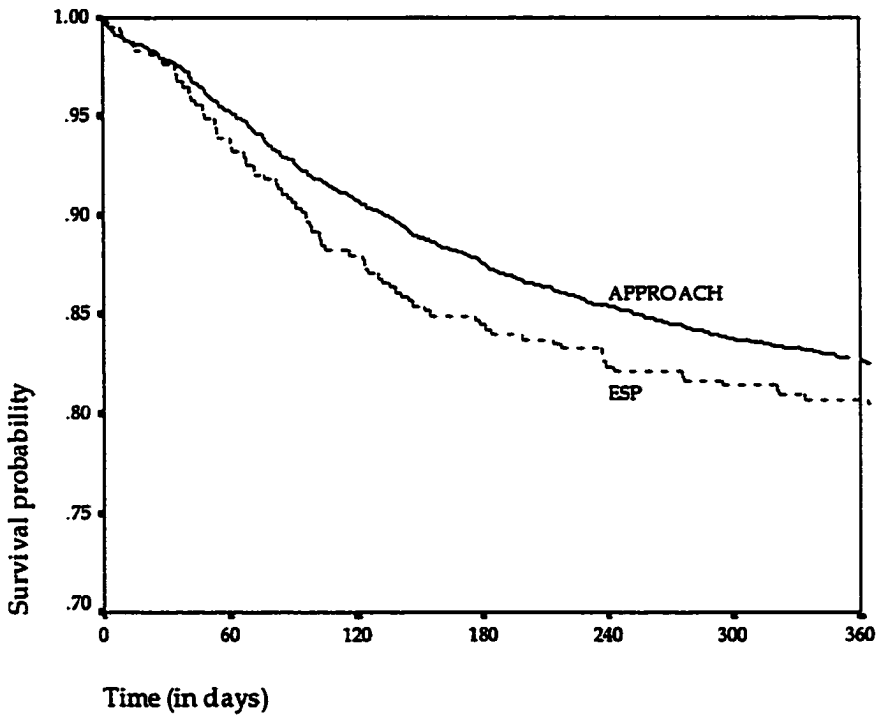
Figure 2. Kaplan-Meier curves of survival free of repeat revascularization of patients enrolled in the ESP study and other APPROACH patients.



As mentioned before, sensitivity analysis was conducted assuming all patients who died within one-year had instead had a repeat procedure. Figure 3 shows curves of survival free of repeat revascularization for the ESP study patients and the non-ESP APPROACH patients under this assumption. Given the relatively small number of deaths, the assumption did not have a major impact on the

curves, though they did move slightly closer. The log-rank test statistic comparing the two curves was 1.38 (p = 0.24).

Figure 3. Sensitivity Analyses: Kaplan-Meier curves of survival free of repeat revascularization of patients enrolled in the ESP study and other APPROACH patients after assuming all patients who died had undergone revascularization



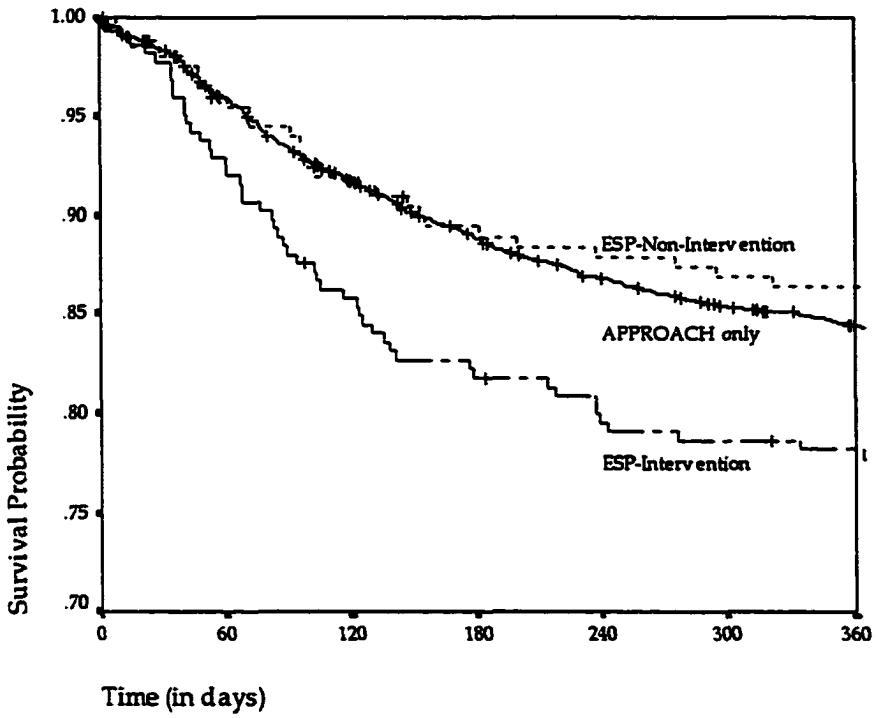
Both figures (2 and 3) show that non-ESP APPROACH patients underwent fewer repeat revascularizations than APPROACH patients enrolled in the ESP study. Although not statistically significantly different, the rate of repeat revascularization was higher in the ESP-APPROACH population even after assuming that all patients who died within one-year had undergone repeat revascularization.

3.2 ESP Intervention versus non-intervention Patients

Figure 4 shows Kaplan-Meier curves of survival free of repeat revascularization for three groups of patients: APPROACH only patients (N=4195), patients in the ESP intervention arm (N=225), and patients in the ESP non-intervention arm (N=200). The rate of repeat revascularization within one year was the highest among ESP intervention patients (22%) and their curve was statistically significantly different from both the APPROACH only patients (log-rank statistic = 7.85, p = <0.01) and non-intervention ESP patients (log-rank statistic = 5.36, p=0.02). There was no significant difference in survival free of repeat revascularization between APPROACH only patients and non-intervention ESP patients (log-rank statistic = 0.53, p=0.46). These differences remained even after assuming all patients who had died had undergone repeat revascularization (log-rank statistic of 6.08, p=0.01 between ESP intervention and non-ESP

APPROACH patients; and log-rank of 4.88, p=0.03 between ESP intervention and non-intervention patients).

Figure 4. Survival free of repeat revascularization: APPROACH only patient intervention and non-intervention ESP patients.



Tables 3 and 4 compare baseline, procedural and outcome variables between patients in the intervention and non-intervention arms of the ESP study. There were no statistically significant baseline and procedural differences in the two groups. As mentioned before, death was an infrequent outcome among these

Table 3. Comparison of baseline characteristics between Intervention arm and non-Intervention arms of ESP project

Variable	Intervention	Non-Intervention	p-value
Sample size	225	200	
Demographics			
Age	60.9	60.4	0.716
Sex			0.295
Male	66.7	71.5	
Female	33.3	28.5	
AMI on admission	58.2	61.5	0.552
Congestive heart failure	11.6	16.5	0.161
Prior MI	79.6	74.0	0.204
Prior PTCA	19.1	16.0	0.445
Prior CABG	8.4	5.0	0.181
CCS class			0.058
1	1.3	1.5	
2	3.6	7.0	
3	13.3	12.0	
4a, b, c	76.0	67.0	
Other*	5.8	12.5	
Comorbidities			
Cerebrovascular disease	5.8	5.0	0.831
Pulmonary disease	11.1	13.5	0.463
Renal disease	1.3	0.5	0.626
Diabetes Type I	0.9	0.5	1.000
Diabetes Type II	19.1	20.0	0.903
Dialysis	0.4	0.5	1.000
Lipids	55.6	64.5	0.074
Hypertension	56.0	54.0	0.697
Liver/GI disease	5.3	5.0	1.000
Malignancy	6.2	6.0	1.000
PVD	6.7	6.0	0.844
Family history of CAD	59.1	58.5	0.922
Current smoker	31.1	32.0	0.410
Past smoker	37.3	30.5	0.152
Prior thrombolytic therapy	32.4	33.5	0.837

