The relationship between cardiac rehabilitation and long-term outcomes in a post CABG population – a clinical and administrative database study

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The relationship between cardiac rehabilitation and long-term outcomes in a post CABG population – an observational study

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Brief Summary

This is a single center retrospective study of 5,000 patients evaluating the effect of cardiac rehabilitation on long-term outcomes following coronary artery bypass surgery. A multivariable Cox proportional hazard model showed that cardiac rehabilitation was associated with a reduction in the composite of all-cause mortality, acute myocardial infarction, stroke or repeat revascularization, hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.75-0.91, $p<0.0001$ and mortality HR 0.76, 95% CI 0.68-0.84, $p<0.0001$ over 20 years of follow-up.

Conclusions: There was a reduction in MACCE, and late mortality associated with CR attendance, highlighting the importance of patient referral and sustained participation in cardiac rehabilitation after CABG.

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Abbreviations

Abbreviations list:

CHD	Coronary heart disease
CABG	Coronary Artery Bypass Grafting
PCI	Percutaneous coronary intervention
CR	Cardiac Rehabilitation
TRI	Toronto Rehabilitation Institute
ICES	Institute for Clinical Evaluative Sciences
CCI	Canadian Classification of Health Interventions
CIHI	Canadian Institute for Health Information
ICD	International classification of Diseases
MACCE	Composite of Death, MI, Stroke, or Repeat Revascularization
AMI	Acute Myocardial Infarction
SMD	Standardized Mean Difference
HR	Hazard ratio
RR	Relative risk
OD	Odds ratio
CI	Confidence interval

Chapter 1

Introduction and Background

1.1 Cardiac Rehabilitation (CR) it's evolution in practice

Cardiac rehabilitation (CR) is an important component in the management of chronic cardiovascular disease. The benefit of early ambulation after coronary events was first explored very cautiously and conservatively in a few small studies during the 1950's where patients were allowed a daily short walk of 3-4 minutes 4 weeks after the coronary event [1]. In 1968 Saltin et.al published a small study which showed the importance of exercise and the detrimental effect of prolonged bed rest [2]. Since then, various investigators have clearly demonstrated the physiological benefits of exercise in patients with heart disease looking at modifiable and non-modifiable factors. As a result over the past five decades CR has evolved to a multi-disciplinary program targeting patient care not just from an exercise prescription but also through optimization of cardioprotective therapies, psychological counselling, nutritional counselling, and stress management [1].

The first objective of CR is to improve regular physical activities and help patients regain their normal lifestyle. The next objective of CR is to control modifiable risk factors, such as smoking, diabetes, blood pressure, cholesterol and emphasize therapeutic education which would improve lifestyle changes. The therapeutic education involved counselling which would make the patients aware of their medical conditions and understand strategies to manage them. Lastly, the final objective is to help cardiac patients cope with their psychological problems, like depression, anxiety and develop stress management techniques [1]. The World Health Organization (1993) has defined cardiac rehabilitation as "The sum of activities required to influence favorably the underlying cause of the disease, as well as to provide the best possible physical, mental and social conditions, so as the patients may, by their own efforts, preserve or resume when lost as normal a place as possible in the community " [3]. CR is a chronic disease management programme, supporting provision of secondary prevention and lifestyle changes, which successfully reduces the risk of recurrence and short-term mortality [4].

The first time CR was explored in Canadian patients was in 1970 [5] and today there are approximately 220 CR programs in Canada, predominantly in Ontario [6]. In Toronto, Ontario there are six CR centers with Toronto Rehabilitation Institute (TRI) being one of the oldest and largest CR centers in Canada [7]. The Canadian Association for Cardiovascular Prevention and Rehabilitation (CACPR) is the national leader in cardiovascular disease prevention and rehabilitation and their mission is the enhancement and maintenance of cardiovascular health of Canadians through CR practice, research, and advocacy [8]. There are also some regional CR networks, like the Canadian Rehabilitation Network of Ontario and the Atlantic Cardiac Rehabilitation Network. The core components of CR published in the Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention, 3rd Edition in Chapter 11 are: 1] systematic patient referral processes, 2] patient assessments, 3] health behavior interventions and risk factor modification, 4] adaptations of program models to improve accessibility, especially for under-served populations, 5] development of self-management techniques based around individualized assessment, problem-solving, goal-setting and follow-up, 6] exercise training, 7] leisure-time activities, 8] outcomes assessment and performance measurement, 9] continuous quality improvement programs, and 10] professional development programs [8]. These guidelines were developed and produced in accordance with the principles of the AGREE (Appraisal of Guidelines, Research and Evaluation) collaboration and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence classification scheme [9, 10].

1.2 The global variation in CR programs

Globally there is variation in CR programs depending on the available resources and regional variations depending on the regional health policies and funding options. In North America, most of the rehab programs are ambulatory while in some European countries they can be delivered at a patient's home or at an old age residential facility as well. In most countries, the CR program consists of three phases; Phase I is an in-patient program started in-hospital and continued until the patient is ready for discharge, Phase II is a supervised ambulatory outpatient program of 3 to 6 months duration and Phase III is the lifetime maintenance phase. Phase III focuses on physical fitness (exercising at home or joining a community fitness program) and additional risk-factor reduction by maintaining a healthy diet, adhering to preventative medications and stress management techniques. There are CR quality performance measures established by American, Canadian, Australian and European CR societies. The 2011 American College for Cardiology Foundation / American Heart Association Task Force on Practice Guidelines for Coronary artery bypass graft surgery (CABG) recommends Cardiac Rehabilitation (CR, Class 1, Level of Evidence A) for all eligible patients post Coronary artery bypass graft surgery beginning 4-8 weeks after CABG, 3 times per week for 3 months [11]. The 2016 European Guidelines on cardiovascular disease prevention in clinical practice recommend participation in CR for all patients hospitalized for revascularization (Class 1, Level of Evidence A) [12].

A survey was collected from 93 countries to assess the nature of the CR programs, specifically targeting the type of patients served, number of health care professionals providing the service, and the service delivered [13]. Countries were identified based on previous communication and the reviews and responses were then compared by World Health Organization region allocation. Out of 203 countries, 111 countries (55%) offered CR services which were mostly led by physicians. These CR services included patients with acute myocardial infarction (AMI), percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). Characteristics of the selected CR programs included initial assessment, structured exercises and at least one strategy to control CV risk factors. All countries that offered Phase II CR services were identified and in countries where several programs existed a random sample of 250 programs was selected for this survey. Most of the programs were in urban areas (72.8%) with referrals from a tertiary center (46.1%) and the overall responsibility for the CR program was most often with the cardiologist (48.4%). The median duration of supervised exercises was 8 weeks with 2.5 ± 1.3 frequency of sessions / week. Functional capacity tests such as the six-minute walk were used more often than a graded exercise stress test. Programs on average offered 9 of 11 recommended core components. The most frequently delivered components were initial assessment, risk factor management and patient education. There were significant regional differences with return to work, tobacco cessation and women-only classes between countries. The components which were less commonly delivered were, stress management, electronic patient charting, other forms of exercise (yoga, dance) and follow-up programs post completion of Phase II.

1.3 The CR program at Toronto Rehabilitation Institute (TRI)

The Toronto Rehabilitation Centre was founded in 1922 to meet the rehabilitation needs of Canadians wounded in the First World War and was the first free-standing rehab facility in North America. In 1968, it became home to the first outpatient cardiac program in Ontario. In 1998, the Toronto Rehabilitation Institute (TRI) was created by the amalgamation of the Rehabilitation Institute of Toronto, the Toronto Rehabilitation Centre, and Lyndhurst Hospital. The TRI cardiac rehab program receives about >2,400 referrals / year and provides comprehensive CR care in accordance with the recommended CACPR guidelines. On July 1, 2011, Toronto Rehab officially became part of University Health Network (UHN), joining the Princess Margaret Hospital, Toronto Western Hospital and Toronto General Hospital. Patient services at the TRI-CR program are billed to the Ontario Ministry of Health. There is a Toronto Rehab Foundation funded by donors which supports the infrastructure for the rehab activities.

Once a patient is ready to be discharged from a hospital following CABG or valve surgery, PCI, or after an acute coronary syndrome, a referral is sent to TRI by their cardiologist or surgeon, or other healthcare professional. When the referral is received the patient is contacted by the CR program and an intake assessment (clinical – physical assessment) is done, following which participation in the program begins. After referral and collection of additional medical history documents by the CR team, patients are scheduled for a cardiopulmonary exercise stress test (CPET) appointment a minimum of 6 weeks after surgery. At the CPET appointment, the first

CR session is scheduled. The program is led by an interprofessional team of physicians, physiotherapists, nurses, kinesiologists, psychologists, social work and dietitians. During the time frame of this study, patients attended 90-minute exercise classes once per week for 6 months and were offered another CPET at the end of 6 months. There were additional optional monthly classes for 4 to 12 months afterwards (duration varied depending on date of CR entry). Exercise classes include aerobic and resistance training, education sessions, as well as psychosocial and dietary counseling. Each patient is assigned to a case manager, and patients are required to complete 5 aerobic and 2 to 3 resistance training sessions per week, which are tracked via an exercise diary. One exercise session is conducted in the facility, with the balance of the exercise being completed in the home/community. The initial walking prescription is on average set at a distance of ≈1.6 km per day (but very individualized) and prescriptions are progressed to a moderate intensity of 6.4 km. Ventilatory anaerobic threshold (VAT) is used to measure exercise tolerance; it is measured at rest and at maximal exercise. Individualized exercises (maximum duration of 60 minutes) are prescribed based on the baseline peak oxygen intake during exercise (VO2peak) and are targeted to achieve 60% to 80% of the baseline VO2peak. Resistance training exercises included 3 lower body (2 with dumbbells and 1 with exercise bands), 5 upper body (dumbbells), and 2 trunk-stabilizing exercises (depending on the patient's body weight)[14]. Ideally at program completion, patients will have completed all the required CR sessions, risk factors are within the recommended target and patients are meeting the nutritional guidelines. A discharge letter is sent to the referring physician within one month of graduation from the program. At completion patients are provided a written summary of the care received outlining future goals to achieve an optimal risk profile. Patients are encouraged to implement long-term self-management strategies through community services and patient support groups.

