Cardiac Medical Therapy Following Coronary Artery Bypass Graft Surgery

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Abstract

Despite the benefits of coronary artery bypass graft surgery (CABG), graft closure can still occur and lead to the development of unstable angina, myocardial infarction (MI) and death. Secondary prevention is thus greatly needed in order to prevent future cardiovascular events in the post-CABG patient. Few studies have examined the benefits of cardiac medical therapy specifically among CABG patients. A review of randomized controlled trials (RCT's) was first conducted in order to understand what constitutes appropriate cardiac medical therapy in the post-CABG patient. Very few trials were found to examine the efficacy of cardiac medical therapy specifically in the post-CABG patient. Evidence suggests that the routine use of aspirin and anti-lipid agents seems warranted following CABG. More trials are needed on the efficacy of angiotensin converting enzyme (ACE) inhibitors in the post-CABG patient. Similarly, insufficient evidence exists to support the use of beta-blockers, calcium-channel blockers (CCB's) and nitrates following CABG.

The use of aspirin, clopidogrel, coumadin, anti-lipid agents, anti-ischemic medications (beta-blockers, CCB's, nitrates) and ACE inhibitors was then examined among patients enrolled in the Routine versus Selective Exercise Treadmill Testing After Coronary Artery Bypass Graft Surgery (ROSETTA-CABG) Study. We examined the use of these medications among all patients as well as patients with various co-morbidities. Univariate and multivariate logistic regression was used to identify determinants of medication use at 12-months and to control for confounders. Although some variation between patient subgroups was found in the use of aspirin, anti-lipid agents and ACE

inhibitors, this variation was modest. The use of anti-lipid agents, ACE inhibitors and beta-blockers was found to be lower than expected among certain subgroups of patients with co-morbidities that dictate the use of proven medical therapies. Lastly, we found that two of the most important determinants of 12-month use are baseline co-morbidities and use at discharge.

In conclusion, there is a need for greater use of secondary prevention among patients undergoing CABG. Our results suggest that the use of appropriate cardiac medical therapy can best be modified when the patient is discharged from the hospital following CABG. More research is necessary in order to guide physicians on the use of appropriate cardiac medical therapy specifically among post-CABG patients.

Résumé

Malgré les avantages du pontage aorto-coronarien, la fermeture des greffes demeure tout de même une réalité pour plusieurs patients après la chirurgie, entraînant souvent l'angine instable, l'infarctus du myocarde, et parfois même la mort. Ainsi, il y a un besoin urgent de méthodes de prévention secondaire des événements cardiovasculaires chez ces patients. Nous en savons très peu sur l'utilisation des médicaments cardiaques par les patients porteurs d'un pontage aorto-coronarien.

Nous avons réalisé une revue des essais randomisés afin de mieux comprendre les médicaments cardiaques appropriés pour les patients qui ont eu un pontage. En effet, nous avons trouvé peu d'essais randomisés sur l'efficacité de médicaments cardiaques après le pontage. Notre revue démontre que l'utilisation régulière de l'aspirine et des hypolipidémiants sont nécessaires après un pontage. Par contre, les essais randomisés portant sur l'efficacité des inhibiteurs d'enzymes de conversion de l'angiotensine (ECA) après un pontage sont peu nombreux. De plus, il y a un manque d'essais démontrant l'efficacité des bêta-bloquants, inhibiteurs calciques et dérivés nitrés.

L'utilisation de l'aspirine, clopidogrel, coumadin, hypolipidémiants, bêta-bloquants, inhibiteurs calciques, dérivés nitrés et ECAs a été examinée parmi les patients inscrits dans le registre ROSETTA-CABG « Routine versus Selective Exercise Treadmill Testing After Coronary Artery Bypass Graft Surgery ». Nous avons aussi examiné l'utilisation de ces médicaments parmi ces patients avec co-morbidités. Des analyses de régression univariées et multivariées ont été utilisées afin d'identifier les déterminants de l'utilisation de ces médicaments à 12 mois et pour contrôler pour les facteurs de confusion. Bien qu'une variation ait été observée parmi plusieurs sous-groupes de

patients atteints de co-morbidités dans leur utilisation d'aspirine, d'hypolipidémiants, et des ECAs, la variation de l'ensemble des médicaments cardiaques reste modeste. L'utilisation des hypolipidémiants et des ECA's est plus faible qu'attendu parmi certains groupes de patients qui pourraient en bénéficier. Finalement, les déterminants de l'utilisation de médicaments les plus importants sont les co-morbidités et l'utilisation du médicament à la sortie de l'hôpital.

En conclusion, il existe un besoin d'utilisation des méthodes de prévention secondaire parmi les patients qui ont eu un pontage. Nos résultats suggèrent que l'utilisation des médicaments appropriés peut être modifiée à la sortie du patient du l'hôpital. Il est essentiel que des essais cliniques soient réalisés afin de mieux guider les médecins sur l'utilisation appropriée de médicaments cardiaques chez les patients qui ont subi un pontage.

Preface

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

> Candidates have the option of including, as part of the thesis, the text of one or more papers submitted or to be submitted for publication, or the clearly duplicated text of one or more published papers. These texts must be bound as an integral part of the thesis.
>
> If this option is chosen, connecting texts that provide logical bridges between the different papers are mandatory. The thesis must be written in such a way that it is more than a mere collection of manuscripts; in other words, results of a series of papers must be integrated.
>
> The thesis must still conform to all other requirements of the "Guidelines for Thesis Preparation." The thesis must include a table of contents, an abstract in English and French, an introduction which clearly states the rationale and objectives of the study, a review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.

Additional material must be provided where appropriate (e.g. in appendices) and in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.

In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers.

Suggested Short Title

Cardiac Medical Therapy Following CABG

Acknowledgements

I would like to acknowledge the members of the Department of Epidemiology and Biostatistics at McGill University and of the Center for Community Studies and Clinical Epidemiology at the Jewish General Hospital for their direct help and support. First, I must acknowledge Dr. Mark Eisenberg for his excellent supervision and mentorship. I would like to thank him for providing constructive criticism of my work and the numerous opportunities he has given me in cardiovascular research over the last 4 years. Second, I also wish to thank Dr. Robert Platt for his supervision and help as co-supervisor for my thesis. His thoughtful criticism of the methods and interpretation of the results was greatly appreciated. I also wish to thank Dr. Louise Pilote, as thesis committee member, for reviewing my written work and providing valuable feedback. The investigators and research nurses at the participating centers for the ROSETTA-CABG Registry should also be acknowledged for their hard work in enrolling patients and collecting data at their institution. I would also like to acknowledge the help of Jonathan Marsan and Karen Wou on collecting the data and helping with the ROSETTA-CABG Registry. Finally, personal support was provided through a M.Sc. scholarship from the Fonds de Recherche en Santé du Québec. The acquisition of the data for the ROSETTA-CABG Registry was also funded through both the Heart and Stroke Foundation of Canada and the Fonds de Recherche en Santé du Québec.

Dedication

This thesis would be incomplete without a mention of the support given me by my cherished family and friends, to whom this thesis is dedicated.

> "They were my own soul out of my soul, who kept my spirits up when the muses failed me. Without them lifting me up when this thesis seemed interminable, I doubt it should ever have been completed." (John B. Padgett)

Table of Contents

List of Tables

List of Figures

Manuscript: Use of Cardiac Medical Therapy Among Patients Undergoing Coronary Artery Bypass Graft Surgery: Results from the Routine versus Selective Exercise Treadmill Testing After Coronary Artery Bypass Graft Surgery (ROSETTA-CABG) Study

5.4 Causal Models

List of Appendices

1- INTRODUCTION

Cardiovascular disease continues to be the leading cause of death in industrialized countries, with coronary artery disease (CAD) accounting for the greatest percentage of deaths (1-2). Coronary artery bypass graft surgery (CABG) is a widely performed procedure which relieves angina and improves survival in selected groups of patients with CAD (3). Despite the benefits of CABG, graft closure can still occur and lead to the development of unstable angina, myocardial infarction (MI) and death (5-11). Secondary prevention among patients who have undergone CABG consists of prescribing appropriate cardiac medical therapy after hospital discharge. Many of the factors that place a patient at increased risk for post-CABG cardiac events are co-morbidities for which targeted medical therapy already exists (12-34). In spite of the publication of a large number of clinical trials and guideline statements, several studies have demonstrated a lack of optimal use of cardiac medical therapy among subgroups of patients with CAD including: those with a history of prior MI, those with a history of congestive heart failure (CHF), and those who have undergone percutaneous coronary intervention (PCI) (35-44). However, few studies have examined patterns of cardiac medical therapy among patients who have undergone CABG. All patients undergoing CABG have CAD, and many of these patients have co-morbidities that dictate the use of proven medical therapies. Thus, the purpose of this thesis is to describe the use of cardiac medical therapy in post-CABG patients.

1.1- Coronary Artery Disease in Canada

Cardiovascular disease is comprised of congenital diseases, CHF, CAD, hypertension, rheumatic heart disease, stroke and other diseases of the cardiovascular system (1-2). Of the 80,000 Canadians whose deaths were attributed to cardiovascular disease in 1999, approximately 54% were due to CAD (1). Consequently, CAD mortality, including deaths due to MI accounted for 20% of all deaths in Canada (1).

1.2- CABG and Need for Secondary Prevention

CABG has been found to relieve angina in 83% of patients at 5 years and in 63% of patients at 10 years (3). Survival rates of 92% and 81% have been found in patients at 5 years and 10 years, respectively, following CABG (3). In Canada, the number of CABG's increased from approximately 14,000 in 1990-1991 to just under 25,000 in 2000 (1,4). CABG is now also being performed in high-risk subgroups, such as the elderly, patients with CHF, and patient with diabetes.

Despite the benefits of CABG, 15% to 25% of patients develop graft closure by 1 year (5-9). Patients who have undergone CABG are also at risk for atherosclerotic progression of their native coronary arteries. Both graft closure and atherosclerotic progression of native coronary arteries can lead to unstable angina, MI and death, as well as the need for further revascularization by PCI or repeat CABG (10). Nineteen percent of patients undergo further revascularization by 10 years following CABG (11). Secondary prevention with medical therapy is therefore warranted following CABG in order to prevent the progression of CAD and in order to prevent future cardiac events.

1.3 Targeted Medical Treatment Post-CABG

Patients who have CAD often have risk factors that promote the progression of atherosclerotic disease. In the post-CABG patient, many of these factors are co-morbidities for which medical treatment already exists (12-25). For example, unless specific contraindications exist, all patients with a prior MI should receive aspirin, anti-lipid agents, beta-blockers and ACE inhibitors for the prevention of recurrent events (26). This type of targeted intervention has not only been the focus of many randomized clinical trials and observational studies in the past two decades but has led to the publication of the several practice guidelines in both Canada and the United States (26-34). These guidelines exist for the management of patients with CHF, diabetes, hypertension, MI, stable angina and unstable angina.

No Canadian guidelines currently exist for patients undergoing CABG. According to the American College of Cardiology (ACC) /American Heart Association (AHA) Guidelines for Coronary Artery Bypass Graft Surgery, both aspirin and anti-lipid agents are recommended postoperatively (3). Aspirin is recommended in all patients for the first postoperative year in order to prevent early saphenous vein graft (SVG) closure. All patients with low-density lipoprotein (LDL) cholesterol levels of higher than 100 mg/dL (or 2.6 mmol/L) should receive anti-lipid agents in addition to a low fat diet following CABG. There are no recommendations in the ACC/AHA Guidelines regarding the use of any other cardiac medications following CABG.

1.4 Study Rationale

Despite the extensive evidence that supports secondary prevention and the use of targeted therapy for patients with certain co-morbidities, many studies have demonstrated a lack of optimal treatment among patients with CAD (35-44). Previous studies suggest both an underutilization and an overutilization of medical therapy among patients following acute MI and PCI and among patients with CHF, documented CAD and low left ventricular ejection fraction (LVEF). For example, past researchers found anti-ischemic medications to be overutilized among patients who had been revascularized with PCI and who did not have any clinical indications for their use (36-38). However, to our knowledge, no study has examined the use of cardiac medical therapy among CABG patients. Because CABG is a major cardiac procedure and is associated with significant risk for subsequent cardiovascular events, it is important that the use of medical therapy in the post-CABG patient be studied. We are responding to this need by first conducting a review of randomized clinical trials (RCT's) that examined the efficacy of cardiac medical therapy post-CABG. We then examine the patterns of use of cardiac medical therapy among CABG patients enrolled in a multicenter cohort study.

2- LITERATURE REVIEW

2.1 Preface to Manuscript #1

The main objective of this thesis is to investigate the use of cardiac medical therapy for secondary prevention in post-CABG patients. Since we are interested in knowing if CABG patients are receiving appropriate cardiac medical therapy, it is important to first establish a consensus on what is considered appropriate therapy among CABG patients. To this end, we reviewed randomized controlled trials (RCT's) that examined the efficacy of cardiac medication use after CABG. Cardiac medications of interest are aspirin, anti-lipid agents, anti-ischemic agents (beta-blockers, calcium-channel blockers, nitrates) and ACE inhibitors.