* Other category includes "Not done" and "Atypical"

Table 3. Continued

Variable	Intervention	Non-Intervention	p-value
Sample Size	225	200	
Ejection Fraction			0.057
>50%	62.2	73.0	
30-50%	20.0	12.5	
<30%	2.2	4.0	
Not done	13.8	8.5	
Missing	1.8	2.0	
Graft	5.3	4.0	0.648
Proximal LAD	24.4	23.0	0.734
Left Main disease	2.7	1.0	0.291
Procedural variables			
IABP	1.3	0.0	0.251
Direct PCI	14.7	11.0	0.311
Emergent PCI	14.2	16.0	0.684
Stents	76.0	71.5	0.320
Complete revascularization	40.4	49.5	0.064
In-hospital cardiac complications	8.0	6.0	0.454

AMI = acute myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Surgery; NYHA = New York Heart Association; CCS = Canadian cardiovascular society; CAD = Coronary artery disease; IABP = intra-aortic balloon pump; PCI = Percutaneous Coronary Intervention

Table 4. Comparison of outcomes ESP Intervention arm and Non-intervention arm

Variable	Intervention	Non-Intervention	p-value
Sample size	225	200	
Death within 30 days	0.0	0.5	0.471
Death within 1 year	2.2	1.5	0.728
Repeat PCI within 1 year	17.8	10.5	0.038
CABG within 1 year	6.2	4.5	0.522
Repeat revasc within 1 yr	22.2	13.5	0.023

patients. Although mortality at one-year was higher among intervention patients, the difference was not statistically significant. The increased rate of repeat revascularization among intervention appears to be driven primarily by differences in the repeat PCI rates.

Figure 5 shows the Kaplan-Meier curves of survival free of repeat revascularization for these two groups of patients. Although this is a repeat of the data presented in Figure 4, it is useful to re-examine the curves for these patients separately. This examination reveals that there is an initial period (before 30 days) when the curves associated with intervention arm patients and non-intervention arm patients appear intertwined. Figure 6 provides a magnified view of this time period. However, after 30 days the survival curves separate quite dramatically revealing the increased rate of repeat revascularization in the intervention arm.

Figure 5. Kaplan-Meier Curves of Survival Free of repeat revascularization for patients in the intervention and non-intervention arms of the ESP study

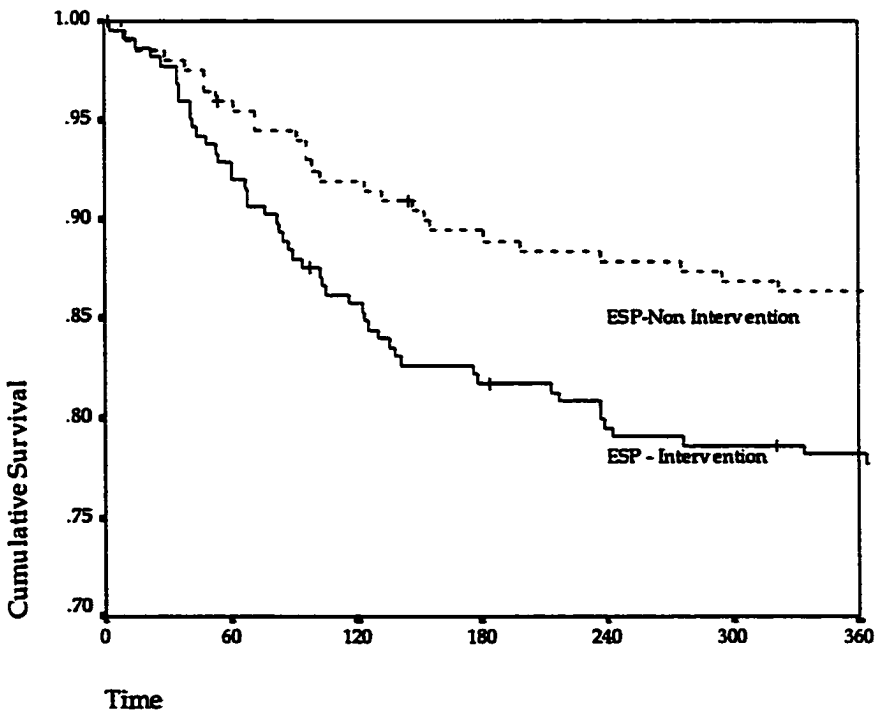
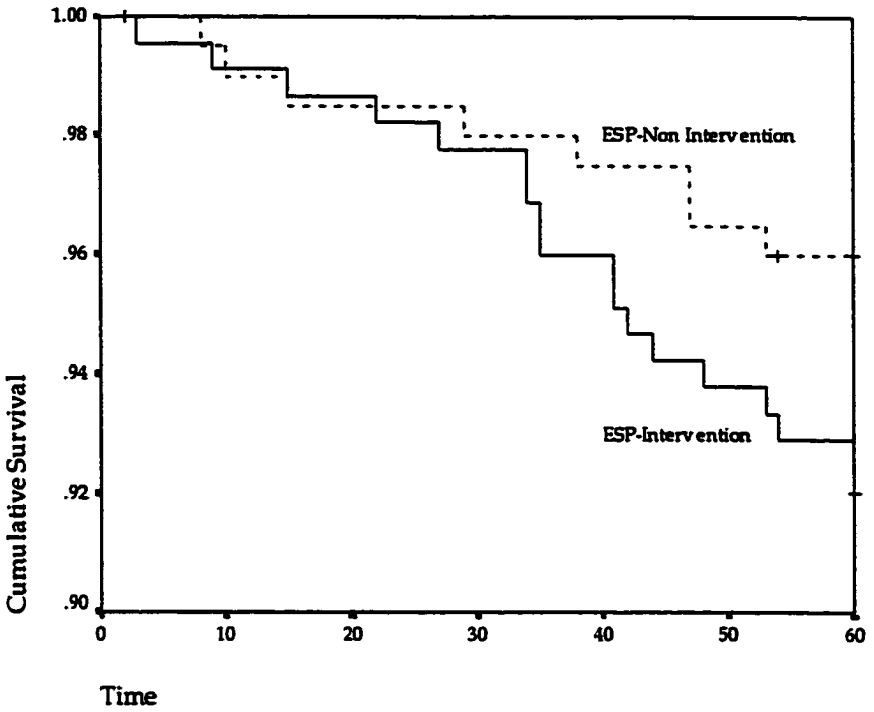


Figure 6. Kaplan-Meier Curves of Survival Free of repeat revascularization for patients in the intervention and non-intervention arms of the ESP study during the first 60 days following PCI



3.3 Medications at discharge

The ESP project tracked the use of five categories of medications: angiotensin-converting-enzyme (ACE) inhibitors, Aspirin (ASA), beta-blockers, lipid lowering agents and Warfarin. Table 5 shows the frequency with which intervention and non-intervention patients were prescribed these medications at discharged from their enrollment visit. Almost all patients were discharged on aspirin. The next most frequent discharge medications were beta-blockers, followed by lipid-lowering agents and ACE inhibitors. Very few patients were

discharged on warfarin therapy. There were no statistically significant differences in the rates of discharge therapies between intervention and non-intervention patients.