The study population reviewed in this thesis attended a CR program which comprised of the active phase and the maintenance phase. The active phase consisted of 24 to 36 prescheduled weekly supervised exercise sessions, while the maintenance phase consisted of monthly on-site visits and continued home-based exercise sessions recommended five times per week [15] . This program fits into the recommended framework of Phase II CR which comprises of an initial assessment, structured supervised exercises and maintenance strategy to control the risk factors.

1.4 **Barriers to CR care**

CR attendance rate is low (around 30% of all eligible patients) in most centers and it is dependent on both patient related factors and administrative delays [16-19]. In Canada there is a Cardiac Rehabilitation Barrier Scale which has been developed and validated that assesses the patient's perceptions of the health system-level and personal barriers to cardiac rehabilitation utilization [20]. Patients from 11 hospitals completed a one-year follow-up survey to investigate the structure and psychometric properties of the Cardiac Rehabilitation Barriers Scale. Participants were asked to rate 21 cardiac rehabilitation barriers on a five-point Likert scale regardless of cardiac rehabilitation referral or enrolment [20]. Some of the main hurdles which have been identified are 1] delayed entry into a program due to a longer wait-time to get referred by a physician, 2] wait-time for a CR program to get a patient assessed and started, 3] poor socio-economic status (SES) affecting patients motivation to attend 4] long travel distance to the CR facility and 5] time constraints.

Despite the evidence in regards to CR in patients with coronary heart disease, many patients are unable to or prefer not to attend a CR program. Various researchers have tried to identify the nature of the barriers among vulnerable groups using the psychometrically validated and comprehensive CR barrier scale [20]. A survey study tried to evaluate the sex differences in CR barriers by participation status and found that there was no significant sex difference in total number of barriers, but the nature of the barriers was different in non-participants [16]. For women it was mostly related to family responsibilities, lack of CR awareness and experiencing exercise as tiring or painful [16]. Also, due to cultural restraints some female patients are reluctant to wear exercise clothing in front of others or prefer women-only group or CR for the family [21]. Studies have shown that other patient oriented factors like education, employment and income also affect CR enrollment and completion. Patients with at least high school education are more likely to participate in a CR program [22]. Employment also plays an important role in CR adherence; as most young eligible patients working part-time or full-time although they are motivated to attend must return to work due to employment obligations and are not able to fulfill all the required sessions in a CR program. Patients without medical insurance coverage or under a family economic burden tend to have a lower CR attendance [22, 23]. Age is also another barrier to CR participation as studies have shown that the peak participation is between ages 50-65 and drops significantly after 80 years of age [24].

Another important barrier is the CR referral time frame due to access issues. CR referral rates vary, and most eligible patients never get referred or many referred patients do not initiate or complete the program [14]. Studies have shown that delay in referral results in lower adherence and worse long-term outcomes [14]. In Ontario due to the limited number of publicly funded CR centers, there is generally a long wait time until the program starts and there is only enough capacity to provide CR services to 34% of the eligible population [25]. The Canadian Cardiovascular Society Access to Care Working Group explored the actual wait time and factors that affect these wait times. They found that the main barriers negatively affecting these wait times were patient travel and staff capacity [26]. To implement and better coordinate the program across 24 centers in Ontario, in 2001 the Ontario Ministry of Health and Long-Term care announced a pilot project [27]. To be eligible for the pilot program, patients were required to have had a cardiac event related to hospitalization or change in cardiac status within two years of referral. The most common referring events were coronary artery bypass surgery (CABG)-31.9%, percutaneous transluminal coronary angioplasty (PTCA)-21.3% and myocardial infarction (MI)-17.8%. The objective was to design, coordinate and evaluate a health service delivery model for CR and secondary prevention center. This streamlined process was implemented by 94% of the sites and was able to serve 60% more people in a single year [27]. Unfortunately, these advances in enrollment and capacity were not sustained after the pilot project as volume accountability "report-back" requirements were removed by the Ministry of Health, associated with a reduction of funding to the CR programs (*personal communication PO and NS*).

Additionally, over the years various other new strategies have been adopted to increase the CR referral and enrollment rate. A meta-analysis of 14 studies tried to analyse the enrollment rates based on referral strategy and found that innovative referral strategies such as patient letters, as well as a combined systematic and liaison strategy increased the CR use [28]. A recently published study showed that a strategy of automated referral should be advocated to improve CR participation and completion in CABG patients. Although, it resulted in near doubling of the proportion of patients referred to CR, there was only a modest increase in overall CR completion. Before automation, referral rates were increasing at 0.9% (absolute) per 6 months while with automation the referral rates increased to 21.4%. Mortality benefit was seen only in CR completers whereas a mortality benefit was not seen simply with CR enrolment [29] .

1.5 **Role of CR after Coronary artery bypass grafting**

Coronary heart disease (CHD) remains the leading cause of hospitalization and death in Canada [30]. Coronary artery bypass graft surgery (CABG) was first performed in 1960 and is the standard surgical intervention for patients with advanced CHD when other modalities such as lifestyle changes, medical and minimally invasive procedures such as angioplasty fail to correct the condition [31]. In Canada, about three quarters of the revascularization procedures are done through PCI and one quarter through CABG [32]. The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization published in 2018 (Class 1, level A) and the 2011 American Heart Association guidelines (Class 1, level B) recommend CABG surgery in stable patients to improve survival [11, 33]. These recommendations are based for patients with stable CHD, with suitable anatomy and with low surgical predicted mortality. CABG is still the preferred line of treatment in patients with triple vessel disease with or without diabetes and left main disease [34].

A] Risk of mortality after CABG

The Canadian average 30 day in-hospital mortality rate with isolated CABG is 1.3% with provincial rates ranging from 0.5% - 3.1% [32]. A recent meta-analysis of 11 randomized controlled trials (RCT) showed that the 30-day all-cause mortality after CABG was 1.4% and at 5-year it was 8.9% [35]. The ART multi-center randomized trial compared CABG patients with single versus bilateral internal thoracic artery grafts with all- cause mortality as the primary outcome. At 10 years the mortality rate in the single graft group was 21.2% vs 20.3% in the bilateral graft group [36]. Another population-based Ontario study compared all-cause mortality and composite outcomes at a mean follow-up of 9.1±3.9 years between South Asians (SA) and General Population (GP) in a propensity matched CABG population (N=2,473). The primary outcome was a composite of major adverse cardiac and cerebrovascular events (MACCE) and all-cause mortality was the secondary outcome [37]. The study showed the risk of adverse events gradually progressed overtime. Freedom from MACCE at: 1 year-SA: 93.9%, GP: 93.8%; 5 years-SA: 84.0%, GP: 83.5%; 10 years-SA: 67.6%, GP: 64.4%. Freedom from all-cause mortality at: 1 year-SA: 97.3%, GP: 97.2%; 5 years- SA: 92.9%, GP: 92.2%; 10 years-SA: 83.0%, GP: 78.7% [37].

B] Some known benefits of CR in a CABG population

It is known that the secondary events after CABG can be prevented by cardiovascular risk factor control through intensive lifestyle behavioural changes such as regular physical activity, eating well and medication adherence [38, 39]. In the view of the existing evidence, authors from a review article studied the impact of pre-existing comorbidities on short and long-term outcome of patients undergoing CABG and implications for CR. They felt that this particular patient population with multiple pre-existing comorbidities may potentially benefit more through a multidisciplinary CR prevention program [40]. Additionally, studies have shown that undertaking pre-surgical CR has long-term survival benefit over patients who do not attend such services [41].

Physical fitness defined by peak oxygen intake (VO2peak) has been identified as an independent predictor for sustained patient health outcomes in patients with CHD [42]. A meta-analysis of 18 RCT's looked at the effect of VO2peak in patients with CHD. The study showed that there was an increase in VO2peak in patients who started CR < 3months after the event as compared to those who started CR > 3 months [43]. CABG patients may benefit more from CR than PCI in terms of mortality reduction. This survival benefit may be related to increase in greater gains in peak oxygen uptake capacity (V̇O2peak) and improvement in pulmonary function [38, 44]. The effect of CR training depends on various factors such as age, initial level of fitness and extent of revascularization. It also depends on the duration, frequency and intensity of the CR sessions. Studies have shown that although exercise training is effective after both CABG and PCI, participation in a three month CR program after CABG increased the VO2peak by 32.8% as compared to an increase of 14.6%in the PCI group [45].

Additionally, due to median sternotomy, mechanical ventilation and longer hospital stay the pulmonary function is more compromised after CABG than after PCI [46 47]. Pulmonary function tests (PFT's) were studied at baseline, 3weeks and 3.5 months in 50 patients undergoing CABG.