This manuscript was submitted for publication to a cardiology journal in the fall of 2003. The subject matter presented here is timely and original in content. Several reviews have been published on the efficacy of cardiac medications in post-CABG patients, and the differences between these previous reviews and the current one should be noted. First, some of the reviews of aspirin use reported outcomes of graft patency and excluded cardiac events (45-46). Others tested the efficacy of aspirin in groups other than CABG patients and provided very little results for CABG patients (46-49). Second, the only review on the use of anti-lipid agents did not use strict inclusion or exclusion criteria and reviewed both non-experimental studies and studies not conducted strictly in CABG patients (50). Third, the only review on the efficacy of beta-blockers was restricted to patients who had suffered a prior MI (51). Lastly, the only review on the efficacy of ACE inhibitors also included studies of post-PCI patients (52). To our

knowledge, no review has ever been published on the benefits of all of these medications in the post-CABG patient.

2.2 Author's Contributions

As first author, I was responsible for collecting all the data, writing the manuscript, and performing all revisions. Dr. Mark Eisenberg, as supervisor, contributed to all stages of the research including the conception of the research question, interpretation of results and critical revision of the manuscript. Dr. Robert Platt, as co-supervisor, provided guidance on methodology and constructive comments on the preparation and revision of the manuscript. Dr. Louise Pilote, as thesis committee member, also provided feedback as to the presentation of the data, interpretation of the results and revision of the manuscript.

2.3 Manuscript #1

Cardiac Medical Therapy in Patients Undergoing Coronary Artery Bypass Graft Surgery: A Review of Randomized Controlled Trials

Short Title: RCT's of post-CABG medical therapy

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ABSTRACT

Introduction: Little is known regarding what constitutes appropriate cardiac medical therapy in the post-CABG patient. The purpose of this paper is to review the literature on cardiac medical therapy for patients following CABG.

Methods: We identified randomized controlled trials (RCT's) published in the English language literature that examined the effects of cardiac medications in post-CABG patients. The MEDLINE and COCHRANE databases were searched for trials conducted between 1966 and 2003 on the following medications: aspirin, anti-lipid agents, beta-blockers, calcium channel blockers (CCB's), nitrates and angiotensin converting enzyme (ACE) inhibitors. Trials that enrolled greater than 100 patients and examined the impact of these cardiac medications on outcomes 1-year post-CABG were included.

Results: Eleven RCT's involving over 4000 patients were conducted on the efficacy of aspirin therapy post-CABG. A benefit of aspirin on graft occlusion as early as one year was demonstrated when aspirin was administered within 1 day following CABG. No differences in cardiovascular events were found between patients on aspirin versus placebo when aspirin was administered prior to CABG or at 1 year post-CABG. Three RCT's involving over 1900 patients were conducted on the efficacy of anti-lipid agents post-CABG. A significant reduction in the progression of atherosclerosis of bypass grafts and native arteries was found as early as 2 years post-CABG with the use of anti-lipid agents. The risk of cardiovascular events was also found to be decreased by the use of anti-lipid agents at 7 years post-CABG. One RCT involving over 900 patients failed to find a difference in the incidence of cardiovascular events at 2 years post-CABG between patients treated with beta-blockers versus placebo. One RCT involving 120

patients also failed to find a difference in the incidence of cardiovascular events at 4 years between patients who continued treatment with CCB's at one-year post-CABG and those who stopped treatment. No RCT's have examined the impact of nitrates among patients following CABG. Lastly, one RCT involving over 140 patients found a significant reduction in the incidence of cardiovascular events at 1-year post-CABG among patients treated with ACE inhibitors versus placebo.

Conclusion: Very few RCT's have examined the efficacy of cardiac medical therapy in post-CABG patients. Current evidence indicates that aspirin and anti-lipid agents should be used routinely following CABG. Further research is needed to support the use of ACE inhibitors post-CABG. Evidence is currently insufficient to recommend the use of beta-blockers, CCB's and nitrates in post-CABG patients.

INTRODUCTION

The efficacy of coronary artery bypass graft surgery (CABG) is well established in patients with coronary artery disease (CAD) (1-6). However, patients undergoing CABG are still at risk for unstable angina, myocardial infarction (MI), and death through the progression of atherosclerosis and the occlusion of native arteries and bypass grafts (7-10). In the post-CABG patient, secondary prevention includes the use of appropriate medical therapy to prevent the occurrence of clinical events. Numerous randomized clinical trials (RCT's) and observational studies have been published on the efficacy of cardiac medical therapy for patients with known CAD who have specific cardiovascular co-morbidities (11-26). For example, patients with CAD benefit from anti-platelet agents and anti-lipid agents (11-15), whereas patients with depressed left ventricular ejection fraction (LVEF) and diabetes benefit from angiotensin converting enzyme (ACE) inhibitors (21-23). However, there is a lack of consensus on what is the appropriate medical therapy for patients who have undergone CABG. Thus, the purpose of this paper is to review the RCT literature on cardiac medical therapy for patients following CABG.

METHODS

Study Selection

We identified RCT's that examined the effect of cardiac medications post-CABG published in the English language and conducted between the years 1966 and 2003. The MEDLINE and COCHRANE databases were searched for RCT's involving the following medications: aspirin, anti-lipid agents, beta-blockers, calcium channel blockers (CCB's), nitrates and ACE inhibitors. We also used the following key terms: coronary artery bypass graft surgery, secondary prevention, randomized controlled trials and long-term

treatment. Lastly, we reviewed references from these articles for pertinent articles not previously found through the MEDLINE and COCHRANE database searches.

Inclusion and Exclusion Criteria

RCT's that tested the efficacy of the aforementioned cardiac medications following CABG were included. This included trials that compared the use of medical therapy with open label non-placebo control groups. We included trials that examined the impact of medical therapy on cardiovascular outcomes including unstable and stable angina, MI, overall mortality and cardiovascular death. We also included trials that examined the impact of medical therapy on outcomes related to clinical ischemic events. These outcomes included native and graft occlusion and the need for further revascularization by percutaneous coronary intervention (PCI) or repeat CABG. Only trials that measured native and graft occlusion by angiography were included. Trials with mixed outcomes of graft occlusion and cardiovascular events were also included.

We excluded all trials that enrolled less than 100 patients. This was done in order to exclude studies conducted with limited enrolment where the quality of the methodology used may have been questionable and was difficult to assess. We also excluded all trials that examined outcomes less than 1 year after CABG. This was done for two reasons: first, we were interested in the effects of medications on long-term secondary prevention and second, we wanted to exclude all trials that studied events that could be a result of the operation itself. Moreover, we excluded all trials that tested the use of cardiac medications prior to CABG or peri-operatively unless the use of the medication continued following discharge from the hospital. Trials that examined the use of cardiac medications in another subset of cardiac patients, such as post-MI or post-PCI,

despite a large majority of these patients having prior CABG, were also not included, because the study population did not include all patients with previous CABG and time since CABG was not always included. Observational studies or in-vitro studies were likewise not included in this review.

MEDICAL THERAPY AMONG CAD PATIENTS WITH COMORBIDITIES

The focus of this paper is to specifically review RCT's of cardiac medical therapy in the post-CABG patient. However, our review would not be complete without the mention of the substantial evidence that exists on the efficacy of these medications among patients with CAD who have co-morbid conditions. These patients often make up a large proportion of patients who undergo CABG, and much of the research described in this section have patient populations that include patients who underwent CABG.

Numerous RCT's have shown aspirin to be beneficial in reducing the risk of adverse cardiovascular events such as MI and death in a wide range of high-risk patients. The use of aspirin has been found to significantly decrease the incidence of both non-fatal MI and non-fatal stroke among patients with CAD and patients with various co-morbidities including: atrial fibrillation, prior MI, peripheral vascular disease (PVD), and unstable angina (24). Anti-lipid agents have been found to be efficacious for plaque stabilization in native arteries, and in preventing MI and cardiac death among patients with CAD (12-15). Moreover, a reduction in clinical events has also been found among patients with lowered low-density lipoprotein levels following use of anti-lipid agents (12-14).

Beta-blockers have both anti-ischemic and anti-hypertensive properties. These agents have been found to be of benefit in the prevention of recurrent MI and death

among prior MI patients (16). The beneficial effect of beta-blockers has been extended to include several post-MI patient subgroups such as those with diabetes, hyperlipidemia and the elderly (17). An improvement in survival has also been found with the use of beta-blockers in patients with congestive heart failure (CHF) (18-19). Both CCB's and nitrates have been found to be beneficial in treating angina among patients with unstable and stable angina who have contraindications to beta-blockers (20). Nitrates have been found to be especially useful among patients with angina who also have left ventricular dysfunction (20). However, because beta-blockers have also been found to reduce mortality in MI patients, beta-blockers are often used as the first line agents for the treatment of angina. Lastly, both beta-blockers and CCB's are also used in treating hypertension.

ACE inhibitors have been shown to be of benefit in patients with CHF, diabetes, depressed or normal left ventricular function post-MI and hypertension (21-23). A reduction in the risk of MI has been found among patients with depressed LVEF and CHF who were treated with ACE inhibitors (21). A reduction in 30-day mortality among patients with prior MI receiving ACE inhibitors was also found (23). Lastly, risk reduction in the composite endpoint of MI, stroke or death was demonstrated among patients receiving ACE inhibitors with diabetes, PVD, or a history of CAD without heart failure or LV dysfunction (22).

MEDICAL THERAPY IN THE POST-CABG PATIENT

A total of 16 randomized clinical trials were found that examined the efficacy of aspirin, anti-lipid-agents, beta-blockers, CCB's, nitrates and ACE inhibitors specifically among patients following CABG.

ASPIRIN

It is well recognized that post-CABG graft occlusion causes anginal symptoms and may lead to MI or death (28-30). A previous study found 13% of patients without occluded grafts to have angina one year after CABG, with rates increasing to 25% for patients with 1 occluded graft and 54% for patients with 2 or more occluded grafts (31).

In our review of the literature, 9 RCT's involving over 2500 patients were found that studied the use of aspirin post-CABG (Table 1) (31-39). Three of the 9 trials that examined the effect of aspirin on graft occlusion and graft patency post-CABG found aspirin to be beneficial when administered within 1 day following CABG (33, 35, 36). The two RCT's that also studied the effect of aspirin on cardiovascular events did not find any significant benefit on the incidence of angina, MI, or death among patients treated with aspirin when administered prior to CABG or at 1 year post-CABG (32, 34).

In contrast, six of the nine trials found graft occlusion and patency to be similar between patients receiving aspirin when compared to patients receiving placebo (31-32, 34, 37-39). The number of patients randomized in these trials ranged from 147 to 772 patients. Four of these trials initiated aspirin between 2 and 4 days post-CABG (31, 37-39), one initiated aspirin prior to CABG (32) and one initiated aspirin at 12-months post-CABG (34). Time to follow-up varied between one year and three years post-CABG.

Several of the trials had study methodologies that differed greatly from each other. Some trials reported both number of bypass grafts and number of patients as their units of analysis (31-35, 37-39). Aspirin was found to be beneficial on graft occlusion when the number of bypass grafts was reported as the unit of analysis instead of the number of patients for one of these trials (32). In Goldman et al.'s study, when the

results were presented using number of bypass grafts as the unit of analysis, results were found to be significant for combined aspirin versus placebo (15.8% versus 22.6%, respectively, p=0.029) and aspirin daily versus placebo (13.2% versus 22.6%, respectively, p=0.050) (32). However, no difference was found in patency rates among those grafts that had been patent early following CABG (median of 9 days), nor among grafts that had been placed next to vessels greater than 2.0mm in diameter (32). In Pirk et al.'s study, the unit of analysis was only presented using the number of bypass grafts, and results for the number of patients were not presented (36). Unlike the other trials, this study also used an open-label control group and did not use a placebo group. Other studies had more than two treatment arms that included the use of warfarin (38) and aspirin + dipyridamole (39). Finally, in another study by Goldman et al., patients were randomized to continued treatment with aspirin or placebo for an additional 2 or 3 years at 1 year post-CABG (34). Graft occlusion was not found to be significantly different between patients treated with aspirin when compared with patients treated with placebo (Table 1).

Several of these studies had a significant proportion of patients excluded from the final analyses due to a smaller proportion receiving angiography at follow-up (Table 1). Reasons cited by authors were patient refusal, loss to follow-up, death, intolerance or discontinuation of medications, occlusion of grafts early in the study, medical complications such as psychiatric problems and unavailable data. Most authors reported there to be no differences between patients included and excluded in the analyses 31-35, 37-39). Thus, it is unlikely that patients not included in the final analyses represent a source of potential bias in the results of these studies. However, it is difficult

to infer the generalizability of these results to a larger population of CABG patients without the use of intention-to-treat analyses. It is also possible that the exclusion of patients decreased the power to demonstrate an effect of treatment between both treatment groups.

In summary, aspirin was found to decrease graft occlusion at 12-months following CABG when administered within 1 day post-CABG. Consequently, aspirin should be started immediately after CABG and should be continued for at least one-year. Previous RCT's have not demonstrated a benefit in the use of aspirin after one-year post-CABG or in the reduction of clinical events > 1 year after CABG. Although not the focus of this review, aspirin has been found to be beneficial for multiple patient subgroups with CAD, many of which undergo CABG, and has been the subject of other large reviews and meta-analyses (24). Aspirin should therefore be continued indefinitely post-CABG unless contraindications exist.

ANTI-LIPID AGENTS

Among patients undergoing CABG, there exists a need for a delay of disease progression in SVG's, arterial grafts and native arteries. Past research has found the progression of atherosclerosis to be as high as 12% in native arteries, 21% in both native arteries and SVG's, and 44% in SVG's 15 years after CABG (40). Moreover, SVG's and native artery occlusion have also been found to be significantly associated with clinical events post-CABG (40, 44).