Table 5. Medications at discharge by treatment arms

Variable	Intervention	Non-Intervention	p-value
Sample size	225	200	
ACE Inhibitors	12.4	12.5	1.00
ASA	92.4	95.0	0.32
Beta Blockers	57.3	61.0	0.49
Lipid lowering agents	35.6	36.5	0.84
Warfarin	1.3	2.5	0.48

The hazard ratios (and 95% confidence intervals) measuring the associations between medications at discharge and repeat revascularization within one year based on all study patients are provided in Table 6. Although not statistically significant, the hazard of a repeat revascularization was lower if the patient was discharged on ASA or beta-blocker therapy. Conversely, patients discharged on ACE inhibitors or lipid lowering agents were more likely to undergo a repeat revascularization within one year. The association between lipid lowering agents and repeat revascularization was the only association bordering on statistical significance.

It must be noted here that only univariate associations between each drug prescribed and the outcome of interest were measured. Due to the study's small sample size and the complexity of multiple combinations, combined effects of

drugs, for example, aspirin and beta blockers or aspirin and lipid lowering agents, were ignored.

Table 6. Univariate associations between medications at discharge and repeat events at one year (N=425)

Variable	HR	Lower 95% CI	Upper 95% CI	p-value
ACE Inhibitors	1.52	0.84	2.76	0.17
ASA	0.65	0.30	1.41	0.28
Beta Blockers	0.78	0.50	1.22	0.28
Lipid lowering agents	1.56	1.00	2.44	0.05
Warfarin	1.52	0.30	7.68	0.56

The interaction between medications at discharge and intervention status was examined using Cox proportional hazard analysis. None of the interaction terms were found to be statistically significant.

Tables 7 shows the univariate associations between medications at discharge and repeat revascularization within one year for the non-intervention patients only which may be considered to be indicative of usual practice patterns. Again, the small numbers of patients not on ASA therapy and on warfarin make any analysis meaningless. Non-intervention patients discharged on ACE-inhibitors, beta-blockers or lipid lowering agents were all more likely to undergo a repeat revascularization within one year than patients who were not discharged on these medications.

Table 7. Associations between medications at discharge and repeat events at one year – non-intervention arm only (N=200)

Variable	HR	Lower 95% CI	Upper 95% CI	p-value
ACE Inhibitors	2.25	0.91	5.57	0.08
ASA	-	-	-	-
Beta Blockers	0.79	0.37	1.69	0.54
Lipid lowering agents	1.72	0.81	3.66	0.16
Warfarin	-	-	-	-

3.4 Appropriateness

Preliminary analyses around the issue of "appropriateness" were conducted by examining whether patients with certain clinical characteristics were prescribed the most common therapy recommended for the condition. In the case of congestive heart failure, only 24% of the patients were discharged on ACE Inhibitors. In contrast, 56% of hyperlipidemic patients were prescribed lipid-lowering agents and 57% of hypertensive patients were prescribed beta-blockers at discharge.

3.5 Follow-up

Overall, the median follow-up for the intervention patients was 2.05 years (inter-quartile range: 1.57, 2.18) and 2.08 years (inter-quartile range: 1.59, 2.56) for the non-intervention patients (Table 8). The median number of "encounters",

defined as follow-up telephone calls, contacts or questionnaires returned, were higher for patients in the intervention arm (12, inter-quartile range of 11, 14) compared to the non-intervention arm (9, inter-quartile range: 8, 11). As the outcome was restricted to one-year follow-up, the follow-up encounter data were restricted to one-year as well. The total number of encounters per patient within one-year were marginally higher for intervention patients compared to non-intervention patients.

At each encounter, patients were asked whether they had visited the doctor since their last encounter. In 83% of the encounters (909/1100), intervention patients reported that they had been to a doctor between the time of the last encounter and the current encounter. Similarly, in 83% (694/839) of the encounters, non-intervention patients reported a visit to the doctor since the last questionnaire.

Overall, the intervention arm patients reported 1563 visits to the family physician and 248 visits to their cardiologist. These numbers translate into a mean of seven family physician visits and one cardiologist visit in a year. In the non-intervention arm 1511 visits to the family physician and 237 visits to the cardiologist were reported. However, on average, the number of visits was the same for the two groups.

Table 8. Data on Utilization of Services during the follow-up period by intervention group.

Variable	Intervention	Non-intervention	p-value
Sample size	225	200	
Total follow-up in years	2.05 (1.57, 2.18)	2.08 (1.59, 2.56)	<0.01
Median number of encounters	12 (11, 14)	9 (8, 11)	<0.01
Total number of encounters within one year	1100	839	
Median number of encounters within 1 year	4.5 (3, 6)	4 (3, 5)	<0.01
Total number of visits to family physician within 1 year	1563	1511	
Total number of visits to the cardiologist within 1 year	248	237	
Median number of family physician visits	6 (4, 9)	6 (4, 11)	0.39
Mean	7.04	7.75	0.16
Median number of cardiologist visits within 1 year	1 (0, 2)	1 (0, 2)	0.99
Mean	1.12	1.22	0.18

3.6 Compliance

Patient reported data on compliance with medications are presented in Table 9. As mentioned before, patients who were not prescribed a particular type of medication during the entire year of follow-up were classified as "not prescribed". If a patient had been prescribed a particular medication *at any point* in the follow-up period he/she was included in the "prescribed" category. The rates in this category are therefore higher than the rates reported in Table 5, which document prescription rates at discharge. The "not-compliant" column

indicates the percentage of patients who reported non-compliance (defined as missing even a single dose) at any point in the follow-up period.

Despite the stringent definition of non-compliance, overall compliance with medications was very high (over 80%) in this patient population. The highest non-compliance rate was for beta-blockers, followed by lipid lowering agents and ACE inhibitors. Aspirin had the highest complete compliance rate.

Table 9. One-year compliance with medications (N = 425)

Medication	Prescribed	Not compliant
ACE Inhibitors	49.6	19.0
ASA	98.1	10.8
Beta blockers	82.6	18.8
Lipid lowering agents	73.9	18.5

Table 10 shows one-year compliance rates by intervention group. Although not statistically significantly different, there was a trend towards complete compliance being higher in the intervention arm compared to the non-intervention arm across all medication categories.

Table 10. Difference in prescription and one-year compliance rates by intervention group

Medication	Intervention	Non-Intervention	p-value
Sample size	225	200	
ACE Inhibitors			
Not prescribed	50.2	50.5	1.00
Prescribed			
100% Comp	83.9	77.8	0.29
ASA			
Not prescribed	2.2	1.5	0.73
Prescribed			
100% Comp	90.9	87.3	0.27
Beta blockers			
Not prescribed	18.2	16.5	0.70
Prescribed			
100% Comp	83.7	78.4	0.22
Lipid lowering agents			
Not prescribed	24.0	28.5	0.32
Prescribed			
100% Comp	84.2	78.3	0.19

Table 11 documents the associations between level of compliance and repeat revascularization within one-year among patients who were prescribed a certain type of drug. For example, among the 211 patients who were prescribed ACE inhibitors at discharge or at any point during the one-year follow-up, the hazard of repeat revascularization among patients who were 100% compliant was no different (HR 1.18, 95% CI: 0.52, 2.64) from those patients who were not fully compliant. None of the associations between complete compliance repeat

revascularization were significant and complete compliance with all medications appeared to be associated with higher likelihood of repeat procedures.