The study showed that the PFT's deteriorated significantly for at least 3.5 months post CABG. The forced vital capacity dropped from 98% at baseline to 63% at 3 weeks and 75% at 3.5 months [46].

A recent single center Canadian observational study examined how CR referral and program completion are related to survival benefits in 8,118 CABG patients. This study showed that the survival rate at 10 years was 67.4% in those who were not referred and 84.2% in those who were referred and completed CR [29].

Apart from the above effects CR attendance also has some other direct physiological benefits on the heart and coronary vasculature in patients with CHD [48, 49]. Oxidative stress is known to have adverse effects on heart, kidney, lungs and brain. Reactive oxygen plays an important role in aging as well in age-related diseases such as CHD. Oxidative stress results from imbalance between reactive oxygen species and anti-oxidant defense mechanisms and heart tolerance to oxidative stress decreases with age because of reduction in anti-oxidative enzymes. This affects the coagulation system and myocardial oxygen demand in patients with CHD. Studies have shown that there is an association between atherosclerosis and oxidative low density lipoprotein [50]. In a single center study of 100 patients with CHD the reactive oxidative metabolite levels decreased 3-6 months after CR with an increase of the percentage of the predicted values of $\dot{V}O2$ peak [49].

C] Core components of CR following cardiac surgery

A recent update to the 2010 position paper about CR program models was published in the European Journal of Preventive Cardiology [51]. This was done to update the practical recommendations of the core components in different cardiovascular conditions, so as to ensure favorable functional outcomes of the CR program and decrease the risk of disability and death. In this paper advances in different training modalities were added targeting challenging populations such as patients undergoing cardiac transplantation, coronary artery or valve surgery, trans catheter aortic valve implantation, MitraClip procedures and patients with ventricular assist device who would benefit from secondary prevention. Therefore, in this update some novel components of CR have been recommended for this specific population.

The five main core components which were updated with regards to a CABG population are: 1] patient assessment, 2] physical activity counselling (exercise training), 3] nutritional counselling, 4] tobacco cessation and 5] psychosocial management. It is also necessary in this population to assess the wound healing, complications and disabilities with a special focus on perioperative events. The exercise training can be started in the early in-hospital phase and out-patient programmes should initiate early after discharge. After six weeks when the sternum is healed and the chest is stable, upper body exercises can be started. Since cardiac surgery patients are on a mechanical ventilator post-op, it is important to consider inspiratory muscle training techniques. These patients are usually on antithrombotic and at times on anti-arrhythmic drugs and therefore during nutritional counselling it is important to make sure that there is no interaction with any dietary supplements. A large sternal incision and leg incisions when a vein graft is harvested during CABG, impairs quality of life for a long time and these patients need close attention to wound care and additional psychological support.

D] Significance of CR referral timeframe in CABG

Apart from adherence and lifestyle changes, CR attendance within a certain time frame post CABG holds important implications for patient outcomes [14]. The Canadian and International guidelines recommend early referral to CR [11]. Usually after a CABG procedure, at time of hospital discharge a referral is sent to the rehabilitation center based on the patient's geographical location. A CR referral can also be made afterwards by a family physician, cardiologist, surgeon, or other healthcare professional. A study published in Circulation Cardiovascular Quality and Outcomes in 2015 recommends initiating CR within 60 days of surgery for better outcomes [14]. In this study the investigators examined the effects of later entry on CR outcomes (i.e. CR use, anthropometrics, and functional capacity) in post coronary artery bypass graft surgery patients while accounting for demographic, environmental, and physiological correlates of longer wait time in both phases: wait time to get referred by a physician and the wait time for the CR program to get a patient assessed and started. Among 6,497 post- coronary artery bypass graft participants, mean and median total wait time (time from surgery to first exercise session) was 101.1±47.9 and 80 days, respectively. Patients with longer wait-times were more likely to have poorer adherence and diminished gains in cardiovascular fitness.

E] Barriers to CR attendance in a CABG population

There are some unique barriers that delay entry to CR in a CABG population as compared to nonsurgical patients. Although studies have shown that CR attendance improves survival in a CABG population, many referred patients experience barriers as previously described and are thus unable to or choose not to attend a CR program [14]. A high percentage of the CABG population is elderly, and recurrent events, hospital admissions, physical and social limitations can prevent them from attending the CR program. Studies have shown that only 31% of CABG patients who are over the age of 65 actively participate in all the recommended out-patient CR sessions. Higher median household income, higher level of education, and shorter distance to the nearest CR facility were important predictors of higher CR use [52]. Due to a long recovery time, CABG patients are financially and emotionally dependent on others and need support for transportation. They are also more vulnerable in terms of recurrent events and there is still a lack of awareness of the importance of secondary prevention measures amongst CABG patients. Poorer utilization of CR in elderly CABG patients is concerning as they are at higher risk of later mortality and morbidity.

Therefore, there is a strong need to emphasize supervised physical activity and comprehensive CR which can bring about beneficial lifestyle changes and improve quality of life especially in this patient population [38, 45, 49].

Some of the future goals for CR and chronic cardiovascular care as outlined in the Canadian guidelines include: 1] plan for the development of healthy communities by patient education, 2] maximize physical activity opportunities to maintain cardiometabolic fitness, 3] advertising and marketing the CR program and the types of services offered within health professionals, 4] Educating health professionals and patients about the CR program within their vicinity so that there is expedited referral with increase in enrollment rate and 5] CR services should be treated as an integral part of cardiac care and not just as a secondary prevention program [8].

Chapter 2

Literature review

2a. **Existing literature**

A systematic review of the literature using both MEDLINE and EMBASE from years 1946 to May 2020 was performed. The following key terms and MeSH terms were used for studies that looked at the effectiveness of Cardiac Rehabilitation in cardiac patients, and for studies that examined in particular postop cardiac rehabilitation strategies that may benefit patients with coronary artery bypass graft surgery: [Coronary artery bypass /Coronary Artery Disease/ or exp Exercise Therapy/ or exp Cardiac Rehabilitation/or exp Postoperative Complications/ or exp Treatment Outcome] (**appendix 1**). In addition, the reference list of relevant studies and reviews was hand searched for studies published in the last five years (2015- present) to ensure a review that reflects contemporary practice.

The evidence base looking at the effectiveness of CR programs in patients with CHD has been around for over two decades. One of the first systematic reviews and meta-analysis was published in 2004 of 48 RCT's with a total of 8,940 patients with CHD. It included studies with a six month or more follow-up period. The review showed that exercise –based CR resulted in a reduction in all-cause mortality (Odds ratio (OR) 0.80, 95% CI 0.68 - 0.93) and cardiac mortality (OR 0.74, 95% CI 0.61- 0.96) [53]. Since then, various investigators have updated the systematic review to include newer studies with a follow-up period extending beyond a year. In order to better understand the effectiveness of CR in patients with CHD, the updated meta-analysis also tried to evaluate the effect of CR care on other significant cardiac endpoints such as MI or revascularization after CHD in addition to fatal outcomes (mortality and CV mortality) [4, 54]. In the 2016 update, apart from clinical endpoints it also assessed the effects of exercise-based CR with regards to quality of life and cost-effectiveness [54] .

A] CR survival effects in patients with CHD based on previous meta-analysis of randomized controlled trials - observational studies and individual single center studies.

The most recent 2016 Cochrane systematic review and meta-analysis of 63 randomized controlled trials (RCT) with over 14,486 participants with CHD, showed that with a median follow-up of 12 months, CR led to a reduction in cardiovascular mortality and reduced risk of hospital admissions [54]. Selection criteria included men and women who have had myocardial infarction (MI), coronary artery bypass surgery or percutaneous transluminal coronary angioplasty (PTCA). Exercise-based CR was associated with a significant reduction in cardiovascular mortality, relative risk (RR) (0.74, 95%CI 0.64-0.86). The overall reported all-cause mortality in 47 out of the 63 studies was not significant between the two groups (RR 0.96, 95% CI 0.88-1.04) at a median follow-up period of 12 months. In this meta-analysis the outcome effects were consistent across the studies, irrespective of the patient population, nature of CR program, location, and study characteristics.

While the above meta-analysis focused on the effects of CR in RCTs of patients with CHD, the Cardiac Rehabilitation Outcome Study (CROS) was predominantly an observational study meta-analysis (one RCT and 24 observational studies). It included 219,702 patients – [46,338 (ACS patients), 14,583(CABG) and 158,781(mixed population i.e. patients with chronic stable coronary artery disease with or without PCI)]. There was a significant reduction in mortality after CR participation following acute coronary syndrome (OR 0.20, 95%CI 0.08-0.48) at a mean follow-up of 40 months [55]. With a large sample size from a mixed population, this study also found that participation in a structured multi-component CR is associated with better survival.

Thus, both the Cochrane and the CROS meta-analysis have provided a comprehensive better estimate of the relationship between CR and mortality as compared to previous small single center studies and earlier systematic reviews. Nevertheless, the existing literature was able to evaluate only short and mid-term survival benefits with CR attendance in patients with CHD.

To evaluate the long-term outcomes, a large registry based study from Alberta, Canada not included in the above meta-analysis - The Alberta provincial project for outcome assessment in coronary heart disease (Approach) Registry study - compared > 13,000 patients (South Asians and the European Canadian population) who had a clinical diagnosis of coronary artery disease on angiography with ≥ 70% stenosis in at least 1 coronary vessel. Results showed that participation in a CR program improved the long-term survival rate as compared to those who did not attend irrespective of the ethnicity (HR 0.57, 95%CI 0.52-0.63). After propensity adjustment, improved long-term survival was observed in South Asians who attended CR as compared to European-Canadian patients who attended CR (HR 0.66, 95%CI 0.43-1.00) [56]. This study did provide a new insight into the effect of CR in a high-risk ethnic group; however the follow-up period was restricted to a median of 6 years.