Three RCT's involving over 1900 patients have examined the effect of anti-lipid agents on graft occlusion and the risk of cardiovascular events post CABG; the Post-CABG Trial, the Lopid Coronary Angiography Trial (LOCAT) and the Cholesterol

Lowering Atherosclerotic Study (CLAS) (41-46) (Table 2). These trials differed in terms of study population, time since CABG when treatment with anti-lipid agents was initiated, and type of anti-lipid agent used. Two of these trials also reported long-term follow-up (42, 45-46). All three RCT's found a significant reduction in the progression of atherosclerosis in bypass grafts and native arteries. Anti-lipid agents were found to only provide benefit at decreasing the risk of cardiovascular events at 7 years post-CABG and longer (46).

The Post-CABG Trial randomized 1351 patients with prior CABG between 1 and 11 years before randomization to aggressive versus moderate lipid-lowering treatment with lovastatin (41). A significantly lower number of patients treated with aggressive anti-lipid therapy were found to have progression of graft atherosclerosis, graft occlusions and new graft lesions. A total of 27% of patients treated with aggressive lipid-lowering treatment were found to have a 0.6 mm or more decrease in lumen diameter when compared with 39% of patients who received less aggressive treatment ($p<0.0001$). The composite endpoint of need for revascularization, MI, stroke, and cardiac death were all significantly lower among patients treated aggressively at 7.5-year follow-up (42).

The LOCAT Trial randomized 395 males with low HDL at a mean of 22 to 33 months post-CABG to gemfibrozil vs. placebo for a mean of 2.7 years of follow-up (43). Patients with diabetes and low LVEF, two important subgroups of CABG patients, were excluded from the LOCAT Trial. Anti-lipid treatment was found to significantly reduce the number of new lesions in SVG's (2.4% in anti-lipid group vs. 14.3% in placebo group, $p<0.001$). The primary endpoint of change in mean diameter of native arteries was also found to be significantly lower among patients treated with anti-lipid agents

(0.01±0.10 mm in anti-lipid group vs. 0.04±0.11 mm in placebo group, p=0.009). The composite endpoint of repeat CABG or PCI, MI, or death was not significantly different between treatment groups.

In the CLAS Trial, 162 non-smoking males who underwent CABG at least 3 months prior to enrollment were randomized to colestipol and niacin vs. placebo (44). After treatment with anti-lipid agents for 2 years, the investigators found the number of subjects with new lesions in both native vessels and grafts to be significantly lower among patients treated with anti-lipid agents than those with placebo. Ten percent of patients treated with anti-lipid agents were found to have new lesions within the native vessels when compared to 22% of patients treated with placebo (p=0.03). Likewise, 18% of patients treated with anti-lipid agents were found to have new lesions within bypass grafts when compared to 30% of patients treated with placebo (p=0.04). Cardiovascular events such as cardiac death, MI or angina were not significantly different between treatment groups at 2 or 4 years following CABG (44-45). However, by 7 years post-CABG, the composite endpoint of repeat CABG or PCI, MI, or cardiac death was significantly lower among patients treated with anti-lipid agents (RR=0.6, P=0.02) (46).

In summary, long-term treatment with anti-lipid agents in post-CABG patients prevents graft atherosclerosis and future cardiovascular events. Although it is not yet clear if anti-lipid agents reduce the incidence of clinical events early after CABG, the use of anti-lipid agents was found to decrease the progression of atherosclerosis of bypass grafts as early as 2 years post-CABG. Moreover, as past research has also demonstrated a benefit of anti-lipid agents in reducing the progression of atherosclerosis of native

arteries among CAD patients, the use of anti-lipid agents in post-CABG patients is well justified.

BETA-BLOCKERS

In our review of the literature, only one RCT was found that examined the effect of beta-blockers following CABG (Table 3) (47). No significant difference in clinical endpoints was found between patients treated with beta-blockers and patients treated with placebo at 2-years. Sjoland et al. conducted a double blind placebo-controlled RCT of 967 patients undergoing CABG (47). Patients were randomized to metoprolol versus placebo between four and 21 days post-CABG and treated for two years. There was no difference between the two arms with respect to improvement in exercise capacity, their primary endpoint. However, patients treated with placebo were found to have a higher (worse) chest pain score when compared with patients treated with beta-blockers (Table 3). In another analysis of the same patients, none of the primary endpoints of repeat CABG or PCI, unstable angina, non-fatal MI, or death were found to be significantly different between the two groups at 2 year follow-up (48).

In summary, although the use of beta-blockers is clearly indicated among CAD patients with prior MI, very few RCT's examined the use of beta-blockers in post-CABG patients who have not had an MI. It remains unclear from the current literature whether the use of beta-blockers should be used routinely following CABG.

CALCIUM CHANNEL BLOCKERS & NITRATES

Some cardiac surgeons recommend the routine use of CCB's and nitrates to prevent vasospasm of radial artery grafts (50). Vasospasm has been found to contribute to ischemia, thrombosis and subsequent failure of radial artery grafts following CABG (50-

52). In our review of the literature, only one RCT was found which examined the effect of CCB's post-CABG (Table 3) (52). No RCT's were found which examined the effect of nitrates.

Gaudino et al. evaluated the benefits of CCB's beyond the 1st year post-CABG on radial artery graft patency (52). One hundred and twenty patients with normal perfusion of the radial artery were randomized at one year to either continued care with CCB's or suspended treatment. There were no significant differences at four-year follow-up in recurrence of angina, residual ischemia and cardiac deaths found between the group that continued CCB therapy and the group whose treatment was discontinued.

In summary, there is little evidence to support the routine use of CCB's or nitrates post-CABG. As CABG is primarily indicated for the relief of anginal symptoms, the incidence of angina is very low among patients within the first year. With the lack of any evidence on the benefits of these agents in post-CABG patients, there does not appear to be much need for the use of CCB's or nitrates following CABG.

ACE-INHIBITORS

Previous trials have demonstrated a benefit of ACE inhibitors in reducing the incidence of MI and mortality among CAD patients with several co-morbidities, including prior revascularization. Only one RCT involving 149 patients specifically evaluated the benefit of ACE inhibitors post-CABG: the Quinapril on Clinical Outcome After Coronary Artery Bypass Grafting (QUO VADIS) Study (Table 3) (53). This RCT demonstrated a significant reduction in ischemic events post-CABG.

The primary objective of the QUO VADIS study was to evaluate the efficacy of ACE inhibitors on the change in total exercise time at 1-year (53). Patients underwent

exercise testing both prior to CABG and at one-year post-CABG, as well as Holter monitoring for 48 hours at one-year. ACE inhibitors were started one month prior to CABG and were continued for one year. Among 149 patients with normal LVEF, 3.5% of patients receiving quinapril following CABG experienced ischemic events versus 15% of patients receiving placebo ($p=0.02$). However, there was no effect of treatment found on the change in total exercise time or the incidence of ischemia on Holter between the two treatment groups.

In summary, few RCT's were found that examined the use of ACE inhibitors among CABG patients. Although current evidence demonstrates positive effects of treatment on clinical events up to 1 year post-CABG, more trials are needed in order to recommend the routine use of ACE inhibitors post-CABG.

LIMITATIONS

There are several potential limitations of our study that should be noted. First, we only included RCT's that compared the use of one cardiac medication to placebo, no cardiac medication or a less aggressive treatment regimen. It is therefore possible that other studies that have found beneficial effects of cardiac medical treatment post-CABG were not included. Moreover, as we were interested in the effect of aspirin post-CABG, we excluded studies that examined the efficacy of aspirin when compared to other anticoagulants or anti-platelets. Second, these RCT's presented several problematic methodological issues. For example, the time of treatment onset with medications was not always standardized among patients enrolled in each study, making it difficult to draw conclusions as to when treatment with these agents should be initiated. Moreover,

in some RCT's, a substantial number of patients were withdrawn from blind treatment because patients in the control group were open label non-placebo. Thus, patients analyzed sometimes represented a select few of the initial study population. Lastly, patients have a good prognosis for the first several years post-CABG. Therefore, the power to detect differences in clinical events early after CABG among studies with small numbers of patients is not high. The fact that most RCT's had small numbers of patients and short follow-up times is a limitation.

CONCLUSION

Cardiac medical therapy may play a pivotal role in the prevention of angina, MI and death in the post-CABG patient. However, in our review of the literature, very few RCT's were found that examined the efficacy of cardiac medical therapy following CABG. The use of aspirin and anti-lipid agents seems well warranted from the literature. It remains uncertain, however, how long treatment with either of these medications should be continued after CABG. More trials are needed to support the routine use of ACE inhibitors post-CABG. Lastly, little evidence supports the use of beta-blockers, CCB's and nitrates following CABG. The results of this review point to an urgent need for additional studies of cardiac medical therapy in the post-CABG patient.

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Table 1. Randomized Controlled Trials of Aspirin Use in Post-CABG Patients.

Author, Year, Reference	Number Randomized	Treatment Onset (No. Days Pre- or Post-Op)	Follow-up Time (Months)	Number with Follow-up Angiography	Aspirin (%)	Control (%)	P-value
Angiographic Endpoint: Number of Patients with one or more grafts occluded at follow-up angiography							
Goldman et al., 1989[32]	772	-1	12[†]	406[$]	105/299 (35)	47/107 (44)	0.10
Chesebro et al., 1984[33]	407	0[‡]	12[†]	343	12/171 (7)	30/172 (17)	0.003
Goldman et al., 1994*[34]	334	365	36	288	(31)	(38)	0.26
Gavaghan et al., 1991[35]	237	0	12[†]	219	14/119 (12)	30/100 (30)	<0.001
Pirk et al., 1986 [γ#36]	93	0	12	65	13/37 (17)	30/38 (54)	<0.001
Brooks et al., 1985[37]	320	2 to 3	12	266	33/133 (25)	37/133 (28)	>0.05[§]
McEnany et al., 1982[38]	216	3 or 4	21.5	111	15/40 [κ] (37)	16/37 [κ] (43)	>0.05[§]
Sharma et al., 1983 [#39]	176	3 to 5	12	142	22/50 [κ] (44)	20/44 [κ] (46)	>0.05[§]
Brown et al., 1985[31]	147	2 to 3	12	127	10/38 [κ] (26)	18/44 [κ] (41)	>0.05[§]
Clinical Endpoint: Number of Patients or Mean ± SD with MI at follow-up							
Goldman et al., 1989[32]	772	-1	12[†]	502	(4)	(1)	0.12
Goldman et al., 1994[34]	334	365	36	288	1.9 ± 13.6	1.7 ± 13.1	0.93

MI= Myocardial Infarction

[$] The p-value was not explicitly stated in these studies.

[γ] In this study, occlusion was measured per graft. Therefore, the denominators do not add up to the total number of patients with follow-up angiography.

[*] For most studies, the numbers of events were reported as percentages rather than absolute numbers. When possible, the numbers reported here have been derived from the percentages reported using the number of patients with follow-up angiography. For some studies, the breakdown of patients in each treatment group was not reported and cannot be inferred.

[†] Follow-up time occurred at a median of 12 months.
Follow-up time was reported as a mean.

[‡] In these studies, dipyridamole was administered two days prior to CABG.

[κ] In these studies, the denominator of both treatment groups do not add up to the total number with follow-up angiography because there were multiple treatment arms and only aspirin vs. placebo are reported here. Other treatment arms included aspirin and dipyridamole or warfarin.

[$] In this study, the total number with follow-up angiography do not include the treatment arm that received sulfinpyrazone only.

[#] In these studies the control group had no treatment (open label). In all other studies of aspirin use, patients in the control group received placebo.
In these two studies, other clinical events were also reported and are described in the manuscript.

Table 2. Randomized Controlled Trials of Anti-Lipid Agents in Post-CABG Patients.

Author, Year, Reference	N	Medication Used	Treatment Onset (No. Months Post-Op)	Follow-Up (Years)	Endpoints	Anti-Lipid Agent* (%)	Control* (%)	P-value
Post-CABG, 1997[† 41]	1351	Lovastatin	12-132	4[Ψ]	Composite Endpoint[‡]	85/676 (13)	103/675 (15)	0.12
Follow-up, 2000[42]	1351	Lovastatin	12-132	7.5[Ψ]	Composite Endpoint[‡]	207/676 (31)	271/675 (40)	0.001
Frick et al. (LOCAT), 1997[43]	395	Gemfibrozil	9-36	2.6[§]	Composite Endpoint [Ψ]	7/197 (4)	7/198 (4)	>0.05[γ]
Blankenhorn et al. (CLAS), 1987[44]	188	Colestipol/ Niacin	3	2	Cardiac Death	0/94 (0)	1/94 (1)	>0.05[γ]
					MI	1/94 (1)	4/94 (4)	>0.05[γ]
Follow-up, 1990[45]	103	Colestipol/ Niacin	3	4	Cardiac Death	0/56 (0)	0/47 (0)	>0.05[γ]
					MI	3/56 (5)	4/47 (9)	>0.05[γ]
Follow-up, 1996[46]	162	Colestipol/ Niacin	3	7	Composite Endpoint[#]	32/80 (40)	50/82 (61)	0.04

N= Number of patients randomized
MI= Myocardial infarction
* For most studies, the numbers of events were reported as percentages rather than absolute numbers. The numbers reported here have hence been derived from the percentages given and the initial number of patients cited.
† In this study, the control group received moderate treatment of 2.5 mg per day versus 40 mg per day in the aggressive treatment group.
‡ Composite Endpoint: Death, MI, Stroke, CABG or PCI.
§ Time of follow-up occurred at a mean of 'x' years post-CABG.
Ψ Composite Endpoint: Death, MI, CABG or PCI.
γ The p-value was not explicitly stated in these studies.
Composite Endpoint: Cardiac Death, MI, CABG or PCI.