Table 11. Univariate associations between one-year compliance and repeat procedures (using Cox-proportional hazard models)

Medication	HR	Lower 95% CI	Upper 95% CI	p-value
ACE Inhibitors				
Sample size	211			
Non Comp	1.00	Ref.		0.69
100% Comp	1.18	0.52	2.64	
ASA				
Sample size	417			
Non Comp	1.00	Ref.		0.46
100% Comp	1.37	0.59	3.15	
Beta blockers				
Sample size	351			
Non Comp	1.00	Ref.		0.18
100% Comp	1.61	0.80	3.24	
Lipid lowering agents				
Sample size	314			
Non Comp	1.00	Ref.		0.64
100% Comp	1.17	0.61	2.23	

3.7 Checking Proportional Hazards Assumption

Before proceeding with the analyses to determine univariate predictors of one-year survival free of repeat revascularization using Cox proportional hazards model, the proportional hazards assumption for all baseline and procedural variables was verified using log-minus-log survival plots.

Age, a continuous variable, was categorized into three categories based on a visual plot of age versus the outcome variable: ≤ 50; 51 - 70; and > 70. The log-minus-log plot of age is presented in Figure 7a. The variable cannot be considered to have met the proportional hazard assumption, it was therefore reclassified into two categories: ≤ 70 and > 70. The log-minus-log plot was regenerated (Figure 7b) and the transformed variable appears to meet the proportional hazard assumption based on the parallel survival curves.

Similarly, the number of lesions with greater than 70% stenosis, was initially categorized into four categories (1; 2-3; 4-5 and 6+) but after the log-minus-log plot was generated, it was reclassified into a dichotomous variable of 1 and 2+ lesions (Figure 8a and 8b).

Other recategorizations included reclassifying ejection fraction from 5 categories (>50; 30-50; <30; not done, and missing) into two by collapsing the 30-50, <30, not done and missing into one category.