Additionally, studies have also shown that supervised exercise session for 6 months improves pulmonary function and increases VO2 peak which is usually compromised in patients with CHD, which in turn improves survival [42, 49]. The mortality reduction with exercise-based CR can also be attributed to reductions in major risk factors such as caseation in smoking, weight loss and improvement in oxygen consumption. Risk factors can be controlled through healthy behaviour, exercise training protocols and self-management techniques which are some of the fundamental components of a CR program [7, 51]. The published evidence does support that CR is an important asset in the management of patients with CHD, although there is still uncertainty regarding the long-term CR effects.

B] The impact of CR attendance on mortality in patients with advanced CHD who require CABG.

While the above studies have looked at the benefits of CR in heterogeneous CHD patient cohorts, there are very few studies which have targeted a CABG population. The evidence base around the benefit of CR in those with extensive CHD requiring CABG is smaller. The CROS meta-analysis of retrospective cohort studies analyzed the CABG subgroup (5 studies, 14,583 patients); there was reduced mortality at a mean follow-up of 40 months (HR 0.62, 95%CI 0.54-0.70) after participating in CR within three months of hospital discharge [55]. Additionally, a study by Lee and colleagues in Korea not included in the above CROS meta-analysis found that all-cause mortality was lower with CR in a propensity matched CABG registry cohort. This study showed that there was a 20% reduction in all-cause mortality after phase I (at least one in-hospital) CR (1,097 CR attendees) and 40% reduction after phase II (outpatient) CR (379 CR attendees) within three months of discharge after CABG [57]. Moreover, a single center observational study of 869 CABG patients included in the above CROS meta-analysis, showed that at a 10 year follow-up period there was a decrease in mortality in the patients who attended CR (HR 0.54, 95% CI 0.40-074)[39]. Thus, there is some evidence which shows that CR attendance is associated with early and mid-term survival benefits in a CABG population.

C] Is there a dose – response effect associated with level of CR attendance?

To better understand the impact of CR care, some studies have also tried to evaluate a dose response relationship (dose ≥1,000 U vs. dose <1,000 U) of exercise intervention in patients with ACS [54]. The dose of exercise intervention was calculated as (dose = number of weeks of exercise training x average number of sessions/week x average duration of session in minutes). The results showed that there was no differential CR treatment effect with the CR dose although point estimates for both levels of intervention favoured CR - this lack of difference may be related to sample size and length of follow-up [54]. A single center observational Australian study also looked at the dose response survival benefits associated with CR in patients who had AMI, CABG or PCI with a median follow-up of 14 years (544 patients in total, 155 CABG patients). Patients who attended < 25% of the CR sessions had a higher risk of all-cause mortality (OR 2.57, 95% CI 1.04-6.38) [23]. Though studies have shown that CR attendance maybe associated with a beneficial dose-response in CHD patients, these results were not consistent.

However, a US – Medicare claim database study supports the relationship between level of CR attendance and outcome. The study population included elderly patients who had MI, stable angina, heart failure and CABG and who attended at least one outpatient CR session (overall 30,161 subjects). The date of each patient's first CR claim served as the index date. In CABG patients (N=8,325), full CR attendance (36 sessions) was associated with a lower risk of death and MI at 4 years compared with lesser CR attendance.

Attending 36 sessions was associated with a lower risk of mortality (HR 0.86, 95% CI 0.76-1.00) as compared to attending 15 sessions or lower [58]. Thus, this study has shown that a strong dose–response relationship exists between the number of CR sessions attended and long-term outcomes in a CABG population.

D] Does fatal or non-fatal MI and revascularization vary with CR attendance?

Apart from mortality outcomes, few studies have also reported the following outcomes after CR: fatal and non-fatal MI, revascularizations (CABG or PCI) in addition to CV mortality and all-cause mortality while stroke was not reported [54]. A meta-analysis of 36 studies (9,717 participants) looked at fatal and/or non-fatal MI in patients with ACS and found that there was no statistical difference in the risk for fatal and non-fatal MI for all studies of exercise-based CR (RR 0.90, 95%CI 0.79-1.04). Also, there was no significant difference between exercise based CR and the control group in terms of repeat revascularization by either CABG [(29/63 studies, 5,891 participants), (RR 0.96, 95%CI 0.80-1.16)] or PCI [(16/63 studies, 4,012 participants), (RR 0.85, 95%CI 0.70-1.04)] [54].

The Medicare claim study which looked at the association between level of CR attendance and outcomes, showed that elderly CHD patients who attended all sessions (36 CR sessions) had lower risk of MI as compared to those who attended fewer sessions (24 sessions / 12 sessions / one session) at 4 years. After adjustment, attending each additional 6 CR sessions was associated with a 5% lower risk of MI among CABG patients, 6% lower risk among patients with previous MI and 11% lower risk among patients with stable angina [58].

So although, there is some evidence which shows that attendance of all required CR sessions reduces the risk of nonfatal MI, to date, there is no convincing evidence that CR attendance is associated with a reduction in the risk of fatal or nonfatal MI or repeat revascularization over the long-term.

E] Other significant quality of life measures which are correlated with CR attendance.

A number of studies have also looked at the health costs and quality of life with exercise-based CR [54, 59, 60]. The cost-effectiveness and health-related quality of life (HRQL) between the CR and the control groups was assessed using validated instruments [61-63]. 14 out of the 20 studies that assessed HRQL reported higher level of HRQL in one or more subscales following exercise-based CR as compared to control group. For cost-effectiveness the results varied from no difference in costs between CR and control group (three studies), to higher healthcare costs in the CR group (one study), and lower health-care costs for CR group (one study) [54]. Additionally, a multi centered randomized trial involving 140 CR centers, evaluated the cost-effectiveness of the traditional CR program in comparison to comprehensive cardiac tele-rehabilitation. Cardiac tele-rehabilitation reduced the number of readmissions during the follow up period from 22.9% to 10.1%, achieved an average cost reduction of €564 per patient and increased quality of life [59]. Levin et al. did an economic evaluation comparing a CR program with standard care in patients with MI or CABG with a 5-year follow-up period. He found that that there was a decrease in re-hospitalizations and increase in return to work from 38% to 53% and resulted in overall cost savings per person in patients who attended the CR program [60]. A group of investigators at TRI examined the relationship between CR attendance and expenses in a publicly funded health care system. 7,345 patients were referred to CR following PCI, CABG, ACS, CHD and other heart related conditions. After propensity matching, 6,284 referred and 6,284 non-referred patients were included in the final analysis. The results showed that, as compared with non-referred patients, the health expenditures were lowest in patients who had highest level of CR attendance. Also, high level of CR attendance resulted in overall lower hospital readmissions, emergency department visits, drug usage and physician visits [64]. The above literature has shown variable cost differences between exercise-based CR and usual care. CR attendance has also been shown to decrease re-hospitalizations which in turn results in overall costs savings. It has also shown that the costs with CR compare with other medical interventions performed commonly in patients with CHD.

2b. **Need for this study**

Table 1a]

This table summarizes the studies reported in this thesis, which evaluate the short and mid-term outcomes in patients with CHD who attended CR vs. control.

Study name/ first author and year of publication with reference link	**Sample size**	**Type of study**	**Follow-up period**	**Fatal outcomes and results**	**Nonfatal cardiac outcomes and results**
Updated Cochrane meta-analysis – 2016 [54]	14,486	Meta-analysis of RCTs	Median follow-up = 12 months	1] CV mortality – RR: 0.74, 95%CI 0.64-0.86 2] all-cause mortality – RR:0.96, 95% CI 0.88-1.04	
	9,717				MI – RR: 0.90, 95% CI 0.79-1.04
	4,012				PCI – RR: 0.85, 95% CI 0.70-1.04
	5,891				**CABG** – RR:0.96, 95% CI 0.80-1.16
CROS meta-analysis – 2016 [55]	219,702	Meta-analysis of observational studies	Mean follow-up = 40 months	Mortality – OR: 0.20, 95% CI 0.08-0.48	Not reported
Approach Registry study – 2016 [56]	13,000	Single center observational study	Median follow-up = of 6 years	Mortality – HR: 0.66, 95% CI 0.43-1.00	Not reported

Doimo et al – 2019 [65]	1,280	Dual center observational study	Median follow-up = 82 months	Composite endpoint included - hospitalizations for cardiovascular causes and cardiovascular mortality HR: 0.58, 95% CI 0.43–0.77	Not reported

Table 1b]

This table summarizes the trials reported in this thesis which evaluate the effect of CR in CABG patients or where CABG population has been analyzed as a subgroup.

Study name/ first author and year of publication with reference link	**Sample size**	**Patient population**	**Type of study**	**Follow-up period**	**Fatal outcomes and results**	**Nonfatal cardiac outcomes and results**
CROS meta-analysis – 2016 [55]	14,583	*CABG patients: sub-group analysis*	Meta-analysis of observational studies	Mean follow-up = 40 months	Mortality – HR:0.62, 95% CI 0.54-0.70	Not reported

This thesis will address some of the current gaps in knowledge of CR specifically in a CABG population. While we know about the physiological [42, 49] and survival benefits [4, 23, 39, 54-57, 65, 66] associated with timely CR attendance in patients with CHD, there is limited data in patients with advanced CHD who undergo CABG [39, 54, 55, 57, 66, 67].