Table 3. Randomized Controlled Trials of Beta-Blockers, CCB's, and ACE Inhibitors in Post-CABG Patients.

Author, Year, Reference	N	Medication Used	Treatment Onset (No. Days Post-Op)	Follow-Up (Years)	Endpoint	Treatment (%)	Placebo (%)	P-value
Beta-Blockers								
Sjoland et al., 1995[47]	618[#]	Metoprolol	4-21	2	MI	3/307 (1)	4/311 (1)	>0.05[*]
	618[#]				Mean Chest Pain Score[†]	0.6±0.1 (SEM)	1.1±0.1 (SEM)	0.001
(Another analysis)[48]	967				Composite Endpoint[‡]	42/480 (9)	39/487 (8)	>0.05[*]
Calcium Channel Blockers								
Gaudino et al, 2001[52]	120	Dilitazem	365	5	Cardiac Death	1/63 (2)	0/57 (0)	0.96
ACE Inhibitors								
Oosterga et al. (QUO VADIS), 2001[53]	149	Quinapril	-30	1	Composite Endpoint[§]	3/75 (4)	11/73 (15)	0.02

N= Number of patients randomized SEM: Standard Error of the Mean
ACE: Angiotensin Converting Enzyme
MI= Myocardial Infarction
[*] The p-value was not explicitly stated in this study.
[#] 618 patients received exercise testing at 2 year follow-up of the 967 randomized in the study.
[†] Mean Chest Pain Score was defined using the Borg Scale from 0-10 with 0 being no chest pain.
[‡] Composite Endpoint: Death, MI, Unstable Angina, CABG or PCI.
148 patients were included in the analyses of the 149 patients randomized in this study.
[§] Composite Endpoint: Death, Stroke, MI, Angina, Transient Ischemic Attacks, CABG or PCI.

3- STUDY OBJECTIVES

The main objective of this study is to examine the use of cardiac medical therapy among CABG patients. More specifically, the objectives of this study are to:

1. Determine the frequency of use of cardiac medications among subgroups of patients undergoing CABG.
2. Examine the determinants of use of cardiac medications at 12-months following CABG.

We hypothesize there to be variation in the use of cardiac medications among patients post-CABG. We expect the results of this study to be consistent with the findings of other studies on the use of cardiac medications in CAD patients with no history of CABG. We also expect to find that the determinants of cardiac medical therapy post-CABG reflect baseline co-morbidities and study center.

4- STUDY METHODOLOGY

4.1 The Routine Versus Selective Exercise Treadmill Testing After Coronary Artery Bypass Graft Surgery (ROSETTA-CABG) Registry

The ROSETTA-CABG Study is a multicenter prospective cohort involving over 400 patients from 16 centers in six countries. However, 12-month follow up data have been completed as of June 1st, 2003 for 341 patients from 13 centers in six countries (1 in Belgium, 2 in Canada, 1 in France, 1 in Pakistan, 1 in the United Kingdom and 7 in the United States). The study's primary purpose was to examine the use of stress testing after CABG. As part of the protocol, data were prospectively collected regarding cardiac medical therapy at admission, discharge and at 12-months following CABG. Patients were enrolled in the study between May 1999 and May 2002 following a first successful CABG but before hospital discharge. In order to be enrolled into the study, patients were to have been completely revascularized at the time of their CABG.

4.2 Sample Size and Power

Because our primary objective in this paper is to measure the proportion of patients receiving cardiac medical therapy at 12-months following CABG, we are conducting a descriptive study. The sample size required to detect confidence interval (CI) widths of 0.10 to 0.20 around a proportion ranges from 61 to 384 patients (Table 1) (53). These sample sizes are for a 95% CI and an alpha of 0.05.

Table 1. Sample Size for Common Values of Proportions on Medication at 12-Months.

Proportion at 12-Months	Width of Confidence Interval		
	0.10	0.15	0.20
0.90	138	-	-
0.85	196	87	-
0.80	245	109	61
0.75	288	128	72
0.70	323	143	81
0.65	349	155	87
0.60	369	164	92
0.55	380	169	95
0.50	384	171	96

For example, Table 1 shows that for a proportion of 70%, we would need a sample size of 323 patients in order to have a CI Width of 0.10. In other words, if the true proportion is 70%, upon many repetitions of this study, the confidence interval for the proportion would be, on average, approximately 10 points wide.

Little work has been done on the use of cardiac medications following CABG. Therefore, the proportion of patients we expect to be receiving cardiac medical therapy following CABG was estimated from two studies conducted in post-PCI patients (36, 54). If we were to find similar proportions in our population as those found in PCI patients, a fixed sample size of 320 patients would give us CI widths ranging from 0.06 to 0.11 (Table 2). It is important to note, however, that as patients post-CABG are more likely to be angina-free compared with post-PCI patients, the use of CCB's and nitrates may be substantially lower than found in the two post-PCI studies.

Table 2. Width of CI achieved for a fixed sample size of N=320 and proportions found from prior research post PCI.

Medication	P(%)	Width of CI achieved
Aspirin	93	0.06
Anti-lipid Agents	61	0.11
Beta-Blockers	59	0.11
CCB's	42	0.11
Nitrates	43	0.11
ACE inhibitors	32	0.10

P= expected proportion of patients to be receiving the medication at 12-months following CABG
CI= confidence interval

For example, Table 2 shows that if we expect 93% of patients to be receiving aspirin at 12-months following CABG, with a fixed sample size of 320 patients, we will be able to detect a CI width of 0.06 (i.e. 90% to 96%.)

The results seen in Tables 1 and 2 demonstrate that we have sufficient sample size to measure a wide range of proportions with relatively narrow 95% CI's.

5- RESULTS

5.1 Preface to Manuscript #2

Several studies have demonstrated a lack of optimal medical therapy among subgroups of patients with CAD including: CHF, prior MI and prior PCI (35-44). However, patterns in the use of cardiac medical therapy among patients who have undergone CABG remains unclear. Using the data from a prospective cohort of patients undergoing CABG, we were able to examine the use of cardiac medical therapy in post-CABG patients.

The following manuscript describes the result of this research. The manuscript was submitted for publication in December 2003. I presented an abstract describing the patterns of use of cardiac medications among ROSETTA-CABG patients at the 52nd Annual American College of Cardiology Conference in Chicago in March 2003.

5.2 Author's Contributions

As first author, I was responsible for writing the manuscript, conducting the statistical analyses, interpreting the data and making all revisions. As coordinator for the ROSETTA-CABG Registry, I was also responsible for all data collection, correspondence with study centers and database management from May 1999 until June 2003. Dr. Mark Eisenberg, as thesis supervisor and principal investigator of the ROSETTA-CABG Study, contributed to all stages of the research study planning and execution, interpretation of the results and critical revision of the manuscript. Dr. Robert Platt, as co-supervisor with an expertise in biostatistics, was involved in the interpretation of the statistical results and critical revision of the manuscript. He also provided valuable feedback regarding issues of statistical power, building the appropriate models and issues surrounding causal models. Dr. Louise Pilote, as thesis committee member, was also involved in the interpretation of the results and critical revision of the manuscript. She also contributed her expertise in the area of cardiovascular epidemiology and health services research. As co-investigator for the ROSETTA-CABG Study, she was involved in study planning and execution.

5.3 Manuscript

Use of Cardiac Medical Therapy Among Patients Undergoing CABG: Results from the ROSETTA-CABG Registry

Short Title: Cardiac Medical Therapy Following CABG

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ABSTRACT

Introduction: Secondary prevention is greatly needed following CABG in order to reduce the risk of unstable angina, myocardial infarction (MI) and death. However, very little research exists on the use of cardiac medical therapy in CABG patients. The objective of this study is to describe the use of cardiac medical therapy among patients discharged after CABG.

Methods: The use of aspirin, clopidogrel, coumadin, anti-lipid agents, beta-blockers, calcium-channel blockers (CCB's), nitrates, and ACE inhibitors was examined among 320 patients who were enrolled in the Routine versus Selective Exercise Treadmill Testing After CABG (ROSETTA-CABG) Registry. This registry was a prospective multicenter study that examined the use of stress testing after CABG. The use of cardiac medical therapy was also examined among patients with various co-morbidities. Logistic regression was used to identify the determinants of use of medications at 12-months following CABG.

Results: Most patients were male, hyperlipidemic, and had CABG for relief of anginal symptoms. At admission, discharge and 12-months, use of aspirin was 71%, 92% and 87%. Eight percent of patients were not receiving any form of anti-platelet or anti-coagulant therapy at 12-months. The use of anti-lipid agents remained constant from 55% at admission to 57% at discharge and increased significantly by 12-months. However, 24% were not receiving anti-lipid agents at 12-months. The use of beta-blockers was 57% at admission, 71% at discharge and 64% at 12-months. Both the use of CCB's and nitrates decreased modestly from admission to discharge and remained stable at roughly 20% and 10%, respectively, at 12-months. The use of ACE inhibitors

remained stable from 33% at admission to 38% at 12 months. Modest variation was found in the use of anti-lipid agents and ACE inhibitors among patient subgroups. In contrast, little variation was found in the use of aspirin, clopidogrel, coumadin, beta-blockers, nitrates and CCB's. Hyperlipidemia, hypertension, obesity, pre-CABG left ventricular ejection fraction of less than 40% were all found to be important baseline co-morbidities that determined the use of cardiac medical therapy at 12-months. Most importantly, the use at discharge was found to be an important determinant of 12-month use for each cardiac medication examined in this study.

Conclusion: The use of anti-lipid agents, beta-blockers and ACE inhibitors is too low among patients known to benefit from their use and the use of nitrates is too high post-CABG. Methods to help physicians better modify the use of cardiac medical therapy for the secondary prevention of cardiovascular events post-CABG are greatly needed. The results of this study suggest that discharge from the hospital provides the best opportunity for physicians to modify the use of cardiac medical therapy among patients undergoing CABG.

INTRODUCTION

Coronary artery bypass graft surgery (CABG) relieves anginal symptoms and decreases morbidity and mortality in patients suffering from coronary artery disease (CAD) (1-2). Despite the benefits of CABG, 15% to 25% of patients develop graft closure by 1 year following CABG (3-6). Cardiac medical therapy is therefore warranted following CABG in order to prevent graft closure and subsequent cardiac events. Very few studies have examined the benefits of cardiac medical therapy specifically among post-CABG patients (7-10). However, many of the factors that place a post-CABG patient at increased risk for cardiac events are co-morbidities for which targeted medical therapy already exists (11-17). In spite of this evidence, a number of researchers have documented a lack of optimal therapy among patients with a history of myocardial infarction (MI), congestive heart failure (CHF), or prior percutaneous coronary intervention (PCI) (18-24). To our knowledge, no study has examined patterns of use of cardiac medical therapy in post-CABG patients. For this reason, we examined the use of cardiac medical therapy among patients undergoing CABG in the Routine versus Selection Exercise Treadmill Testing After Coronary Artery Bypass Graft Surgery (ROSETTA-CABG) Registry. The purpose of our study was: 1) to examine the patterns of use of medical therapy in post-CABG patients, 2) to examine the patterns of use among subgroups of post-CABG patients, and 3) to identify the determinants of 12-month use of cardiac medications.

METHODS

The ROSETTA-CABG Registry

The Routine versus Selective Exercise Treadmill Testing after Coronary Artery Bypass Graft Surgery (ROSETTA-CABG) Registry is a prospective multicenter study

examining the use of functional stress testing after CABG involving 17 centers in Belgium, Canada, France, Pakistan, the United Kingdom and the United States. As part of the protocol, data were prospectively collected on medical therapy at admission, discharge and at 12-months following CABG. A total of 410 patients were enrolled in the study between May 1999 and May 2002 following a successful CABG but before hospital discharge. As of May 2003, 12-month follow-up data was available on 341 patients. The Research and Ethics Committee approved the study at the institutions involved, and written informed consent was obtained before patients were enrolled in the study.

The inclusion criteria for this study were: 1) to have undergone a first successful CABG in which all ischemic areas were considered to be revascularized and the patient had no major in-hospital events, and 2) to have undergone only isolated CABG surgery (i.e. no valve surgery, aortic reconstruction, etc.). Patients with the following criteria were excluded: 1) those who were participating in conflicting studies, 2) those who had contraindications to any repeat cardiac procedures (i.e. cardiac catherization, PCI, repeat CABG), 3) those who had contraindications or an inability to undergo follow-up functional testing, 4) those who were pregnant or likely to become pregnant, 5) those who had a medical condition with a prognosis of less than 1 year, and 6) those who were likely to be unavailable for 12-month follow-up.

Study Population and Data Collection

Of the 341 patients who were due for 12-month follow-up by May 2003, 11 patients were lost to follow-up, 8 patients died, and 2 patients had missing 12-month medications data. Thus, we examined cardiac medical therapy among 320 patients. Data

were specifically collected on the use of aspirin, clopidogrel, coumadin, anti-lipid agents, beta-blockers, nitrates, calcium-channel blockers (CCB's), and ACE inhibitors at admission, discharge and 12-months. The use of nitrates included only oral and patch preparations. We also collected data on contraindications and allergies to these medications. Less than 1% of patients had contraindications or allergies to medications from admission to 12-months following CABG. Thus, these patients were not excluded from the analyses.