Figure 7a. Log-minus-log plots of age categories

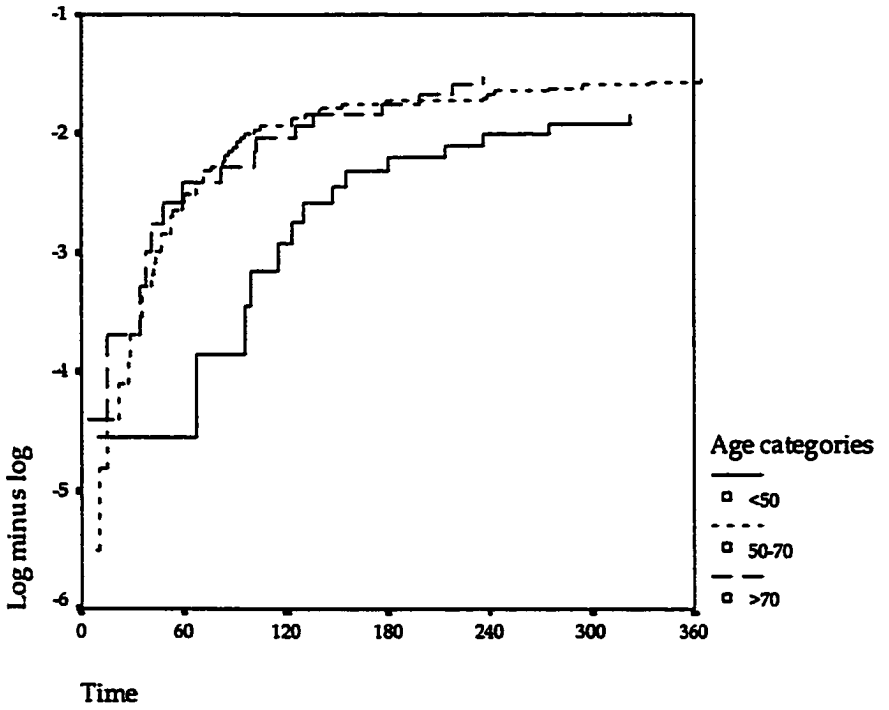


Figure 7b. Transformed Age variable

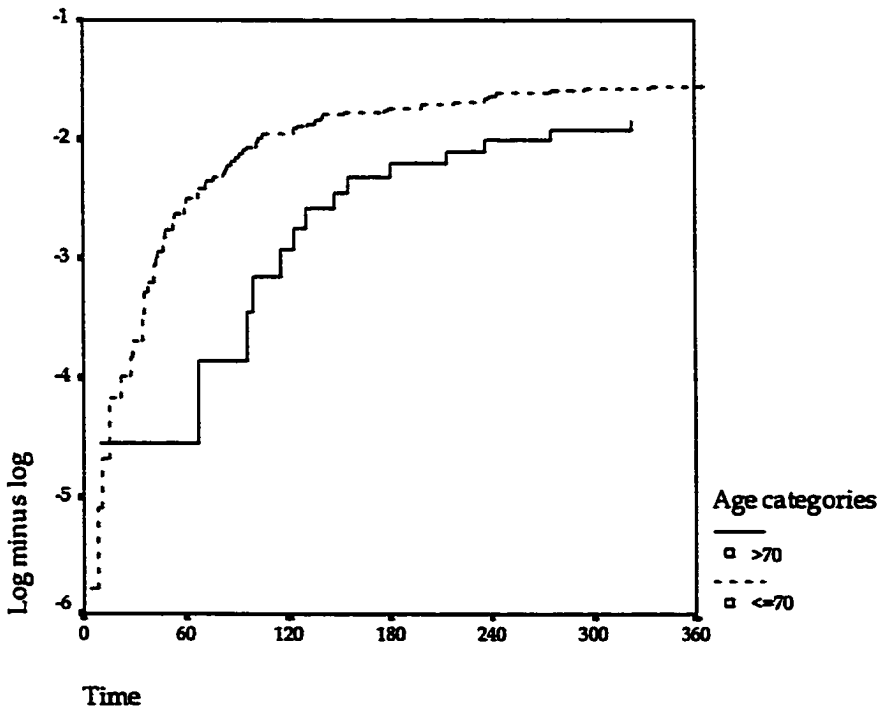


Figure 8a. Log-minus-log plot of number of Lesions with >70% Stenosis

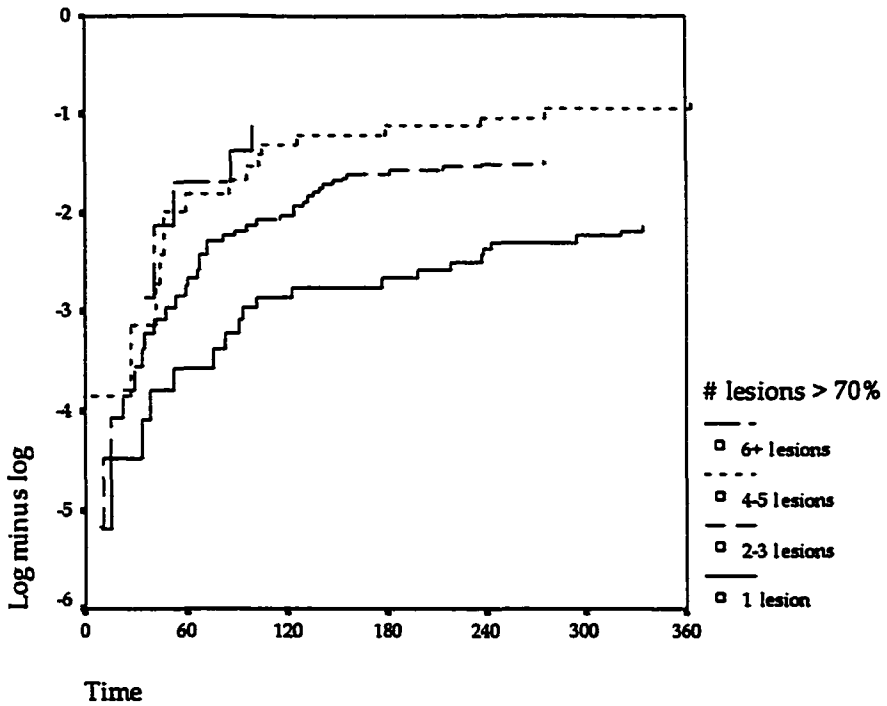
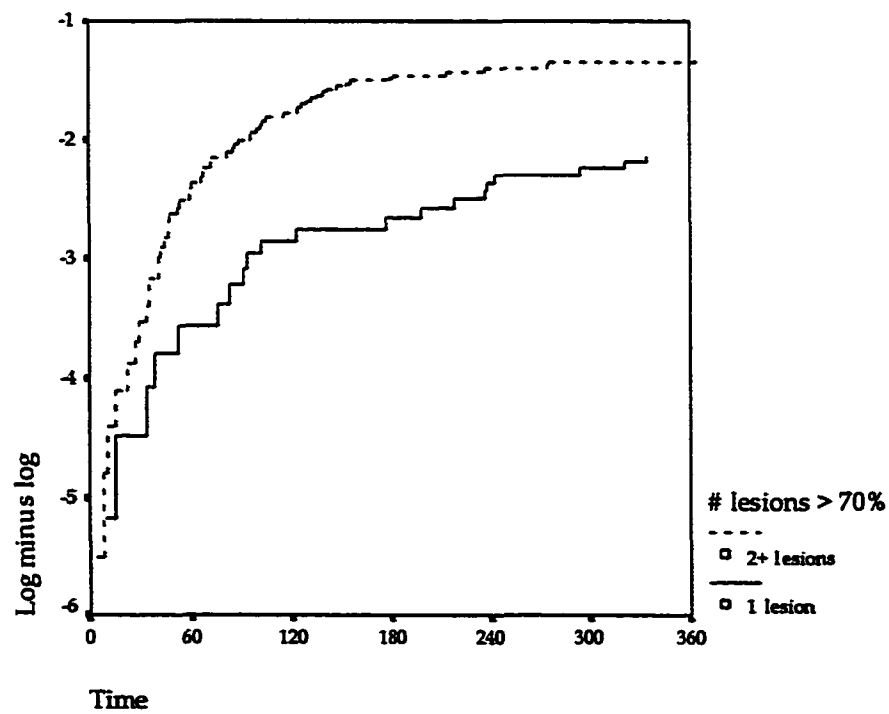


Figure 8b. Log-minus-log plot of transformed lesions variable



Compliance with medications in this patient population (intervention and non-intervention) was fairly high and due to the stringent definition of non-compliance (missing even one dose at any point during the one-year follow-up), the non-compliant group probably consisted of several patients who were equivalent to compliant patients. Based on the results presented in Table 11 and the log-minus-log plots of the medication data, it was clear that the extent of compliance was not a factor in predicting outcomes. Therefore, four dichotomous variables reflecting whether the patient had been prescribed a particular drug at discharge without regard to compliance status were created.

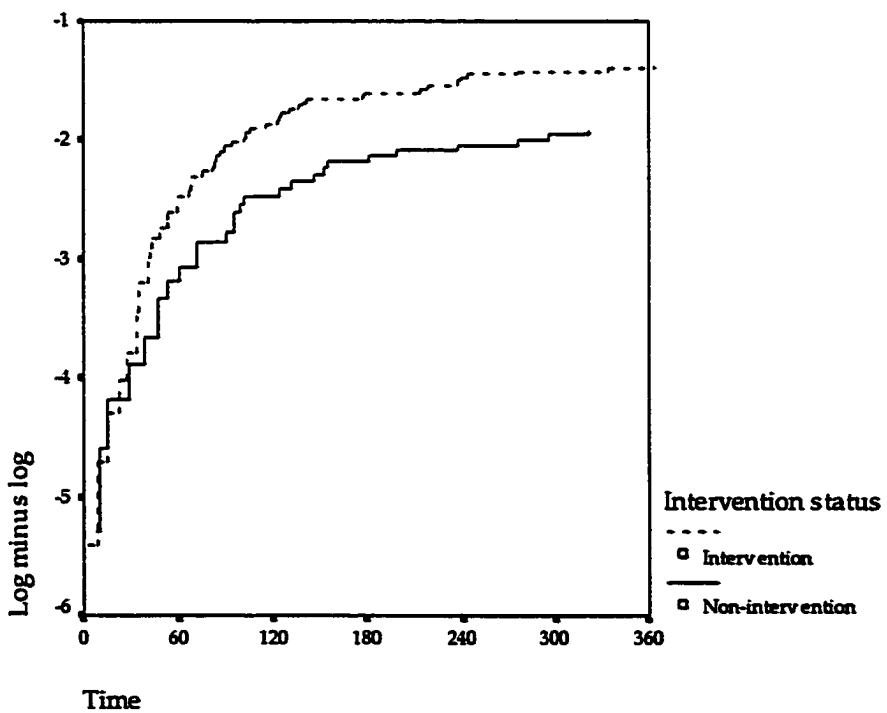
Several comorbidities were extremely infrequent in this patient population which probably was a factor in their not meeting the proportional hazards assumption. These included cerebrovascular disease, renal disease, diabetes type I, dialysis, liver disease and malignancy. In addition, very few patients had grafts or left main disease and almost all patient had aspirin prescribed. These variables were not considered for inclusion into the Cox proportional hazards model.

The re-categorized variables mentioned above (age, # lesions with >70% stenosis, ejection fraction, and variables indicating whether a medication had been prescribed at discharge) all met the proportional hazards assumption, as did chronic obstructive pulmonary disease, diabetes type II, hyperlipidemia, hypertension, family history, and complete revascularization.

Survival curves corresponding to other variables, such as sex, acute myocardial infarction on admission, congestive heart failure, prior myocardial infarction, prior PTCA, prior CABG, past and current smoking, prior thrombolytic therapy, proximal LAD lesion, direct PCI, emergent procedure and stent use, although not perfectly proportional, were considered proportional enough given the small sample size.

The most important variable in this analysis was whether the patient belonged to the intervention arm or non-intervention arm of the study. Figure 9 displays the log-minus-log survival curves corresponding to the intervention variable. As was evident by the Kaplan-Meier analysis (Figures 5 and 6), in the initial thirty-day period the curves criss-cross. However, the curves were not statistically

Figure 9. Log-minus-log plot of intervention status



significantly different during this time-period and given that the log-minus-log curves behave proportionally after the thirty-day period, proportionality for this variable could be assumed.

Again, given the importance of the variable, and to explore the concept of time-dependency, two models were developed. The first was assuming that the intervention variable met the proportional hazards assumption for traditional Cox regression model. And a second, extended Cox model with a Heaviside function partitioning time into two segments (one-pre 30 days during which the curves are assumed to be the same and one post-30 days where they are considered to be different).

3.8 Univariate Analyses Using Cox Proportional Hazard Models

Table 12 provides the univariate hazard ratios and 95 percent confidence intervals for the variables that were considered for inclusion into the Cox proportional hazard model examining survival free of repeat revascularization within one-year. Patients in the intervention arm were almost twice as likely to undergo a repeat procedure than patients not in the intervention arm. Other variables that were significantly associated with repeat revascularization were chronic obstructive pulmonary disease, complete revascularization, two or more

lesions with greater than 70% stenosis, and the prescription of lipid lowering agents at discharge.