Most of the existing evidence had a short and mid-term follow-up period in patients with CHD and lacks extended longitudinal follow-up [39, 54, 55]. Moreover, in a dedicated CABG population , Quinn et al. was the only one study that identified the survival benefits of exercise-based CR over a10 year follow-up period, however this study had a small sample size (N=869) [39]. There is still uncertainty about the effect of post-op CR in CABG patients extending beyond 10 years looking at mortality in a larger population. As most patients who undergo CABG survive more than 10 years [36, 37], the association of CR and late mortality benefits is important.

Lastly, to date there is much less evidence in a dedicated CABG population regarding non-fatal cardiac outcomes such as MI, stroke or repeat revascularization [4, 23, 39, 54-57, 65, 66] during the follow-up period which could be potential drivers for mortality. Although some of the secondary cardiac events - fatal and /or non-fatal MI and repeat revascularization were addressed in patients with ACS, the results were inconclusive [54]. The Medicare claim study by Hammill et al, did project an association between number of CR sessions and MI at 4 years [58], however it failed to include stroke which is a clinically important event in this specific population. The goal for secondary prevention of coronary disease is to control vascular risk factors such as hypertension, diabetes, hyperlipidemia and smoking cessation. This can be brought about by modification in lifestyle habits and exercise which are some of the core components of exercise –based rehabilitation [68]. While we do know that exercise-based rehabilitation also has a beneficial effect on patients who have had a stroke event [69, 70], it is still unclear if CR can prevent the risk of stroke after CABG. It is also unclear if a combination of exercise with education and psychological support can help to reduce the risk of other clinically significant secondary events such as AMI and repeat revascularization in patients after CABG.

To better understand the effect of preventative interventions on secondary non-fatal cardiac events, most large cardiovascular trials have utilized a composite clinical endpoint such as major adverse cardiac and cerebrovascular events (MACCE) as the primary study outcome. The rationale for the cluster is that all events that constitute the composite are individually important and are all potentially modifiable with the intervention. The composite outcome is more comprehensive than a single primary outcome, is clinically meaningful in its own right and is statistically more powerful.

A drawback of using composite outcomes is that the overall significance of the composite outcome cannot be interpreted to be the same for each individual outcome and this may result in some statistical uncertainty. Also, death is a competing event. Therefore, for precise interpretation of the CR effect, in addition to the composite outcome, it would be helpful to also analyze each of the individual nonfatal cardiac events in an adjusted model after accounting for death as a competing risk.

This thesis will attempt to address the limitations and knowledge gaps presented above and aims to determine the influence of CR after CABG beyond 10 years.

Hence, the *primary objective* of this study is to examine the long-term major adverse cardiac and cerebrovascular events (MACCE, defined as the composite of all-cause mortality, myocardial infarction, repeat coronary revascularization, or stroke) in post CABG patients who attended CR versus those who did not attend CR.

The *secondary objective* is to determine whether attending CR is associated with better long-term survival.

The *hypotheses* are that patients who attend postop cardiac rehab care have better long-term MACCE free survival and long-term survival as compared to those who were referred but did do not attend postop cardiac rehab.

The *tertiary objective* is to evaluate the dose response relationship of CR intervention in CABG patients over long-term. The *hypothesis* is that CABG patients with a high level of CR attendance have better long-term MACCE free survival as compared to patients with low level of CR attendance.

Methodology and Methods

3.1 *Database linkages*

Study Design

A retrospective comparison of late outcomes of CABG patients attending CR at Toronto Rehabilitation Institute (TRI) was performed through linkages of multiple clinical and administrative databases housed at the ICES in Toronto, Ontario, Canada. In Ontario, TRI is one of the largest and oldest rehabilitation institutes and it receives > 2,400 referrals per year and provides comprehensive CR care in accordance with the recommended guidelines by the Canadian Association for Cardiac Rehabilitation [8]. ICES is Canada's largest health services research institute and holds multiple population-based health databases of the Ontario population. ICES is a prescribed entity under Ontario's Personal Health Information Protection Act which allows for researchers to link together encoded population-based administrative databases and clinical registries for conducting approved research studies under strict privacy and security policies, procedures and practices (see link to Data and Privacy at www.ices.on.ca). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The need for individual patient consent was waived under this framework. These datasets were linked using unique encoded identifiers and analyzed at ICES.

As required by the Institute of Health Policy Management and Evaluation (IHPME), this study was submitted and received approval by the institutional review board of the University of Toronto.

Study Population

All adults identified from the CorHealth Ontario Cardiac registry (a repository of patients undergoing any cardiac procedure in Ontario) who had isolated CABG with the surgery date between January 1, 1996 and September 30, 2008 and who were referred to TRI were linked at ICES to create our patient population. All patients were followed to March 31, 2017 and this end date was selected based on the linkages which were available at ICES when the data creation plan was executed. The index date used for this study was the "Referral Date" defined as the date when the referral was processed at TRI and contact with the patient was initiated. We excluded patients who died before the referral date and those who had a CABG to referral timeframe greater than 365 days based on the recommendations of the existing literature. The rationale for exclusion was that they represent a unique group and studies have shown that CABG patients who have delayed referral and entrance into the CR program have poorer compliance and outcome [14]. The study cohort was divided into two groups (CR and No-CR) based on attendance. Patients in the CR group were referred and attended at least the intake CR session; the No-CR group were referred but did not attend any CR sessions.

Baseline demographics such as age and sex were derived from Registered Persons Database. The ethnic origin was extracted from the Canadian Immigration database and ICES ethnic database. Variables such as body mass index, hypertension, diabetes, Canadian Cardiovascular Society Class (CCS), left ventricular ejection fraction (LVEF), smoking, previous myocardial infarction, prior percutaneous coronary intervention, peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease and cerebrovascular disease were identified by linkage to

CorHealth Ontario Cardiac Registry. The ICES hypertension and diabetes databases were used to identify missing hypertension and diabetes variables. All the databases had a look-back window of 15 years. The income quintile for this study was computed by cross-referencing patient postal codes with the average household income by area from census data, with "1" being the lowest. This was ascertained from completed referral forms and administrative databases. A detailed list of the specific datasets for specific variables is presented in (A**ppendix 2**). The number of arterial and overall coronary bypass grafts was based on the physician's billing through the Ontario Health Insurance Plan (OHIP) [71]. Perioperative and postoperative outcomes were identified by linkage to the Canadian Institute for Health Information Discharge Abstract Database (CIHI) and International Classification of Diseases, ninth and tenth Revision (ICD 9 and ICD10). The Ontario Registered Deaths Database was used to identify all-cause mortality. Patients with an invalid identification number, missing age and who died on or before the cohort entry date were excluded.

Outcome definition

The primary outcome was MACCE, a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization (percutaneous coronary intervention (PCI) or redo-CABG). The secondary outcome was all-cause mortality. The tertiary outcomes were AMI, stroke, and repeat revascularization (PCI or redo-CABG).

The Canadian Classification of Health Intervention codes, graft codes (OHIP) and codes for AMI, stroke: (ICD 9 and 10) are presented in (**Appendix 3**). As referral date was used as the exposure date for analysis, only outcomes which occurred after the referral date contributed to the primary outcome of MACCE. However, we did examine in-hospital perioperative outcomes including AMI, Stroke, and Dialysis, as well as all-cause readmissions that occurred after discharge from the CABG hospitalization and before the referral date. In-hospital outcomes (AMI, Stroke and Dialysis) and all-cause readmissions after discharge were treated as covariates in the adjusted multivariable models as these non-fatal events may have occurred differentially between the two groups. However, patients who were readmitted for AMI, stroke or repeat revascularization prior to the referral date (n=56) were censored for the MACCE outcome as the dataset included only the first date of any of the non-fatal cardiovascular events. These patients remained at risk for mortality, and for the other non-fatal cardiovascular events which could affect the outcomes.

3.2 *Type of analysis & modelling*

Statistical analyses

Continuous variables were reported as the mean ±standard deviation or median (interquartile range). Categorical variables were reported as frequencies and percentages. Baseline demographics were compared between groups (CR and No-CR) using two sample t-tests (continuous data) or chi-square tests (categorical data). A two-tailed *p-value <0.05* was considered statistically significant. Standardized mean differences (SMD) were determined to compare the baseline balance in variables between the two groups and a SMD of >10% was considered to indicate substantial imbalance[72]. Kaplan-Meier curves were used to compare the event free survival and all-cause survival rates (i.e. the primary and secondary outcomes). Effect estimates for CR for the primary and secondary endpoints are presented as hazard ratios (HR) and their associated 95% confidence intervals (CI). A multivariable Cox proportional hazards model was used to derive a measure of the CR treatment effect in the unadjusted and adjusted analyses (adjusting for baseline characteristics, in-hospital outcomes and all-cause readmissions before the referral date. Prior to modelling we tested for multicollinearity by calculating tolerance statistics for all predictor variables. A tolerance value less than 0.2 was considered to indicate the presence of multicollinearity and in such cases only one member of a correlated set of variables was retained for the models. The assumptions of proportional hazards were assessed for MACCE and all-cause mortality by examining the cumulative hazards graph for proportional parallel lines (log-negative log survival graph for 'parallel lines') [73]. The cumulative incidence functions for AMI, stroke and repeat revascularization were determined and Fine-Gray sub-distribution hazard models were generated in the presence of death as a competing risk [74]. To validate our findings, we compared the results to a model in which we imputed missing data using the Markov chain Monte Carlo method [75].