In addition to data on medical therapy, we collected data on demographic, clinical and procedural characteristics at baseline and discharge following CABG. For example, we collected data on baseline characteristics such as CHF, Canadian Cardiovascular Society (CCS) Angina Class, diabetes, hyperlipidemia, hypertension, left ventricular function and prior MI.

Statistical Analysis

Descriptive analyses were performed to determine the frequency of use of each cardiac medication at baseline, discharge and 12-months. In addition to examining the overall proportion of patients taking these medications, we also examined the use of combination anti-ischemic therapy defined as two or more of the following agents: beta-blockers, CCB's and nitrates. We also examined the use of these medications in patients with various co-morbidities. Continuous data are presented as the mean ± standard deviation, and dichotomous data are presented as percentages. We used univariate and multivariate regression in order to identify determinants of use of cardiac medications at 12-months post-CABG, and to control for confounding. All variables with a p-value of <0.10 in univariate analyses were entered into the multivariate model. Chi-square tests

were used for the univariate analyses, and logistic regression was used for multivariate regression.

RESULTS

Most patients were men over the age of 60 years with multiple risk factors for CAD (Table 1). More than half of the patients had hyperlipidemia and hypertension, and more than a quarter were diabetic and had previously suffered from an MI. Most patients had CABG for the relief of anginal symptoms. The vast majority of patients had at least 3 vessels bypassed and virtually all had the left internal mammary artery used as a bypass conduit. Over half of patients had saphenous vein grafts used, and only 15% of patients had the radial artery used as a bypass conduit.

ANTI-PLATELET AND ANTI-COAGULANT THERAPY

Patterns of Use

Aspirin use increased from 71% at admission to 92% at discharge (Figure 1). Importantly, 13% of patients were not receiving aspirin at 12-months. Among patients not receiving aspirin at 12-months, 6% were receiving clopidogrel and/or coumadin. Seven percent of patients were not receiving any anti-platelet or anti-coagulant therapy at 12-months. Each of these patients had been discharged with some form of anti-platelet or anti-coagulant agent.

The use of aspirin was similar at discharge among different patient subgroups (Figure 1). However, among each patient subgroup, less than 90% were receiving aspirin at 12-months. Patients with peripheral vascular disease were particularly less likely to

receive aspirin at 12-months. Nonetheless, many of these patients were receiving clopidogrel and/or coumadin.

Determinants of use

Only 2 variables were significant determinants of aspirin use at 12-months in the multivariate model (Table 2). Patients who had a CABG because of unstable angina were 80% less likely to be receiving aspirin at 12-months than patients who had a CABG for other reasons (OR=0.2, 95% CI=0.1-0.5). The use of aspirin at discharge was also an important determinant of 12-month use (OR=18.6, 95% CI=3.7-94.1). The use of clopidogrel and coumadin were also found to be highly associated with the use of aspirin at 12-months. Clinically speaking, patients with CAD should be receiving aspirin irrespective of whether they are on clopidogrel and/or coumadin. However, we found 54% of patients on clopidogrel at 12-months to not be on aspirin at 12-months, and likewise, 55% of patients on coumadin at 12-months to not be on aspirin at 12-months. We therefore felt that the use of both these medications were important enough predictors to be left in the multivariate model. Patients who had been treated with clopidogrel or coumadin at 12-months were both less likely to have been treated with aspirin at 12-months.

ANTI-LIPID AGENTS

Patterns of Use

The use of anti-lipid agents did not change from admission to discharge but did increase substantially post-discharge (Figure 2). However, 24% of patients were still not receiving anti-lipid agents at 12-months. The use of anti-lipid agents was similar among

patients with prior MI and diabetes. Although patients with hyperlipidemia were more likely to receive anti-lipid agents at admission, discharge and 12-months, 15% of patients with hyperlipidemia were still not receiving anti-lipid agents at 12-months.

Determinants of Use

In the multivariate model, hyperlipidemia, unstable angina as the reason for CABG and use at discharge were all found to be determinants of the use of anti-lipid agents at 12-months (Table 2). Patients with Hyperlipidemia were more likely to receive anti-lipid agents at 12-months than patients without hyperlipidemia (OR=3.3, 95% CI=1.8-6.0). In contrast, patients who had unstable angina as the reason for CABG were 50% less likely to receive anti-lipid agents at 12-months (OR=0.5, 95% CI=0.3-0.9). Lastly, patients who were receiving anti-lipid agents at discharge were much more likely to receive anti-lipid agents at 12 months (OR=5.1, 95% CI= 2.7-9.6). Contrary to expectations, prior MI, diabetes, and obesity were not found to be significant determinants of 12-month use of anti-lipid agents.

ANTI-ISCHEMIC THERAPY

Patterns of Use

The use of beta-blockers increased from 57% at admission to 72% at discharge and decreased slightly to 64% by 12-months (Figure 3). Use of CCB's and nitrates decreased modestly from admission to discharge and decreased or remained constant by 12-months. Just over 60% of patients who were not on beta-blockers at admission were prescribed beta-blockers by discharge and an additional 25% were prescribed these

agents by 12-months. In contrast, 22% of patients were taken off these agents by discharge and an additional 21% by 12-months. Fifteen percent of patients who were not receiving CCB's at discharge were receiving them at 12-months and 60% were no longer receiving them. Similar trends were found for the use of nitrates where 11% were prescribed these agents and 60% were taken off these agents in the 12-months following discharge from the hospital. There were no substantive differences between patient subgroups for any of the 3 anti-ischemic medications. Of note, however, patients with hypertension were more likely to receive beta-blockers and CCB's than other patient subgroups. Moreover, patients with prior MI and CHF were more likely to receive nitrates and less likely to receive CCB's than other patient subgroups.

A large proportion of patients were still receiving anti-ischemic agents at discharge and 12-months. Over half of all patients were receiving beta-blockers at 12-months, and approximately 20% were receiving CCB's and nitrates. At hospital admission, 45% were receiving combination anti-ischemic therapy (two of more of the following: beta-blockers, CCB's or nitrates) (Table 3). Although double therapy decreased from discharge to 12-months, only 23% of patients were receiving no form of anti-ischemic agents at 12-months. Most importantly, among patients whose main reason for CABG was relief of anginal symptoms, more than half were still receiving anti-ischemics at discharge and 12-months. Among patients with no CHF, hypertension, or prior MI, for example, beta-blocker use was 48% at admission, 62% at discharge and 56% at 12-months.

Determinants of Use

Only one variable was found to be a significant determinant of 12-month use of beta-blockers in the multivariate analyses (Table 2). Patients received beta-blockers at discharge were much more likely to receive them at 12-months than patients not receiving them at discharge (OR=10.0, 95% CI=5.7-17.6). Hypertension was also found to increase the odds of receiving beta-blockers at 12-months (OR=1.78, 95% CI=1.1-2.9). However, when including both variables in the same multivariate model, only beta-blocker use at discharge remained a significant determinant. In other words, patients with hypertension receiving beta-blockers at discharge continue to receive them at beta-blockers, and it is this relationship that overwhelms any other determinant. Therefore, it was decided that only the use at discharge would remain in the model. Neither prior MI, history of CHF or LVEF < 40 were found to be determinants of 12-month beta-blocker use.

Three determinants were found for the use of CCB's at 12-months in the multivariate analyses (Table 2). Both patients with hypertension and obesity were more likely to receive CCB's at 12-months (OR=3.4, 95% CI=1.6-7.4 and OR=2.2, 95% CI=1.1-4.2, respectively). The use of CCB's at admission and discharge were also found to be important determinants of 12-month use. However, as these variables were highly correlated, and use at discharge was a stronger determinant, only use at discharge was left in the model. Surprisingly, use of the radial artery as a bypass graft or CCS Angina Class prior to CABG or at 12-months were not found to be associated with the 12-month use of CCB's.

Two variables were found to be determinants of 12-month use of nitrates (Table 2). Patients with a pre-CABG LVEF <40% were more likely to receive nitrates at 12-months (OR=5.0, 95% CI=1.1-7.6). Similar to the use of beta-blockers, the use of nitrates at discharge was also found to be highly correlated with baseline determinants. Women were 77% more likely to be receiving nitrates at 12 months and patients with a history of CHF were also more likely to receive nitrates at 12-months (OR= 3.6, 95% CI=1.2-10.8). However, when controlling for the use at discharge, female gender and history of CHF were no longer found to be significant determinants of 12-month use. Thus, only pre-CABG LVEF< 40% and the use of nitrates at discharge were left in the model.

ACE INHIBITORS

Patterns of Use

The use of ACE inhibitors was low at admission, discharge and at 12-months (Figure 4). Patients with CHF and diabetes were much more likely to receive ACE inhibitors at discharge and at 12-months when compared with other patient subgroups (Figure 3). In contrast, only 65% of those with a history of CHF were receiving ACE inhibitors at 12-months. Patients with prior MI or hypertension were only slightly more likely to receive ACE inhibitors at discharge and 12-months than other patient subgroups.

Determinants of Use

In the multivariate model, four variables were found to be significant determinants of use of ACE inhibitors at 12-months (Table 2). Patients with a pre-CABG LVEF< 40% or with hypertension were 2.7 times and 2.2 times, respectively, more likely

to receive ACE inhibitors at 12-months (95% CI=1.3-5.7, 95% CI=1.2-4.0, respectively). In contrast, men were 60% less likely to receive ACE inhibitors at 12-months when compared to women (OR=0.4, 95% CI=0.2-0.8). Interestingly, diabetes, prior MI and history of CHF were not found to be significant determinants of 12-month ACE inhibitor use in the multivariate model. The use of ACE inhibitors at discharge was found to be an important determinant of use of ACE inhibitors at 12-months (OR=6.0, 95% CI=3.2-11.1). Lastly, the use of angiotensin II inhibitors at 12-months was also found to be inversely associated with the use of ACE inhibitors at 12-months.

DISCUSSION

This study was designed to examine the patterns of use of cardiac medical therapy among patients undergoing CABG. Although previous studies have shown a lack of optimal therapy among patients with CAD, CHF, prior MI and prior PCI, no study has, to our knowledge, examined the use of cardiac medical therapy among CABG patients. In general, we found little variation in the use of aspirin, CCB's and ACE inhibitors from discharge to 12-months following CABG. On the other hand, the use of anti-lipid agents increased substantially post-discharge whereas the use of nitrates and beta-blockers decreased modestly.

Although many patients had co-morbidities suggesting that they would benefit from specific medical therapy, these subgroups were not always more likely to receive a specific medication than other patients. For example, the use of beta-blockers among patients with prior MI is well known to decrease mortality (16-18). However, patients with prior MI were found to be just as likely as other patient subgroups to receive beta-blockers at discharge and at 12-months following CABG. Similarly, patients with

diabetes or prior MI were only slightly more likely to receive ACE inhibitors at 12-months than patients without these co-morbidities. These differences were not statistically significant, nor were these co-morbidities found to be significant determinants of 12-month use.

Past research has demonstrated the efficacy of aspirin and anti-lipid agents among CAD patients with multiple co-morbidities, including CABG patients (13-16). Thus, we expected fewer differences among patient subgroups. On the other hand, very little research exists to support the use of beta-blockers, CCB's or nitrates specifically among CABG patients. Therefore, we would have expected only patients with co-morbidities that are known to benefit from these medications to have significantly higher frequencies of use than patients without these co-morbidities. We would not have expected the use of beta-blockers to be zero due to their use in the treatment of hypertension and in post-MI and CHF patients. However, patients with these co-morbidities were no more likely to receive these medications than patients without these co-morbidities. In contrast, nitrates are principally indicated for the treatment of angina. However, patients undergoing CABG have very low rates of angina post-CABG and patients enrolled in this study were to have been completely revascularized. Thus, the necessity for nitrate use should have been quite low in these patients. Moreover, only 4% of patients were hospitalized for unstable angina in the 12-months following CABG. Despite this fact, over 15% of patients were prescribed nitrates between discharge and 12-months following CABG.

When examining the determinants of use of cardiac medical therapy at 12-months, the most important determinants found were baseline co-morbidities and the use of the medication at discharge. However, some of these baseline co-morbidities were so

highly correlated with the use at discharge, that after accounting for the use at discharge in the model, they were no longer significant determinants of 12-month use. This finding suggests that the most important time when the patient is being prescribed appropriate therapy might occur in-hospital and not post-discharge.

Comparison with Other Studies

To our knowledge, no previous study has examined the patterns of use of cardiac medical therapy among patients undergoing CABG. However, when comparing the results found in our study to previous studies that examined the use of cardiac medical therapy among other patient subgroups, similar trends were observed. Previous studies have demonstrated a lack of optimal therapy among CAD patients, patients with CHF, and those undergoing PCI (22-28). Spencer et al. found lipid-lowering agents to be underutilized post-MI, with less than one-quarter of patients discharged from the hospital on this therapy (22). Allen et al. found only 47% of patients eligible for lipid lowering agents to be receiving them at admission and 58% at discharge (24). Likewise, Hasdai et al found that although patients had been successfully revascularized following PCI, the use of anti-ischemic agents at 6 months was over-prescribed (26). Thirty-nine percent of patients were receiving beta-blockers, 57% were receiving CCB's and 36% were receiving nitrates, despite a lack of angina in 69% of patients. This trend of overuse of anti-ischemic agents persisted at 12 months, where only 23% of patients did not receive either of the anti-ischemic medications. In our study, we similarly found the use of anti-lipid agents to be too low at 12-months. Although hyperlipidemia was a significant determinant of 12-month use, 15% of patients with this co-morbidity were not receiving

anti-lipid agents. Moreover, the use of anti-ischemic agents at 12-months following CABG among fully revascularized patients was also found to be unexpectedly high.