Table 12. Univariate hazard ratios of associations between baseline and procedural variables and repeat revascularization within one-year using Cox proportional hazards model. (N=425)

Variable	HR	Lower 95% CI	Upper 95% CI	p-value
Female	1.45	0.91	2.28	0.12
Acute MI on admission	0.67	0.43	1.05	0.08
CHF	0.90	0.46	1.75	0.75
Prior MI	0.85	0.51	1.42	0.54
Prior PTCA	1.34	0.78	2.29	0.29
Prior CABG	0.97	0.40	2.41	0.96
COPD	2.25	1.31	3.86	<0.01
Diabetes Type II	1.21	0.70	2.07	0.50
Hyperlipidemia	1.21	0.76	1.92	0.43
Hypertension	1.03	0.66	1.61	0.91
Family history	1.43	0.89	2.29	0.14
Current smoker	1.07	0.67	1.72	0.76
Previous smoker	1.11	0.70	1.76	0.67
Prior tytic therapy	0.70	0.42	1.16	0.17
Proximal LAD	1.39	0.85	2.26	0.19
Direct PCI-	1.00	0.51	1.93	0.94
Emergent procedure	0.94	0.50	1.78	0.85
Stent	0.96	0.58	1.59	0.86
Complete revascularization	0.36	0.22	0.61	<0.01
Intervention status	1.74	1.09	2.78	0.02
Dichotomized variables				
Age > 70	0.72	0.40	1.28	0.26
2+ Lesion w/ > 70%	2.26	1.36	3.76	<0.01
Ejection Fraction < 50	1.28	0.81	2.03	0.29
Medications prescribed at discharge				
ACE Inhibitors	1.52	0.84	2.76	0.17
Beta blockers	0.78	0.50	1.23	0.28
Lipid-lowering agents	1.56	1.00	2.44	0.05

AMI = acute myocardial infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; CABG = Coronary Artery Bypass Surgery; NYHA = New York Heart Association; CCS = Canadian cardiovascular society; CAD = Coronary artery disease; IABP = intra-aortic balloon pump; PCI = Percutaneous Coronary Intervention

All variables that were significant at the p<0.20 level of significance were included in a multivariable Cox proportional hazard model. Table 13 provides a list of the variables included.

Table 13. Multivariate model including all variables found to be statistically significant at p<0.20 level in univariate analyses (N=425)

Variable	β	Hazard ratio	Lower 95% CI	Upper 95% CI	p-value
Female	0.47	1.59	1.00	2.55	0.05
Acute MI on admission	-0.37	0.69	0.42	1.13	0.14
COPD	0.83	2.28	1.31	3.98	<0.01
Family history	0.29	1.34	0.83	2.16	0.24
Prior lytic therapy	-0.19	0.83	0.48	1.42	0.50
Complete revascularization	-0.85	0.43	0.24	0.77	<0.01
Intervention status	0.46	1.59	0.99	2.55	0.06
2+ lesions > 70% stenosis	0.27	1.31	0.74	2.35	0.36
Proximal LAD	0.28	1.33	0.81	2.18	0.26
ACE Inhibitors prescribed	0.67	1.96	1.03	3.71	0.04
LLA prescribed	0.45	1.58	1.00	2.48	0.05

3.9 Multivariable Cox Regression Models

Non-significant variables were excluded in a systematic fashion in keeping with backward stepwise regression technique. Table 14 provides the details of the exclusionary process along with the likelihood ratio test statistics (and associated p-values) that were used to determine whether removing a particular variable had any impact on the model.

Table 15 lists the coefficients, the hazard ratios, the lower and upper bounds of the 95% confidence interval around the hazard ratio as well as the p-values

associated with the variables in the final model. Complete revascularization and acute myocardial infarction on admission were associated with lower hazards, however, female gender, chronic obstructive pulmonary disease, prescription of ACE inhibitors and lipid lowering agents at discharge, and intervention were associated with a higher hazard of repeat revascularization within one-year. A comparison of univariate (Table 12) and multivariate (Table 15) hazard ratios associated with the significant predictors shows that the relationships remained consistent across the two settings.

Table 14. Model building process

Variable	-2Log Likelihood	Likelihood ratio test statistic	df	p-value
Constant	916.333			
Initial model (Table 13)	870.837	45.497	11	<0.01
Prior Lytic therapy	871.304	0.468	1	0.49
2+ lesions w/ > 70% stenosis	872.111	0.807	1	0.37
Family history of CAD	873.465	1.354	1	0.24
Proximal LAD	874.815	1.350	1	0.25

Table 15. Final multivariate model (N=425)

Variable	β	Hazard ratio	Lower 95% CI	Upper 95% CI	p-value
Sex	0.47	1.60	1.00	2.26	0.05
Acute MI on admission	-0.44	0.65	0.40	1.04	0.07
COPD	0.83	2.29	1.33	3.94	<0.01
Complete revascularization	-1.02	0.36	0.21	0.61	<0.01
Intervention status	0.47	1.59	0.99	2.56	0.05
ACE inhibitors	0.72	2.05	1.09	3.88	0.03
Lipid lowering agents rx	0.47	1.60	1.02	2.50	0.04

3.10 Extended Cox Regression Model: The Issue of Time-dependent Covariates

Tables 16 and 17 correspond to the results of using the extended Cox regression model, which included a time-dependent variable for intervention status. Again, the model building process was started with the variables that were found to be significant at the $p<0.20$ level (Table 13). The results of the backward stepwise elimination are presented in Table 16. The final multivariate Cox regression model is presented in Table 17.

The coefficients associated with the other variables in the model did not change as a result of the inclusion of the time-dependent intervention status variable, however, the coefficient of the intervention status variable did increase and it became slightly more significant. This is consistent with the finding reported

Table 16. Model building process using intervention as a time dependent covariate

Variable	-2Log Likelihood	Likelihood ratio test statistic	df	p-value
Constant	916.333			
Initial Model (Table 13)	870.349	45.984	12	<0.01
Intervention status	870.350	0.001	1	0.98
Prior Lytic therapy	870.804	0.455	1	0.50
Lesions > 70%	871.602	0.803	1	0.37
Family history	872.954	1.348	1	0.25
Proximal LAD	874.322	1.367	1	0.24

Table 17. Final multivariate model with intervention status as a time-dependent covariate. (N=425)

Variable	β	Hazard ratio	Lower 95% CI	Upper 95% CI	p-value
Time-dependent intervention status	0.53	1.70	1.02	2.82	0.04
Sex	0.47	1.60	1.00	2.56	0.05
Acute MI on admission	-0.44	0.65	0.40	1.04	0.07
COPD	0.83	2.29	1.33	3.94	<0.01
Complete revascularization	-1.02	0.36	0.21	0.61	<0.01
ACE inhibitors at discharge	0.72	2.05	1.08	3.88	0.03
LLA agents at discharge	0.47	1.60	1.01	2.50	0.04

previously using Kaplan-Meier analysis of the curves separating more markedly after the initial thirty-day period.