Secondary analyses

An exploratory secondary analysis was performed based on the percentage of attendance after adjusting for baseline characteristics, in-hospital outcomes, and outcomes before referral date for both MACCE and all-cause mortality using a Cox proportional hazards model.

We split the entire study cohort into four groups: High attendance > 67% of CR sessions (25-36 visits out of a full CR program schedule of 36 visits), Mid attendance 33% - 67% of CR sessions (17-24 visits), Low attendance <33% (1-16 visits), and No-attendance 0% (i.e. the No-CR group). Multiple pairwise comparisons were performed – no adjustment for multiple comparisons was performed.

SAS statistical software

All analyses were conducted with SAS version 14.3; (SAS Institute, Cary, NC). As per ICES policy, all cells with fewer than 5 events were presented as a range to avoid patient identification.

Results

The exposure in the analysis was all patients who had isolated CABG during the study time frame who were referred to TRI and attended at least one CR session. The control group was CABG patients who were referred but did not attend any sessions.

Out of the 98,681 CABG patients in Ontario with the surgery date between 01 January 1996 and 30 September 2008, linkage was possible for 90,654 CABG patients who had valid CIHI records on the same day of, or one day before or after the surgery. In total 25,470 patients were referred to TRI during this timeframe for multiple cardiac diagnoses. After linkage between the TRI dataset and the CorHealth Ontario Cardiac registry at ICES, there were 5,000 patients who had isolated CABG surgery and who were referred to TRI between 01 January 1996 and 30 September 2008 (**Figure 1**). We did not include CABG patients during the same time frame who may have been referred to another rehab institute or who were not referred to TRI.

The study cohort was divided into two groups (CR and No-CR group) based on the level of attendance. Patients in the No-CR group were referred but did not attend any session. The final cohort included 3,685 (73.7%) in the CR group and 1,315 (26.3%) in the No-CR group.

The median discharge to referral time was 32.5 days (IQR: 15-56 days) and the median follow-up duration was 13 years (IQR: 10.0-16.6 years). Out of the 5,000 patients, 56 patients had either a MI or stroke before the referral date, i.e. the exposure date, and were excluded from the primary analysis. As a result, 4,944 patients were included in the multivariable analysis for the primary outcome (MACCE).

For the secondary analysis, the study cohort was divided into four groups based on the percentage of attendance: high attendance (N=1,974), mid attendance (N=1,210), low attendance (N= 501) and No-attendance (N = 1,315).

4.1 *Baseline characteristics*

Overall, patients in the CR group were younger (62.6±9.6 vs 64.0±10.5, p<0.001), more likely male (85.0% vs 79.5%), had lower BMI (BMI<30: 73.8% vs 59.0%, p<0.001), more likely from a higher income quintile (31.1% vs 19.3%, p<0.001) and had fewer cardiac comorbidities compared to the No-CR patients (**Table 2**).

4.2 *Early outcomes*

There were no significant differences between groups with respect to the unadjusted in-hospital outcomes (data for CR vs. No-CR group respectively - AMI: 2.1% vs 1.4%, p=0.09; stroke: 0.8% vs 0.8%, p=0.92; and dialysis: 2.4% vs 3.3%, p=0.05) (**Table 3a**). Patients in the CR group had fewer all-cause readmissions (excluding readmissions for cardiac events) in the time period between discharge from CABG hospitalization but before starting CR as compared to the no-CR group (6.2% vs 9.4%, p <0.001) (**Table 3b**). There was no significant difference between the two groups for other cardiac outcomes between discharge and referral date, CR vs No-CR (AMI:

0.6% vs 0.6%, p=0.96; stroke: 0.2% vs 0.3%, p=0.71 and CABG: 0%vs 0%, p= 0.55). However, readmissions for PCI prior to the referral date were lower in the CR patients (0.2% vs 0.6%, p= 0.03) (**Table 3b**).

4.3 *Late Outcomes: MACCE and All-cause Mortality*

The crude MACCE and mortality Kaplan Meier curves are depicted in (**Figures 2a and 3a**). In adjusted analyses using Cox proportional hazards models, MACCE was lower in patients who attended CR compared to those who did not attend CR (HR 0.83, 95% CI 0.75-0.91, p<0.001) (**Table 4a and Figure 2b**) and had higher freedom from MACCE (27.1% vs 21.9%) at 20 years. Freedom from MACCE at 10 and 15 years was 69.9% and 51.0% in patients who attended CR compared to 65.4% and 45.2% in those who did not (**Table 5a**).

Adjusted survival at 10 and 15 years was 84.0% and 66.3% in the CR group versus 80.1% and 60.1% in the No-CR group (**Table 5b**). Adjusted survival at 20 years was higher in the CR group compared to the No-CR group (**Tables 4b, 5b and Figure 3b**; 38.2% vs 31.4%, HR 0.76, 95%CI 0.68-0.84, p<0.001).

4.4 *Late Outcomes: Non-fatal Cardiovascular Events*

Stroke (number of events =407), AMI (number of events=772) and repeat revascularization (number of events=795) were compared using the Fine-Gray model adjusting for death as a competing risk. There was a lower incidence of stroke at 20 years follow-up in the CR group compared to the No- CR group (adjusted sub-distribution HR 0.76, 95% CI 0.60 – 0.96, p=0.025) after accounting for death as a competing risk. There was no statistically significant difference in AMI (adjusted sub-distribution HR 0.84, 95% CI 0.71 – 1.01, p=0.066), or repeat revascularization (adjusted sub-distribution HR 0.90, 95% CI 0.75 – 1.07, p=0.24 during the follow-up period (**Tables 6, 7 and Figures 4a, 4b and 4c**).

Additionally, in a post hoc fashion, the CR group had a lower risk of the composite outcome of AMI, stroke or repeat revascularization compared to the No-CR group (adjusted sub-distribution HR 0.85, 95% CI 0.75-0.96, p = 0.013) after accounting for death as a competing risk.

4.5 *Secondary analysis*

To evaluate the association of low, medium, and high CR attendance on the primary outcome a secondary analysis was done. Baseline characteristics and early outcomes are described in (**Tables 8, 9a and 9b**).

There did not seem to be any benefit from low CR attendance compared to No-attendance for both MACCE and all-cause mortality. There was a graded response, with medium attendance as the minimum effective CR dose. The greatest effect on MACCE and mortality was observed in the high CR attendance group (**Figures 5a, 5b and Figures 6a and 6b**).

4.6 *Sensitivity analysis*

There was less than 4% missing data and the findings were robust after multiple imputations for missing data. Five imputed datasets were created and the summarized results across the five models were compared to the Cox model fit on the original data. In the adjusted analyses, CR continued to be associated with an improvement in MACCE (HR 0.86, 95% CI 0.78-0.93, p=0.0008) and all-cause mortality (HR 0.81, 95% CI 0.73-0.89, p <0.0001) (**Table 10**).

Chapter 3

Discussion

This chapter will summarize the key findings and discuss the limitations of this study.

To my knowledge, this current study is the first to assess major cardiac outcomes of CABG patients following cardiac rehabilitation over nearly two decades of follow-up. This study targeted a study population defined by patients who underwent CABG with MACCE as our primary outcome and all-cause mortality as the secondary outcome. Despite the study being a single center study, the sample size was moderately large (N=5,000) and had a large number of outcome events to inform the analysis over the long follow-up period.

The key findings are:

(1) CABG patients who attended CR following hospital discharge had higher freedom from MACCE and lower all-cause mortality at any given point of time.

(2) There was consistency between the results of the primary analysis and secondary analysis which strengthen the credibility of the findings. A high level of CR attendance (> 67%) was associated with improved outcomes as compared to low level of attendance.

(3) There was a significant reduction in stroke in patients who attended CR compared to those that did not attend CR.

As compared to the No-CR group, patients in the CR group were younger, more likely male, had BMI (between 25-30), belonged to the higher income quintile, and had creatinine, CCS class and LV grade within the normal range. They had a lower prevalence of cardiac risk factors including previous MI, hypertension, diabetes, smoking, peripheral vascular disease, chronic obstructive pulmonary disease, and cerebrovascular disease. Additionally, the extent of coronary disease was slightly greater in the No-CR group while the numbers of bypasses constructed was slightly greater in the CR group. The CR group had a shorter length of stay after surgery and had fewer readmissions within 30 days. However, the prevalence of recent MI (within 30 days of surgery) was higher in the CR group. There was no significant difference between the groups with respect to the other in-hospital outcomes (AMI, stroke, and dialysis).

In this study, patients in the CR group belonged to a higher income quintile (31.1% vs 19.3%, p =<0.001) which can be translated as having a better SES, higher education, and possibly better understanding of the impacts of CR care. This is consistent with previous research which has shown that especially in a CABG population CR compliance is highly dependent on these sociodemographic factors[19]. Patients with low SES experience greater barriers to CR as compared to patients belonging to high SES [19]. Additionally, studies have shown that low SES is associated with higher morbidity and mortality in patients with CHD [76]. A prospective observational study of 2,256 patients following AMI across 53 hospitals in Ontario, found that pre-existing heart disease and comorbidities such as hypertension, diabetes, smoking were higher among poorer and less educated people [77].