LIMITATIONS

There are several potential limitations of this study that should be mentioned. Dosages were not collected, nor were the specific medications within a class of drugs. It is also possible that although patients were prescribed the appropriate medications, they were not compliant in their use. Clinical event rates were low during the 12-month follow-up period, and consequently, the association between medication use and clinical outcomes could not be explored. Moreover, it is possible that there were unknown confounders that were not controlled for in our analyses. For example, patient factors, physician factors and health care system factors which might have affected compliance were not collected in this study. This limitation allows us only to extend the results of this study to patterns of prescription use in CABG patients, and not to the effectiveness of use or the compliance of use. Another factor not controlled for was study center. As this was a multicenter study involving 13 centers in 6 countries, it is possible that differences in the use of cardiac medical therapy between study centers were present. However when including study centers in the multivariate models, study center was not found to greatly affect the beta coefficients of baseline clinical determinants already in the model. This variation could have been explored further with the use of random effects modeling and other correlated data analytic methods. Lastly, some of our results could have been due to spurious associations. For example, there exists no literature that demonstrates an association between obesity and the use of CCB's, nor the association between male

gender and the use of ACE inhibitors in CABG patients. It is therefore possible that these associations were spurious.

CONCLUSION

In conclusion, our study was designed to examine the use of cardiac medical therapy in patients undergoing CABG. Patients with hyperlipidemia were more likely to receive anti-lipid agents and patients with CHF were more likely to receive ACE inhibitors at 12-months than other patient subgroups. Little variation was found between patient subgroups in the use of all other cardiac medications studied. We would also have expected the use of anti-lipid agents, ACE inhibitors and beta-blockers to be higher among patient subgroups with co-morbidities known to benefit from these medications. Moreover, the use of nitrates among patients who were fully revascularized and who had little indication for their use appeared to be inappropriately high. Use at discharge was found to be an important determinant of 12-month use for all cardiac medications examined. Thus, use of appropriate cardiac medical therapy among patients who have undergone CABG might best be modified by physicians at hospital discharge.

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FIGURE LEGENDS

Figure 1. Use of Anti-Platelet and Anti-Coagulant Therapy Among 320 Patients Undergoing CABG in the ROSETTA-CABG Study.

Figure 2. Use of Anti-Lipid Agents Among 320 Patients Undergoing CABG in the ROSETTA-CABG Study.

Figure 3. Use of Anti-Ischemic Therapy Among 320 Patients Undergoing CABG in the ROSETTA-CABG Study.

Figure 4. Use of ACE Inhibitors Among 320 Patients Undergoing CABG in the ROSETTA-CABG Study.

Table 1. Baseline Clinical and Procedural Characteristics Among 320 Patients Enrolled in the ROSETTA-CABG Study.

Characteristic	%
Mean Age ± S.D. (years)	63 ± 10
Male	81
Mean Left Ventricular Ejection Fraction ± S.D.	54 ± 14
CCS Angina Class III-IV	40
Hyperlipidemia	75
Hypertension	65
Diabetes Mellitus	28
History of CHF	8
History of Angina	73
Prior MI	34
Prior PCI	18
Prior CABG	3
Peripheral vascular disease	7
Main Reason for CABG	
Anginal symptoms	69
Positive Functional Test	14
Recent MI	12
Other	5
Numbers of Grafts Bypassed	
1-2	19
3-4	64
5	18
Bypass Conduits	
Left Interior Mammary Artery	97
Radial Artery	15
Saphenous Vein Graft	62

CCS: Canadian Cardiovascular Society
CHF: Congestive Heart Failure
MI: Myocardial Infarction
PCI: Percutaneous Coronary Intervention
CABG: Coronary Artery Bypass Graft Surgery

Table 2. Predictors of Cardiac Medical Therapy at 12 Months Among 320 Patients in the ROSETTA-CABG Registry.

	Odds Ratio	95% Confidence Interval	P Value
Aspirin			
Reason for CABG: Unstable Angina	0.2	0.1-0.5	0.0003
Use at discharge	4.2	1.4-12.6	0.0098
Coumadin at 12 months	0.12	0.02-0.19	<0.0001
Clopidogrel at 12 months	0.04	0.01-0.18	<0.0001
Anti-Lipid Agents			
Hyperlipidemia	3.3	1.8-6.0	0.0002
Reason for CABG: Unstable Angina	0.5	0.3-0.9	0.0300
Use at discharge	5.1	2.7-9.6	<0.0001
Beta-Blockers*			
Use at discharge	10.0	5.7-17.6	<0.0001
Calcium-Channel Blockers			
Hypertension	3.3	1.5-7.2	0.0030
Obesity	2.2	1.1-4.2	0.0252
Use at discharge	3.5	1.8-6.8	0.0002
Nitrates*			
Pre-CABG LVEF < 40	5.0	1.8-13.8	0.0020
Use at discharge	16.5	5.7-47.9	<0.0001
ACE Inhibitors			
Male gender	0.4	0.2-0.8	0.0060
Pre-CABG LVEF < 40	2.7	1.3-5.7	0.0095
Hypertension	2.2	1.2-4.0	0.0121
Use of Angiotensin II inhibitors	0.14	0.04-0.55	0.0050
Use at discharge	6.0	3.2-11.1	<0.0001

*In the multivariate analyses of use of beta-blockers and nitrates at 12-months, other baseline co-morbidities were found to be important determinants. These variables had important associations with 12-month use, but their effects could not be distinguished in the multivariate model from that of use at discharge and are hence not presented in this table.

Table 3. Combination Anti-Ischemic Medical Therapy Among 320 Patients in the ROSETTA-CABG Study*.

	Admission (%)	Discharge (%)	12-Months (%)
Triple Therapy	13	1	3
Double Therapy	32	36	22
Monotherapy	34	52	51
No Anti-Ischemic Medications	22	11	23

*Anti-ischemic medical therapy was defined as one or more of the following: Beta–Blockers, CCB's, and nitrates.

Figure 1.

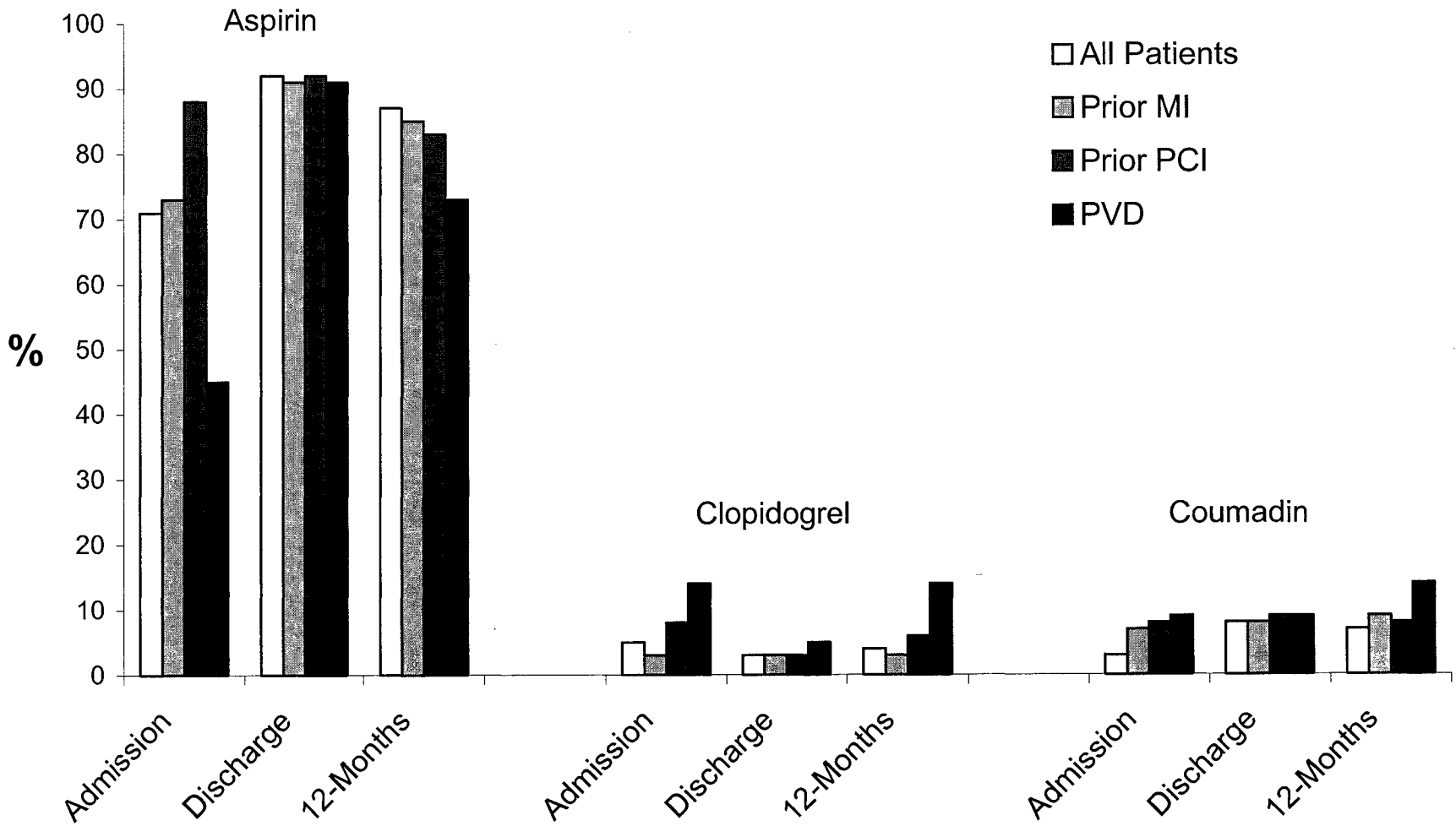

Aspirin
Clopidogrel
Coumadin
All Patients
Prior MI
Prior PCI
PVD
%
100
90
80
70
60
50
40
30
20
10
0
Admission
Discharge
12-Months
Admission
Discharge
12-Months
Admission
Discharge
12-Months

Figure 2.

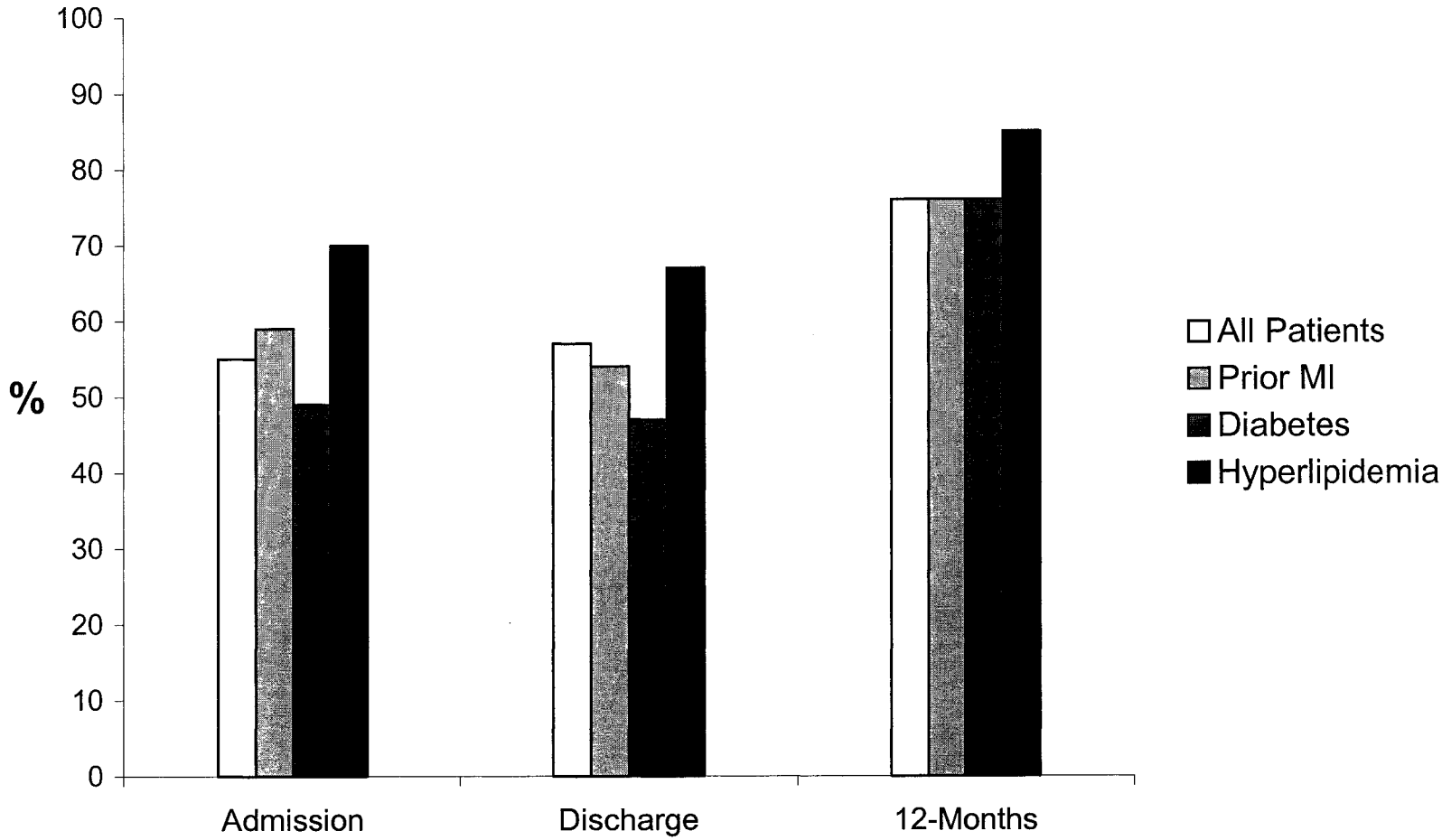

100
90
80
70
60
%
50
40
30
20
10
0
Admission
Discharge
12-Months
All Patients
Prior MI
Diabetes
Hyperlipidemia

Figure 3.