4. DISCUSSION

This study examined the impact of an intervention to improve secondary prevention of coronary artery disease among patients undergoing PCI. Patients were randomized according to their cardiologist into one of two arms. The intervention arm patients were exposed to educational information regarding behaviour modification and benefits of medical therapy during their hospital stay and were contacted by a nurse coordinator to obtain a status report and assess compliance at 1 week, 1 month and every 3 months after discharge. Patients in the non-intervention arm were subjected to normal care and asked to return questionnaires at the same time-points after discharge. The main outcome of interest was repeat revascularization (repeat PCI or CABG) within one-year of the index PCI. Among the 225 patients in the intervention arm, 22% had a repeat procedure within one-year compared to 14% (of 200 patients) in the non-intervention arm (p-value 0.02). In a multivariate Cox regression model, intervention status, particularly after the initial 30-days after intervention, was associated with significantly higher hazard of repeat procedure (1.70, 95% CI, 1.02, 2.82). Other significant predictors or repeat revascularization included female gender, chronic obstructive pulmonary disease, and the prescription of ACE inhibitors and lipid lowering agents at discharge. Complete revascularization and acute myocardial infarction on admission were negatively associated with repeat procedures.

Although the result of intervention being positively associated with repeat procedures may appear counter-intuitive at first, an explanation, though purely speculative, could be offered. In this high-risk patient population, as evidenced by the high acute myocardial infarction rate on admission (60%), close monitoring may have enabled identification of recurring symptoms and prompted corrective action in the form of repeat procedures. The question arises whether the increased rate of repeat procedures in the intervention arm is more reflective of "optimal" care and whether current practice patterns (based on the non-intervention arm) are in some way inadequate. Unfortunately, this study only generates this hypothesis and does not provide any evidence to support or refute it. In order to answer this question effectively, long-term mortality, out to five-years or more, would have to be examined to discern whether initial surveillance resulted in better outcomes for the intervention patients in the long-run.

As mentioned before, a limitation of the study is a possible under-representation of the rates of repeat revascularization because of patients leaving the province to undergo procedures. A second limitation is the unavailability of data pertaining to physicians who were included in the study. If physician practice patterns differed significantly with respect to revascularization in this subgroup of patients, these differences could potentially impact the results.

Prescription rate of ACE Inhibitors documented in this patient population is consistent with those reported by other studies in the pre-Heart Outcomes Prevention Evaluation (HOPE) Study era. In a 1996 study to determine secondary preventive treatment and habits among patients with coronary heart disease in general practice, Cambell et al found ACE Inhibitors were prescribed in approximately 10% of patients [5]. However, it is likely that subsequent to the publication of the results of the HOPE study in January 2000, prescription rates of ACE Inhibitors will increase substantially. The HOPE study, a placebo-controlled randomized trial of the ACE Inhibitor ramipril, included 9297 patients who were given the drug for a mean of five years. The study population was restricted to patients without heart failure or low-ejection fraction (in whom the positive benefits of ACE inhibition had already been established) and found that ramipril significantly reduced the rates of death, myocardial infarction, stroke and revascularization [6].

The benefits of aspirin in preventing adverse events among patients with coronary artery disease have been established [7, 8] and the high rates of its use in the current study population are an indication of the evidence being absorbed into clinical practice.

The rate of lipid lowering agents prescribed at discharge (37%) was substantially higher than the 1993 rates reported by the Clinical Quality Improvement Network (CQIN) investigators [9]. Among 3,333 patients with coronary artery

disease seen at four Canadian acute care hospitals, lipid-lowering drugs were prescribed in only 8% of patients.

4.1 Drugs at follow-up

Two prior studies have documented the rates of prescription drugs at 6-months following PCI. Hasdai et al examined the use of antianginal medication among 3831 patients undergoing PCI between 1979 and 1997. At six-months, 39% of the patients were receiving beta-blocker therapy [10]. In the Action on Secondary Prevention through Intervention to Reduce Events (ASPIRE) study, among PCI patients, the rates of aspirin, beta-blockers, ACE Inhibitors, and lipid-lowering drugs at six months were 93.5%, 47%, 12% and 21%, respectively [11]. In the current study, at encounters that took place between 3 to 6 months after the PCI procedure, medication rates were: 96% for aspirin, 77% for beta-blockers, 44% for ACE inhibitors, and 61% for lipid lowering agents. There may be several explanations for the dramatic increase in prescription rates in the current study. First, the increase may just be a temporal effect of clinical trials data being absorbed effectively into clinical practice. Second, while the other two studies were retrospective reviews of practice patterns, the current study was part of a prospective randomized controlled trial in which patients were randomized according to their cardiologist. Due to the non-blinded nature of the study

protocol, there may have been a "Hawthorne effect", i.e. greater diligence due to a perception of increased scrutiny.

4.2 Compliance

Compliance rates with prescribed medications were very high among the study patients, especially given the stringent definition of non-compliance, i.e. missing even one dose during the one-year follow-up. This definition may have driven the finding of no difference in outcomes between patients who were 100% compliant and those who were non-compliant.

Compliance rates were higher in the intervention group compared to the non-intervention group (though statistical significance was not reached). This is likely attributable to the nature of the intervention. In a meta-analysis to examine the effectiveness of interventions to improve patient compliance, Roter et al found that multidimensional programs that included rapport building with a patient were the most effective in improving compliance [12].

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CHAPTER 7. CONCLUSIONS

1. INTRODUCTION

The main objective of the thesis was to identify predictors of adverse events within one-year following percutaneous coronary intervention (PCI). In order to respond to this objective, data from three sources: the Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease - APPROACH project; the Enhancement of Secondary Prevention in Heart Disease (ESP) study; and administrative data were used.

Using APPROACH data Study I (Chapter 5) examined baseline and procedural factors associated with one-year and 30-day mortality as well as one-year repeat revascularization among 4,695 Alberta residents who underwent PCI between July 1, 1995 and December 31, 1997. This study is the first to use population-level data to examine long-term outcomes following PCI in the post-stenting era.

Although PCI patients are scrutinized extensively while in hospital, little is known about how these patients behave once they have been discharged. The ESP study provided a unique opportunity to examine resource utilization and compliance behaviour of these patients and to evaluate the impact of secondary prevention strategies and increased surveillance on repeat revascularization within one-year of PCI. The patient population for this study (Study 2 – Chapter

6) was a subset of Study 1 patients (N=425) who enrolled into the ESP project within the same hospitalization during which the PCI was performed.

2. SUMMARY OF FINDINGS

Table 1 is a summary of statistically significant predictors of the outcomes examined in Study 1 and Study 2.

STUDY I			STUDY II
One-year Mortality	30-day Mortality	Repeat Procedures within one-year	Repeat Procedures within one-year
+ associated	+ associated	+ associated	+ associated
Age	AMI on admission	Female sex	Female sex
CHF	Cardiogenic shock	Family history of CAD	COPD
COPD	COPD	Lesions > 70%	Intervention status
Dialysis	Renal disease	- associated	ACE inhibitors rx
Malignancy	Ejection Fraction	Prior MI	LLA rx
PVD	Proximal LAD	Stent	- associated
Cardiogenic shock	Left main disease	Complete revasc.	AMI on admission
Ejection Fraction	IABP		Complete revasc.
Proximal LAD	Emergency proc.		
Left main disease	- associated		
IABP	Hyperlipidemia		
Emergency proc.	Current smoker		
- associated	Past smoker		
Hyperlipidemia	Complete revasc		
Lesions > 70%			
Complete revasc.			

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; IABP = intra aortic balloon pump; revasc = revascularization; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; ACE = angiotensin converter enzyme; LLA = lipid lowering agents

To a large extent Study 1's results provide evidence to support the a priori hypothesis that traditional risk factors that have been found to be predictors of short and long-term mortality in the pre-stenting era are significantly associated with short and long-term mortality in the post-stenting era. Factors such as acute myocardial infarction on admission, cardiogenic shock, low ejection fraction, left main disease, intra-aortic balloon pump and emergency procedures were associated with 30-day and one-year mortality. In addition, increasing age, congestive heart failure, malignancy and peripheral vascular disease also took their toll in the long-run.