There was a recent update to the CROS meta-analysis in November 2020 (i.e. after the publication of the manuscript in October 2020 based on this thesis); it included an additional 6 studies (2RCT's and 4 observational studies), in total 31 studies (228,337 patients) with a follow-up period ranging from 9-14 years [78]. CR continued to be associated with a significant reduction in total mortality in patients with acute coronary syndrome (HR: 0.64, 95% CI 0.53-0.76). In this meta-analysis, CABG patients were analyzed as a subgroup (6/31 studies) and results showed that CR remained to be associated with reduced mortality (HR: 0.62, 95% CI 0.54-0.70) in this patient population [78].

Reassuringly, the findings of this thesis project are consistent with the existing literature and provide confirmation regarding the benefits of CR attendance and association with reduced mortality in a CABG population. In this study as well, the CR group had better survival rate and lower MACCE which remained persistent over time both in the unadjusted analysis and multivariable modelling. The adjusted Kaplan-Meier curves showed a reduction in all-cause mortality and MACCE in the CR group, which remained in the same direction even after imputations for the missing data.

There is existing evidence which portrays how individual events like AMI and stroke tend to vary with the intervention in patients with CHD [79 80]. In order to better understand the effect of individual non-fatal cardiac events, in this study additional analysis was done where AMI, stroke and repeat revascularization were analyzed with death as a competing risk. Similar to a recent Cochrane meta-analysis of CR outcomes, our study showed that repeat revascularization was similar in the CR and No CR groups, (15.7% vs 16.4%, p=0.24, adjusted sub-distribution HR 0.90, 95% CI 0.75-1.07). There was no statistically significant difference between the two groups in terms of new myocardial infarction, although numerically there were less events in the CR group (14.3% vs 18.4%, p=0.06, adjusted sub-distribution HR 0.84, 95% CI 0.71-1.01) throughout the follow-up period. However, there was a lower incidence of stroke at 20 years follow-up in the CR group compared to the No-CR group (adjusted sub-distribution HR 0.76, 95% CI 0.60 – 0.96, p=0.025) after accounting for death as a competing risk. The reduction in stroke in this patient population is a novel finding.

Furthermore, in a post hoc analysis, patients in the CR group had a lower incidence of the composite of AMI, stroke or repeat revascularization (adjusted sub-distribution HR 0.85, 95%CI 0.75-0.96, p = 0.013) after accounting for death as a competing risk.

Additionally, in an exploratory fashion, patients in the No-CR group had a higher rate of nonfatal events (AMI or stroke or repeat revascularization) preceding death than the CR patients [CR vs No-CR: 38.0% vs 44.0%, p=0.01]. These are crude results without further adjustment for baseline characteristics and ignore the time to event nature of the data.

None-the-less, these findings are relevant because the results do support the concept that one of the benefits of CR is the reduction in non-fatal events. The protective effect to prevent premature mortality could be mediated through these non-fatal cardiac events and CR attendance could be the potential driver for the outcomes. Further studies are required to corroborate these findings so as to better understand if these non-fatal events are indeed the main driver for the long-term outcomes in a CR-CABG population.

To minimize bias the study population included all referred patients but any attendance was not sufficient to observe a treatment effect. The dose-response in this study showed that high-level of CR attendance had better outcomes as compared to low level of attendance. A secondary interpretation of the dose-response finding would be that the overall CR effect seen in the primary analysis is a true treatment effect rather than one related to unmeasured confounders.

We do not have information about CABG patients who were referred to another CR institute which may have had a different CR program and required level of attendance. Also, we do not have information of patients that underwent CABG and were never referred; these patients may have had different baseline characteristics which could alter the outcomes.

Findings from this study highlight the importance of patient referral to CR after CABG. It also portrays the significance of sustained participation in CR for improved outcomes and better longevity.

Limitations

As with any observational study there were some pertinent limitations with this study. As TRI is one of the oldest and largest rehabilitation centers in Ontario, findings from this single center study may not be easy to replicate at other rehabilitation centers which may reduce external generalizability. The retrospective nature of this study raises concerns for measured and unmeasured confounders which were not resolved with multivariable modelling. In particular, while we used neighbourhood income quintile as a surrogate measure for SES, we recognize that there are limitations to this approach and that true SES measures include other aspects such as education, available social supports, and mental health. Studies have shown that patients that undergo CR are more likely from higher socioeconomic status groups and higher socioeconomic status is associated with improved outcomes [19]. While our exposure definition for the CR group was defined by any attendance, a large majority of the patients had moderate to high attendance (86.5% of cohort) and only 13.5% had low attendance. We were unable to determine the effect of compliance with the program (i.e. home based exercise) outside of the on-site sessions. Furthermore, the study population included only referred CABG patients and did not look at those who were not referred who may have had different baseline characteristics with different outcomes. Despite observing a dose-response effect, there is a possibility that this may reflect a change in the subject's behavior itself rather than a function of the program's effectiveness. A systematic review of 29 studies across different countries showed that factors related to CR attendance and compliance followed a determined pattern irrespective of the CR program. Older patients, women, persons who were unemployed with lower household income, patients with comorbidities, those who did not have transportation and those who were less educated had a decreased CR attendance [24]. Another limitation of this study is that the time to event analysis only included the date for the first event and did not include recurring non-fatal cardiac events. With increasing age and comorbidities CABG patients are at higher risk of AMI, stroke or repeat revascularization. They may experience multiple occurrences of non-fatal events over time. Therefore, to better understand the long-term clinical and survival effects of CR in a CABG population, the inclusion of recurrent non-fatal cardiac events may be informative. In addition, the study population is not a true contemporary cohort as the final year for inclusion into the cohort was 2008; however, the key features of CR delivery have remained the same over the last decade. Finally, it is possible that the long-term outcome difference observed may be attributable to the differences in lifestyle/exercise during the follow-up period rather than the act of CR referral in of itself. While important research has been published looking at CR care, studies specifically evaluating CR practices following CABG are still lacking. There is a need to evaluate other CR centers and analyze parameters such as ethnicity and gender which may have important impacts on long-term outcomes following CABG.

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Conflict of Interest None

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Appendix 1:

Database(s): Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-May 2020

Search Strategy:

#	Searches	Results
1	exp Coronary Artery Bypass/rh [Rehabilitation]	828
2	limit 1 to (English language and humans and (clinical study or clinical trial, all or controlled clinical trial or dataset or English abstract or journal article or meta-analysis or multicenter study or observational study or randomized controlled trial or "review" or systematic reviews))	579
3	exp Coronary Artery Bypass/ or exp Postoperative Complications/ or exp Treatment Outcome/	1289404
4	exp Cardiac Rehabilitation/	1531
5	limit 3 to (English language and humans and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)" or "aged (80 and over)") and (clinical study or clinical trial, all or English abstract or journal article or meta-analysis or multicenter study or observational study or randomized controlled trial or "review" or systematic reviews))	664412
6	4 and 5	134
7	2 or 6	702
8	2 or 4	2093
9	exp Coronary Artery Disease/ or exp Exercise Therapy/ or exp Cardiac Rehabilitation/	95063
10	8 and 9	1658
11	9 or 10	166

Appendix 2: Specific datasets for baseline variables (dataset creation)

Variable	Dataset				
	RPDB	CIC	Corhealth Ontario cardiac registry	ICES database	TRI database
Age	Yes	-	-	-	Yes
Sex	Yes	-	-	-	Yes
BMI	-	-	Yes	-	Yes
Income quintile	-	-	-	-	Yes
Ethnicity	-	Yes	-	Yes	-
Creatinine	-	-	Yes	-	-
CCS class	-	-	Yes	-	-
LVEF grade	-	-	Yes	-	-
Hypertension	-	-	Yes	Yes	-
Diabetes	-	-	Yes	Yes	-
Hyperlipidemia	-	-	Yes	-	-
Smoking	-	-	Yes	-	Yes
PVD	-	-	Yes	-	-
COPD	-	-	Yes	-	-
CVD	-	-	Yes	-	-
Redo CABG	-	-	Yes	-	-
Previous PCI	-	-	Yes	-	-
Previous MI	-	-	Yes	-	-
Previous MI within 30 days	-	-	Yes	-	-

Legend – RPDB: registered persons database; CIC: Canadian Immigration database; TRI: Toronto rehabilitation institute database

CCS: Canadian Cardiovascular Society Class; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; HTN: hypertension; LVEF: left ventricular ejection fraction

Appendix 3: Codes for outcome variables

Outcome	ICD-9 code	ICD-10 code	CCI code	OHIP code
Coronary artery bypass graft surgery			1IJ76	
Double coronary bypass graft				R743
Each additional coronary bypass graft				E654
Total number of grafts				R742 or R743 + (E654 x N)
Total number of arterial grafts				E652 x N
AMI	410	I21.x, I22.x		
Stroke	430,431,434,436,362.3	I60.x I61.x I62.x I63.x, I64.x, H34.1 (excluding I63.6)		
Percutaneous coronary intervention			1IJ50, 1IJ54, 1IJ57GQ	

Legend - AMI: Acute Myocardial Infarction; CCI: Canadian Classification of Health Interventions; ICD: International Classification of Diseases, N: Number of OHIP claims; OHIP: Ontario Health Insurance Plan.