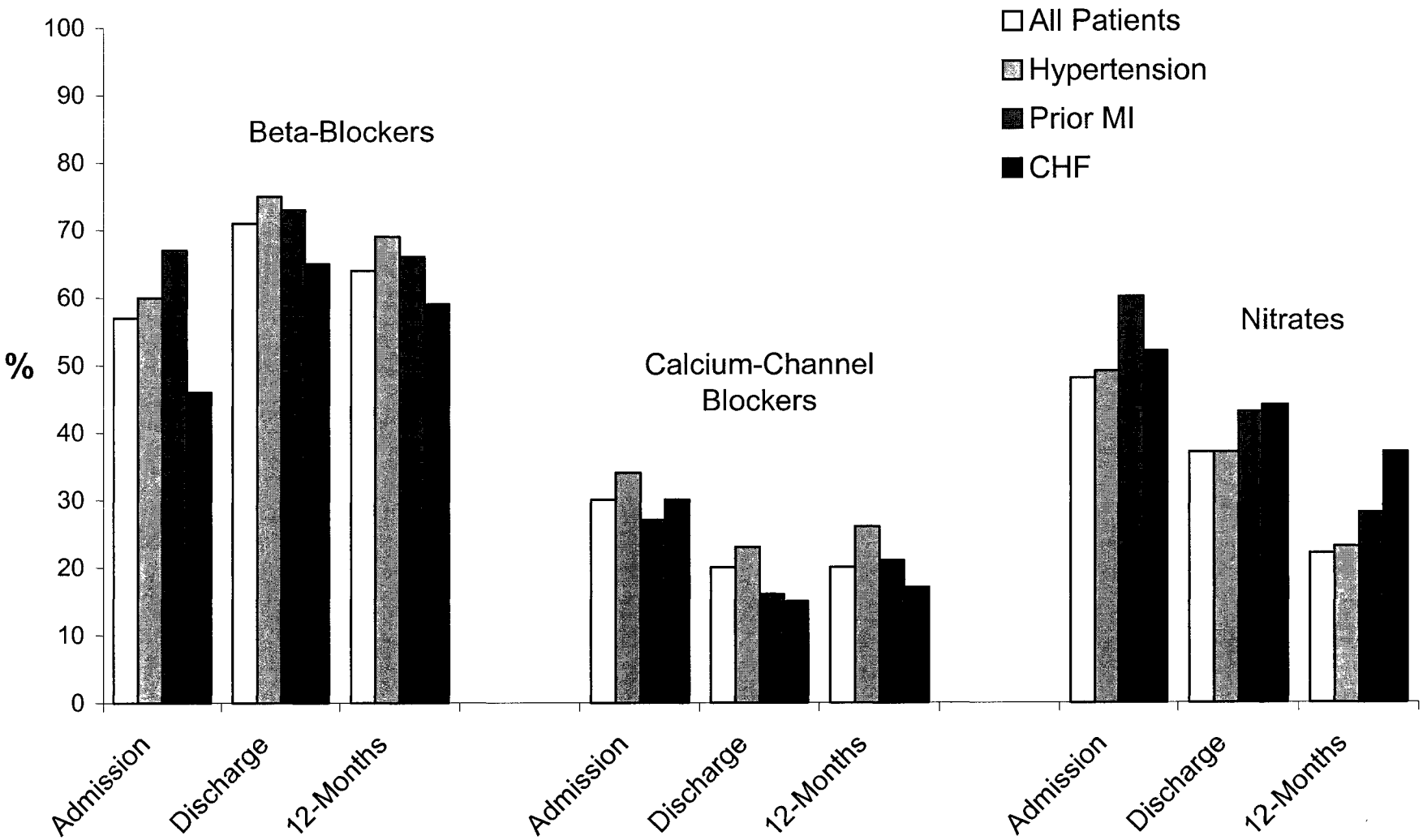
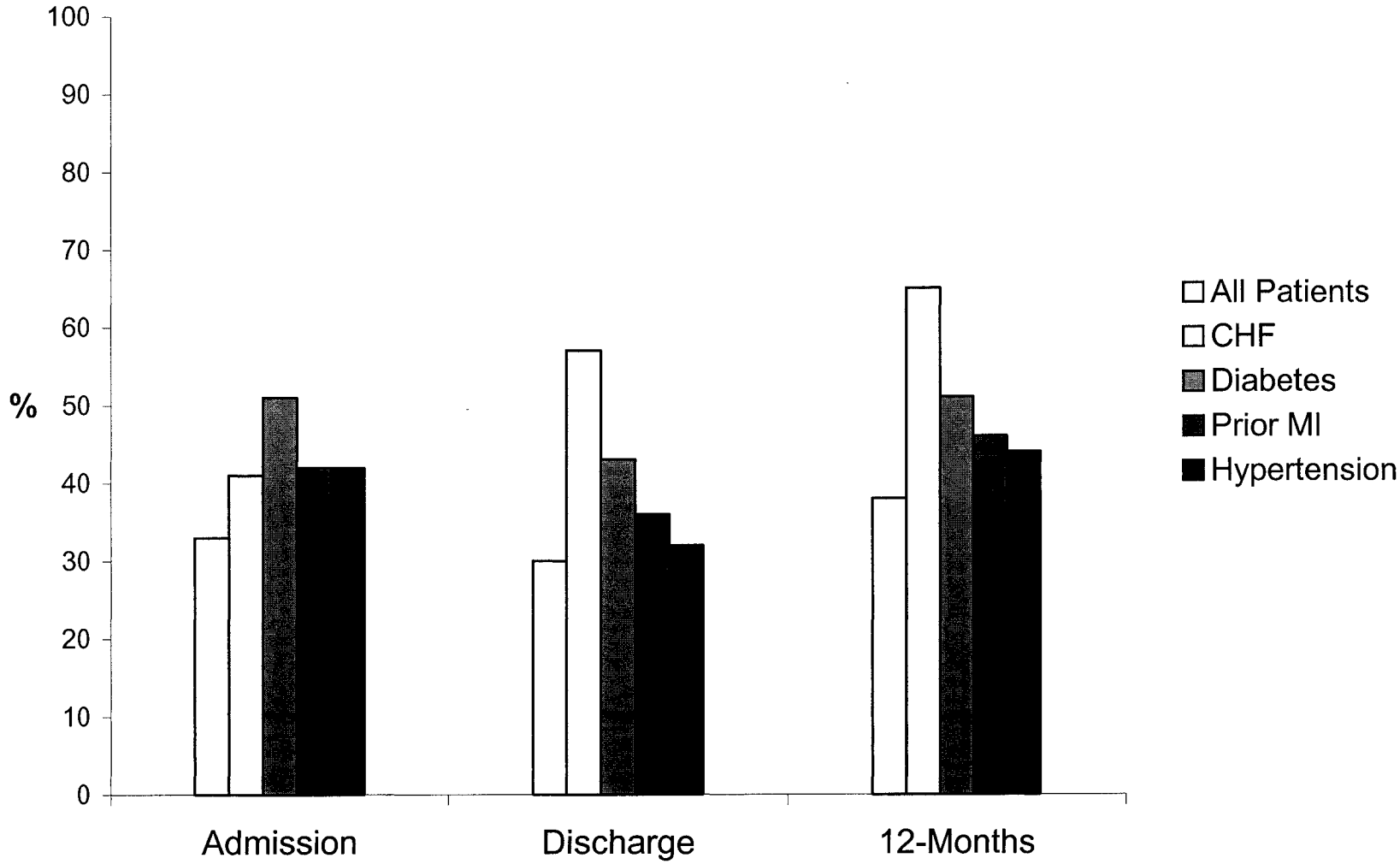

All Patients
Hypertension
Prior MI
CHF
%
100
90
80
70
60
50
40
30
20
10
0
Beta-Blockers
Calcium-Channel Blockers
Nitrates
Admission
Discharge
12-Months
Admission
Discharge
12-Months
Admission
Discharge
12-Months

Figure 4.

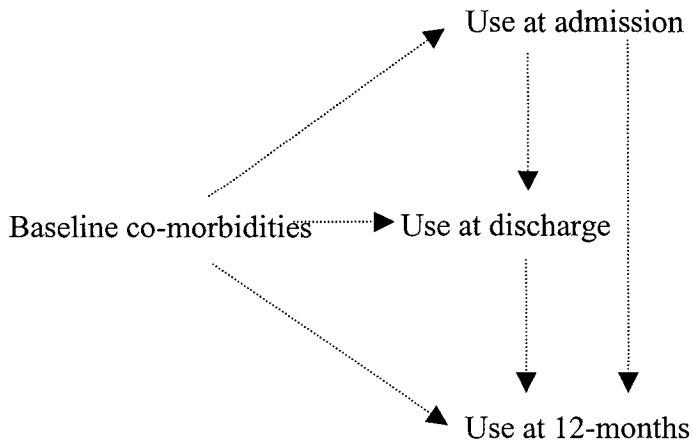

100
90
80
70
60
%
50
40
30
20
10
0
Admission
Discharge
12-Months
All Patients
CHF
Diabetes
Prior MI
Hypertension

5.4 Causal Models

Controlling for confounders by the use of multivariate regression methods is an essential part of any observational study. In our analyses of the use of cardiac medical therapy among patients undergoing CABG, we were interested in examining the determinants of use at 12-months. The use at discharge was often the most significant determinant of 12-month use and on many occasions, hid the effect of common baseline co-morbidities in the multivariate regressions. Consequently, we were interested in examining whether use of these medications at discharge was a determinant of the use at 12-months, independent of their relationship to baseline co-morbidities. Our objective was to build the best model to determine the use of cardiac medical therapy at 12-months.

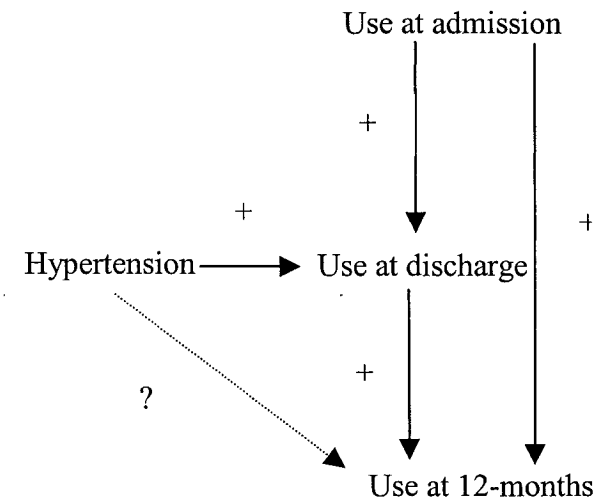
As shown in Figure 1, there were three time points when medication use was noted: at admission, discharge and 12-months following CABG. Baseline co-morbidities could potentially predict the use of medical therapy at any, some or all of these time points. The dotted lines used in Figure 1 are meant to represent the presence, or the lack of presence of an association between two variables.

Figure 1. Causal pathway between baseline co-morbidities and 12-month medication use



This type of complicated causal pathway can be represented by three different scenarios, two of which, when controlling for medication use at discharge lead us to the same conclusion. Using the example of beta-blockers: in the first scenario, hypertension could be a significant determinant of use of beta-blockers at both discharge and 12-months, but not at admission. Moreover, use of beta-blockers at admission and discharge could be positively correlated with each other and the use of beta-blockers at 12-months. This type of scenario is shown in Figure 2.

Figure 2. Causal pathway between hypertension and the use of beta-blockers at 12-months- First scenario.

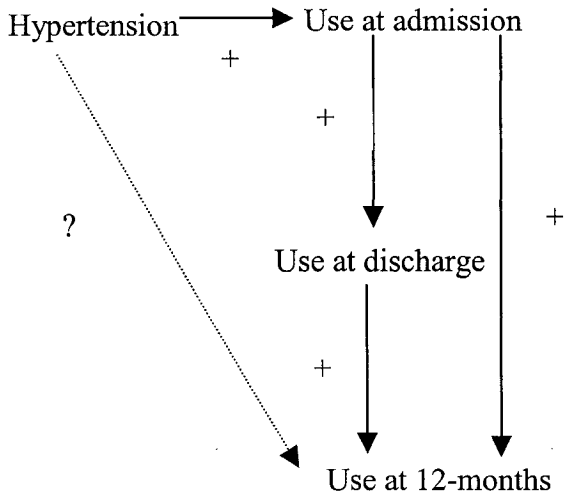


In this scenario, after controlling for the use of beta-blockers at discharge in the multivariate analyses, hypertension is no longer a significant determinant of use of beta-blockers at 12-months. Hence, we would conclude that the only determinant of use at 12-months is the use at discharge. But, it is only because most hypertensive patients are receiving beta-blockers at discharge that hypertension is no longer a significant

determinant of 12-month use. In other words, hypertension is highly correlated with the use of beta-blockers at discharge.