Although these results are generally consistent with those shown in previous studies, there were a few surprises. Unlike previous studies which have found a positive association between multi-vessel disease and mortality, the current study found a negative association between the number of lesions with greater than 70% stenosis and one-year mortality. Although the univariate relationship was positive, i.e., the higher the number of lesions with greater than 70% stenosis, the higher the mortality, in the multivariable setting the association was reversed (negative). There can, however, be several explanations for this finding. One is that the higher risk of diffused disease is absorbed by other coronary anatomy variables in the model, namely proximal LAD and left main disease. Second, if the one-year mortality model is not examined in isolation but evaluated in the context of the findings of the repeat revascularization model,

one can speculate that the lesions greater than 70% stenosis are positively associated with repeat revascularization, which in turn is negatively associated with mortality.

The other counter-intuitive findings were the negative associations between hyperlipidemia and both short and long-term mortality and past and current smoking and short-term mortality. As mentioned before, these findings have been reported in previous studies, but continue to baffle researchers. A purely speculative explanation is that identification of hyperlipidemia implies treatment for it and therefore patients treated with lipid lowering agents are in fact less like to suffer an adverse event than those not being treated. An explanation for the positive effects of current and past smoking even after controlling for age and sex is selection bias. If only healthy smokers are selected to undergo revascularization, this may account for the positive outcomes among this patient population.

In the repeat revascularization model, in addition to multi-vessel disease, female sex was associated with increased repeat procedures, while the use of stents in PCI and the completeness of revascularization had an inverse association with the outcome. The finding that the use of stents in PCI has no impact on either short or long-term mortality, but is associated with a lesser need for repeat procedures is consistent with existing literature.

In Study 2, patients were approximately evenly split between the "usual care" arm and to an "enhanced care" arm. Enhanced care involved increased patient education regarding secondary prevention therapies and periodic follow-up of patients by nurse coordinators to ensure compliance with medications.

The study hypothesis was that patients in the enhanced care arm would have fewer adverse events than patients in the usual care arm. However, the low frequency of deaths in this patient population made any statistical analyses meaningless, and, therefore, only the outcome of repeat revascularization within one-year of the PCI was evaluated.

The main finding of the study was contrary to the initial hypothesis. Patients in the enhanced care arm had significantly higher number of repeat procedures compared to patients in the usual care arm. This counter-intuitive finding generates more questions than answers around the benefits of closely monitoring PCI patients. If surveillance identifies sicker patients and results in timely therapy (in terms of repeat PCI or coronary bypass surgery), it can be argued that the enhanced care patients are receiving "optimal care" while the usual care patients are in some ways being neglected. However, in order to understand the true costs/benefits of intervention, long-term mortality data (extending beyond the study's one-year timeframe) would be required.

In addition to enhanced care, other predictors of repeat revascularization in Study 2 were: female sex, chronic obstructive pulmonary disease, and

prescription of ACE inhibitors and lipid-lowering agents on discharge. Prescription of these drugs is probably a marker for higher severity of disease, which would explain the positive hazard ratios. Completeness of revascularization was associated with lower repeat procedures.

There are consistencies between the repeat revascularization model developed using all APPROACH patients in Study 1 and the one developed using a subset of patients in Study 2. In both models, female sex was found to be associated with higher repeat procedures and completeness of revascularization with lower repeat procedures. The fact there is not a one-to-one overlap between the predictors in the two models is not surprising given the significant differences in the baseline characteristics of the study patients. It is therefore inappropriate to generalize the findings of Study 2 to the entire Study 1 patient population without further analyses.

3. LIMITATIONS

Despite the novelty of these studies, some obvious limitations must be noted. To begin with, the studies are observational and are therefore prone to selection bias by virtue of their design. Therefore, care must be taken when drawing inferences around the studies' results. Multivariable analyses were used extensively in the studies to adjust for baseline and procedural characteristics while making comparisons across groups, however, due to the non-randomized design of the

studies, there may be other factors not accounted for, that may drive the perceived differences in outcomes.

The credibility of the results also hinges on the quality of the data used. Unlike many clinical trials, in which special resources are allocated to ensure accurate and complete collection of data, data collection for the APPROACH project has been incorporated into the day-to-day management of cardiac patients. As a result there is variability in the completeness of data capture across sites giving rise to problems with missing data. Although this problem was somewhat resolved by merging the clinical data with administrative data, gaps in some baseline clinical and coronary anatomy data were still an issue.

The unavailability of data on myocardial infarction admissions following discharge from PCI hospitalization made it impossible to examine this very relevant outcome. Data quality also played a role in the exclusion of 236 patients from the analysis due to unavailability of administrative data corresponding to the PCI hospitalization. Although the numbers are likely to be small, the studies may under-represent repeat procedures as a result of patients migrating out of the province to undergo cardiac procedures.

With respect to Study 2 (Chapter 6), the unavailability of data pertaining to the physicians who were included in the study is a limitation. If physician practice patterns differed significantly with respect to revascularization in this subgroup of patients, these differences could potentially impact the results.

4. POLICY RECOMMENDATIONS

Predictors of adverse events following PCI should be used to flag higher risk patients thereby assisting in discharge planning and follow-up care. The prediction models developed in Study I can be translated into risk scores based on which patients can be categorized into risk strata. These can be used to facilitate discussion between the patient and physician regarding treatment options and potential outcomes.

Given the interesting, yet counter-intuitive findings of Study 2, it would be unwise to make any policy recommendations around intensive monitoring of patients following PCI without conducting additional analyses. In the long-term, it is important to examine the impact of patient intervention status on mortality. In the short-term, alternative outcomes, such as patient quality-of-life should be examined to determine whether patients in the intervention arm have better quality of life as a result of increased interaction with nurses and increased interventions compared to patients who had regular care.

Based on the experience of conducting these analyses, a general recommendation that standardized patient identification data be routinely collected and verified as part of all cardiovascular studies conducted in the province can also be made. As this thesis shows, there are definite benefits to integrating databases to answer questions that would not be possible by querying an individual database.

In these studies, data from three very different sources were merged: the APPROACH database, the ESP database and the administrative database. This ability to link databases, however, is limited by the type and quality of unique patient identification data collected. Patient health number (PHN) and chart numbers were recorded in all three databases, however, some patients had to be excluded due to missing or incorrect data. Therefore, provincial guidelines around the type and quality of identification data would be asset for future analyses.

5. FUTURE RESEARCH

Some of the unexpected results, i.e., the negative relationships between the number of lesions with greater than 70% stenosis, hyperlipidemia and smoking and mortality, are hypothesis generating and suggest future exploratory analyses.

Study 1 was restricted to the time-period between July 1, 1995 and December 31, 1997. Since this time there has been a steady increase in stent use and new adjunct therapies to PCI, such as glycoprotein IIb/IIIa inhibitors, have been introduced into clinical practice. It would therefore be interesting to expand these analyses to include a larger time-period and to examine the impact of these new technologies on outcomes.

An analysis of long-term survival data to examine whether the higher use of repeat procedures in the enhanced care arm translates into better outcomes compared to patients in the usual care arm, is warranted.

Also, a comparison of quality-of-life of patients in the enhanced care arm and the usual care arm would be of value. The hypothesis to be tested is that patients in the enhanced care arm would have higher quality of life due to: a) constant interaction with nurse coordinators, and b) quicker identification and resolution of symptoms.