In the second type of scenario, the same relationship exists between use at admission, discharge and 12-months, but hypertension is only a significant predictor of use at admission.

Figure 3. Causal pathway between hypertension and the use of beta-blockers at 12-months- Second scenario.



In this scenario, we would also conclude that the only determinant of use of beta-blockers at 12-months is its use at discharge even though clinically, this pathway signifies a different pattern.

In the third scenario, the same causal model exists as the first, except after controlling for the use at discharge, hypertension remains a significant determinant of use at 12-months. In this case, more variation existed in the use of beta-blockers at discharge among patients with hypertension so that hypertension acts as an independent

determinant of 12-month use. In contrast to the first scenario, hypertensive patients might not have all received beta-blockers at discharge.

Although it is interesting to note that an important determinant of use at 12-months is its use at discharge, it is also pertinent that we understand the reasons for the use of medical therapy at 12-months. By being aware of these different possibilities in causal modelling, we can conclude that the lack of association between a baseline co-morbidity and 12-month medication use does not necessarily imply that the co-morbidity was not an important determinant. Instead, it might be that the baseline co-morbidity is a significant determinant of discharge use and the high correlation between the two eliminates the effect of the other. In clinical practice, this result signifies that discharge from the hospital presents a significant opportunity for physicians to modify the use of cardiac medical therapy following CABG.

5.5 Biases in Cohort Studies

A major source of bias in cohort studies is due to the effect of losses to follow-up. Patients excluded from the analyses can bias the study results if there is reason to believe that patients excluded have a lower or higher probability of an outcome or exposure, or both (55). In our analysis of the medications data from the ROSETTA-CABG Study, 21 patients (6%) were excluded from the analyses because of missing 12-month medications data. Of these 21 patients, 9 died prior to 12-month follow-up, 11 were lost to follow-up and 2 had missing medications data. Although this proportion is small, we examined baseline data in order to determine if there were any systematic differences between patients excluded and patients included in the analyses (Table 1).

Table 1. Lack of Differences in Baseline Clinical and Procedural Characteristics Among Patients Included and Excluded in Analyses.

Characteristic	Patients Included N= 320 (%)	Patients Excluded N=19 (%)
Mean Age ± S.D. (years)	63 ± 10	63 ± 9
Male	81	79
Mean Left Ventricular Ejection Fraction ± S.D	54 ± 14	50 ± 16
CCS Angina Class III-IV	40	42
Hyperlipidemia	75	47
Hypertension	65	47
Diabetes Mellitus	28	26
History of CHF	8	16
Prior MI	34	42
Prior PCI	18	11
Prior CABG	3	0
PVD	7	11
Main Reason for CABG		
Anginal symptoms	69	58
Positive Functional Test	14	26
Recent MI	12	16
Other	5	0

Abbreviations:

CCS: Canadian Cardiovascular Society

CHF: Congestive Heart Failure

MI: Myocardial Infarction

PCI: Percutaneous Coronary Intervention

CABG: Coronary Artery Bypass Graft

PVD: Peripheral Vascular Disease

Of note, patients excluded from the analyses were less likely to be hypertensive, hyperlipidemic and have had a prior PCI than patients included in the analyses. In contrast, excluded patients were more likely to have had a prior MI and a history of CHF than patients included in the analyses. However, none of these differences were significant by chi-square analysis.

When examining differences in medication use, excluded patients were more likely to have received CCB's at discharge and were less likely to have received nitrates. Excluded patients were also less likely to have received anti-lipid agents at both admission and discharge. None of these differences were significant.

Table 2. Medical Therapy Among 339 Patients Enrolled in the ROSETTA-CABG Study.

Abbreviations:
CCB: Calcium Channel Blocker
ACE: Angiotensin Converting Enzyme

	Patients Included (%)		Patients Excluded (%)	
	Admission	Discharge	Admission	Discharge
Aspirin	71	92	79	95
Clopidogrel	5	3	5	0
Coumadin	4	8	5	5
Anti-Lipid Agents	55	57	32	42
Beta Blockers	57	72	53	74
CCB's	30	20	37	32
Nitrates	48	37	47	26
ACE Inhibitors	33	30	26	32

Summary

There does not appear to be any systematic differences between patients excluded from the analyses due to loss to follow-up or death when compared with patients included in the analyses. It is highly unlikely, due to the small number of patients excluded and their similarity at baseline, that the results of the preceding study were biased.

6- DISCUSSION

The purpose of this thesis was to examine the patterns of use of cardiac medical therapy among patients undergoing CABG. In order to examine these patterns, we first conducted a review of RCT's in order to determine what was the appropriate use of cardiac medical therapy in the post-CABG patient. We then examined medication use among a cohort of patients undergoing CABG. The results of both these sections will now be discussed separately.

Our review of the literature demonstrated that very few trials have been conducted to demonstrate efficacy of cardiac medications post-CABG. In fact, the use of only two cardiac medications is supported from current evidence in the post-CABG patient: aspirin and anti-lipid agents. This finding is strengthened by the ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery that recommends the use of aspirin and anti-lipids in post-CABG patients (3). In addition, much research has demonstrated the benefits of aspirin, anti-lipids and ACE inhibitors in several subsets of patients with CAD (12-16, 20-21, 25). From the results of our review and the results that have been demonstrated among CAD patients, we would recommend the use of aspirin and anti-lipid agents. However, more research is needed, and more emphasis should be placed on clarifying the time to start treatment, appropriate dosages, applicability to various types of bypass grafts and appropriate length of treatment. More research is needed on the use of ACE inhibitors specifically in the post-CABG patient. The results of our review also demonstrated that neither beta-blockers, CCB's nor nitrates have been found to be beneficial if used in a routine fashion post-CABG. Further research should be conducted

to demonstrate the potential benefits these medications may have among patients with co-morbidities such as hypertension or prior MI that undergo CABG.

The descriptive study was designed to examine the patterns of use of medical therapy in patients undergoing CABG. When we examined medication use among a cohort of patients undergoing CABG, we found some variation between admission, discharge and 12-months for anti-lipid agents and nitrates, but subtle differences in the use of other cardiac medications. Given the large amount of research that has recommended the routine use of aspirin and anti-lipid agents in all patients with CAD, we would have also expected the use of these medications to be much higher post-CABG. We would also have expected patients undergoing complete revascularization to be receiving much lower proportions of nitrates by 12-months post-CABG. We also observed only minor differences in the use of these medications among patient subgroups. Patients with hyperlipidemia were more likely to receive anti-lipid agents and patients with CHF and diabetes were more likely to receive ACE inhibitors. But the use of other medications was very similar among patient subgroups. We would have expected patients with prior MI to have a higher likelihood of receiving beta-blockers and ACE inhibitors (26). It is also clear from current evidence that ACE inhibitors are indicated in patients with CHF (20).

Despite these findings, several baseline co-morbidities were found to be significant determinants of use of cardiac medical therapy at 12-months. Hypertension and low LVEF were found to be determinants of 12-month ACE inhibitor use, and hypertension was found to be a determinant of 12-month CCB use. Not surprising, use at discharge was also found to be one of the most important determinants of 12-month use

for every medication studied. Previous research found similar findings among PCI patients (53). These findings signify that physicians may be reluctant to modify the medications patients are receiving at discharge.

7-CONCLUSION

Very little research has examined the use of cardiac medical therapy in clinical practice among CABG patients. In our study, some variation existed in the use of cardiac medical therapy from admission to 12-months following CABG and between patient subgroups. However, this variation was often modest, and patient subgroups known to benefit from certain cardiac medical therapy were often just as likely to receive the medication as patients without these co-morbidities. Discharge from the hospital may provide a unique opportunity for physicians to modify the use of cardiac medical therapy appropriately among CABG patients. In addition, in our review of the literature, we found very few RCT's that examined the efficacy of cardiac medical therapy specifically in the post-CABG patient. An urgent need for more research regarding cardiac medical therapy following CABG is thus needed in order to better guide physicians with respect to the secondary prevention of cardiac events post-CABG.

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APPENDIX A: Proportions of Patients with Predictor Variable using Cardiac Medical Therapy at 12-Months Among 320 Patients in the ROSETTA-CABG Registry

Note: A predictor variable is defined here as all variables which demonstrated statistical ($p<0.10$) or had clinical relevance.

Table 1. Proportion of patients using Aspirin at 12-months

Predictor Variable	Using Aspirin at 12-months (N=277) N (%)	Not Using Aspirin at 12-months (N=42) N (%)	P-Value
Aspirin use at admission	200 (72)	25 (59)	0.10
Aspirin use at discharge	261 (94)	31 (74)	0.0002
Cerebrovascular Disease	10 (4)	5 (12)	0.03
Clopidogrel at 12 months	6 (2)	7 (17)	0.0004
Coumadin at 12 months	10 (4)	12 (29)	<0.0001
Past Smoker	155 (56)	30 (71)	0.07
Peripheral Vascular Disease	16 (6)	6 (14)	0.05
Prior MI	92 (33)	17 (41)	0.38
Prior PCI	47 (17)	10 (24)	0.28
Reason for CABG: Unstable Angina	123 (45)	28 (67)	0.008

Table 2. Proportion of patients using Anti-Lipid Agents at 12-months

Predictor Variable	Using Anti-lipids at 12-months (N=243) N (%)	Not Using Anti-lipids at 12-months (N=75) N (%)	P-Value
Anti-Lipid use at admission	156 (64)	19 (25)	<0.0001
Anti-Lipid use at discharge	165 (68)	17 (23)	<0.0001
Current Smoker	40 (16)	6 (8)	0.09
Diabetes	68 (30)	22 (29)	0.88
Hyperlipidemia	201 (83)	36 (48)	<0.0001
Prior MI	82 (34)	26 (35)	0.89
Reason for CABG: Unstable Angina	104 (43)	47 (63)	0.004

Table 3. Proportion of patients using Beta-Blockers 12-months

Predictor Variable	Using beta-blockers at 12-months (N=204) N (%)	Not Using beta-blockers at 12-months (N=113) N (%)	P-Value
Beta-blocker use at admission	126 (62)	55 (49)	0.03
Beta-blocker use at discharge	179 (88)	47 (42)	<0.0001
Coumadin use at discharge	22 (11)	5 (4)	0.06
Congestive Heart Failure	32 (18)	22 (22)	0.53
Diuretic use at 12-months	57 (30)	14 (13)	0.0004
Hypertension	141 (69)	63 (56)	0.02
Obesity	47 (23)	17 (15)	0.11
Prior MI	71 (35)	37 (33)	0.80
Procedure during 12-month follow-up*	89 (44)	35 (31)	0.03

* Procedure during 12-month follow-up was defined as any patient who had had either a functional test, an angiography or an angioplasty during the 12-month follow-up.

Table 4. Proportion of patients using Calcium-Channel Blockers at 12-months

Predictor Variable	Using CCB's at 12-months (N=61) N (%)	Not Using CCB's at 12-months (N=252) N (%)	P-Value
CCB use at admission	30 (49)	64 (25)	0.0005
CCB use at discharge	25 (41)	37 (15)	<0.0001
Congestive Heart Failure	9 (17)	45 (20)	0.70
Hypertension	52 (85)	149 (59)	<0.0001
Male Gender	44 (72)	207 (82)	0.11
Obesity	20 (33)	44 (18)	0.01
Prior MI	22 (36)	85 (34)	0.76

Table 5. Proportion of patients using Nitrates at 12-months

Predictor Variable	Using Nitrates at 12-months (N=70) N (%)	Not Using Nitrates at 12-months (N=244) N (%)	P-Value
Congestive Heart Failure	20 (32)	34 (16)	0.007
History of Angina	50 (71)	178 (73)	0.88
Hypertension	46 (66)	156 (64)	0.89
LVEF prior to CABG <40	18 (29)	32 (15)	0.02
Male Gender	52 (74)	200 (82)	0.17
Nitrate use at admission	41 (59)	111 (46)	0.06
Nitrate use at discharge	48 (69)	68 (28)	<0.0001
Prior MI	30 (43)	77 (32)	0.09
Reason for CABG: Unstable Angina	38 (54)	113 (47)	0.28

Table 6. Proportion of patients using ACE inhibitors at 12-months

Predictor Variable	Using ACE inhibitors at 12-months (N=120) N (%)	Not Using ACE inhibitors at 12-months (N=193) N (%)	P-Value
ACE inhibitor use at admission	61 (51)	42 (22)	<0.0001
ACE inhibitor use at discharge	66 (55)	28 (15)	<0.0001
Congestive Heart Failure	35 (32)	19 (11)	<0.0001
Diabetes	45 (38)	44 (23)	0.007
Hypertension	89 (74)	112 (58)	0.004
LVEF prior to CABG < 40	33 (30)	17 (10)	<0.0001
Obesity	30 (25)	33 (17)	0.11
Male Gender	90 (75)	161 (83)	0.08
Prior MI	49 (41)	57 (30)	0.05