Table 2: Baseline characteristics of the CR group and No-CR groups

		CR Group	No-CR Group	Standardized difference	P-Value
VARIABLE	VALUE	N=3,685	N=1,315		
Age	Mean (SD)	62.6 ± 9.6	64.0 ± 10.5	0.14	<0.001
Sex	F	552 (15.0%)	270 (20.5%)	0.15	
	M	3,133 (85.0%)	1,045 (79.5%)	0.15	<0.001
BMI	<25	925 (25.1%)	313 (23.8%)	0.03	
	25-30	1,793 (48.7%)	463 (35.2%)	0.28	
	31-35	702 (19.1%)	264 (20.1%)	0.03	
	>35	215 (5.8%)	88 (6.7%)	0.04	
	Missing	50 (1.4%)	187 (14.2%)	0.49	<0.001
Income quintile	1	594 (16.1%)	286 (21.7%)	0.14	
	2	616 (16.7%)	282 (21.4%)	0.12	
	3	640 (17.4%)	242 (18.4%)	0.03	
	4	689 (18.7%)	251 (19.1%)	0.01	
	5	1,146 (31.1%)	254 (19.3%)	0.27	<0.001
Surname-based Ethnic Group	Chinese	92 (2.5%)	39 (3.0%)	0.03	
	General population	3,428 (93.0%)	1,201 (91.3%)	0.06	
	South Asian	165 (4.5%)	75 (5.7%)	0.06	0.12
Charlson Index	Mean (SD)	0.9 ± 0.7	1.0 ± 0.7	0.16	<0.001
Creatinine	<120	3,312 (89.9%)	1,140 (86.7%)	0.10	
	120-180	222 (6.0%)	91 (6.9%)	0.04	
	>180	33 (0.9%)	23 (1.7%)	0.07	
	Missing	118 (3.2%)	61 (4.6%)	0.07	0.003
CCS class	0	16-20	6-10	0.03	
	1	228 (6.2%)	82 (6.2%)	0.00	
	2	579 (15.7%)	179 (13.6%)	0.06	
	3	1,045 (28.4%)	345 (26.2%)	0.05	
	4	1,809 (49.1%)	698 (53.1%)	0.08	
	Missing	4-8	1-5	0.01	0.08
LVEF grade	1	1,770 (48.0%)	563 (42.8%)	0.10	
	2	1,269 (34.4%)	474 (36.0%)	0.03	
	3	542 (14.7%)	224 (17.0%)	0.06	
	4	77 (2.1%)	41 (3.1%)	0.06	
	Missing	27 (0.7%)	13 (1.0%)	0.03	<0.001
HTN		2,502 (67.9%)	986 (75.0%)	0.16	<0.001
Diabetes		1,159 (31.5%)	521 (39.6%)	0.17	<0.001

Hyperlipidemia		2,460 (66.8%)	882 (67.1%)	0.01	0.83
Smoking		2,136 (58.0%)	798 (60.7%)	0.06	0.08
PVD		362 (9.8%)	179 (13.6%)	0.12	<0.001
COPD		192 (5.2%)	86 (6.5%)	0.06	0.07
CVD		271 (7.4%)	122 (9.3%)	0.07	0.02
Redo CABG		96 (2.6%)	47 (3.6%)	0.06	0.07
Previous PCI		243 (6.6%)	104 (7.9%)	0.05	0.10
Previous MI		1,299 (35.3%)	534 (40.6%)	0.11	<0.001
Previous MI within 30 days		719 (19.5%)	225 (17.1%)	0.06	0.05
Number of grafts based on OHIP billing	Mean (SD)	3.2 ± 0.9	3.1 ± 0.9	0.12	<0.001
Number of grafts based on OHIP billing	Missing	90 (2.4%)	33 (2.5%)	0.00	
	1	83 (2.3%)	38 (2.9%)	0.04	
	2	503 (13.6%)	216 (16.4%)	0.08	
	3	1,472 (39.9%)	551 (41.9%)	0.04	
	4	1,191 (32.3%)	391 (29.7%)	0.06	
	5	323 (8.8%)	80 (6.1%)	0.10	
	6	23 (0.6%)	6 (0.5%)	0.02	<0.001
Episode length of stay (LOS)	Median (IQR)	7.0 (6-10)	8.0 (6-12)	0.16	<0.001
Arterial graft	0	240 (6.5%)	106 (8.1%)	0.06	
	1	2,456 (66.6%)	899 (68.4%)	0.04	
	2	796 (21.6%)	252 (19.2%)	0.06	
	3	193 (5.2%)	58 (4.4%)	0.04	0.007
Left Main	1	823 (22.3%)	304 (23.1%)	0.02	
Proximal LAD + one or more Cx & RCA	2	1,918 (52.0%)	689 (52.4%)	0.01	
TVD without proximal LAD	3	126 (3.4%)	56 (4.3%)	0.04	
SVD of proximal LAD	4	296 (8.0%)	83 (6.3%)	0.07	
1 or 2 vessel disease or none of the above	5	497 (13.5%)	171 (13.0%)	0.01	
Disease location	Missing	25 (0.7%)	12 (0.9%)	0.03	0.35

Legend - CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions
CCS: Canadian Cardiovascular Society Class; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; HTN: hypertension; LVEF: left ventricular ejection fraction; previous MI: previous myocardial infarction (any MI within 15 years prior to index CABG); previous MI within 30 days: indicates any myocardial infarction within 30 days prior to index coronary artery bypass graft (CABG);PCI: percutaneous coronary intervention; TVD: triple vessel disease; SVD: single vessel disease; LAD: left anterior descending artery; RCA: right coronary artery; Cx: circumflex, St. Diff: standardized difference (less than 0.1 is negligible).

As per ICES policy, all cells with fewer than 5 events were presented as a range to avoid patient identification.

Table 3a: In-hospital outcomes of the CR group and No-CR groups

	CR Group	**No-CR Group**	**P-value**	Relative risk (95% CI) - *crude*
Variable	N = 3,685	N = 1,315		
AMI	78 (2.1%)	18 (1.4%)	0.09	0.64 (0.38-1.07)
Stroke	29 (0.8%)	10 (0.8%)	0.92	0.96 (0.47-1.97)
Dialysis	87 (2.4%)	44 (3.3%)	0.05	1.41 (0.99-2.02)

Legend – CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions
AMI: acute myocardial infarction

Table 3b: Outcomes between discharge – referral date of the CR group and No-CR groups

	CR group	**No-CR group**	**P-value**	Relative risk (95%CI) – *crude*
Variable	N = 3,685	N = 1,315		
All-cause readmission (excluding readmissions for AMI, Stroke or repeat revascularization)	228 (6.2%)	124 (9.4%)	<0.001	1.52 (1.23-1.87)
AMI	22 (0.6%)	8 (0.6%)	0.96	1.01 (0.45-2.28)
Stroke	9 (0.2%)	1-5	0.71	1.24 (0.38-4.03)
PCI	8 (0.2%)	8 (0.6%)	0.03	2.80 (1.05-7.45)
Redo-CABG	1-5	0 (0.0%)	0.55	1.00 (0.99-1.00)

Legend – CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions

AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft
As per ICES policy, all cells with fewer than 5 events were presented as a range to avoid patient identification.

Table 4a: Multivariable Cox proportional hazards model for Primary Outcome (MACCE)

Variable		Hazard Ratio	95% Hazard confidence limits	P-value	
CR Group		**0.83**	**0.75-0.91**	**<0.0001**	
Age		1.04	1.03-1.04	<0.0001	
Sex	Female	0.99	0.89-1.11	0.95	Ref = Male
BMI	25-30	1.03	0.93-1.14	0.54	Ref = BMI <25
	31-35	1.17	1.03-1.32	0.01	
	>35	1.28	1.06-1.53	0.008	
	Missing	0.90	0.74-1.09	0.28	
Income quintile	1	1.07	0.95-1.21	0.23	Ref = Income quintile 5
	2	1.05	0.93-1.18	0.41	
	3	1.10	0.97-1.24	0.11	
	4	1.06	0.94-1.20	0.28	
Surname-based Ethnic Group	Chinese	0.67	0.49-0.90	0.009	Ref = general population
	South Asian	1.19	0.98-1.44	0.07	
Charlson Index		1.18	1.04-1.34	0.007	
Creatinine	120-180	1.20	1.03-1.39	0.01	Ref = creatinine < 120
	>180	1.65	1.21-2.26	0.001	
	Missing	1.31	1.08-1.58	0.004	
CCS class	2	1.25	1.02-1.55	0.03	Ref = CCS class 1
	3	1.35	1.11-1.64	0.002	
	4	1.30	1.07-1.58	0.006	
	Missing	1.67	0.76-3.67	0.19	
LVEF grade	2	1.02	0.93-1.12	0.58	Ref = LVEF grade 1
	3	1.18	1.05-1.33	0.004	
	4	1.71	1.36-2.14	<0.0001	
	Missing	1.55	1.04-2.29	0.03	
HTN		1.04	0.95-1.14	0.37	
Diabetes		1.29	1.18-1.42	<0.0001	
Hyperlipidemia		0.95	0.88-1.04	0.32	
Smoking		1.12	1.03-1.22	0.005	
PVD		1.35	1.20-1.52	<0.0001	
COPD		1.19	1.01-1.39	0.028	
CVD		1.25	1.10-1.43	0.0007	
Redo CABG		1.18	0.95-1.46	0.13	
Previous PCI		1.09	0.93-1.28	0.24	
Previous MI		1.24	1.07-1.43	0.003	
Previous MI within 30 days		0.80	0.70-0.92	0.003	
Number of grafts based on OHIP billing		0.96	0.92-1.00	0.06	

Episode length of stay (LOS)		1.01	1.01-1.02	<0.0001	
Arterial graft	0	0.95	0.81-1.11	0.54	Ref = Single arterial graft x1
	2	0.87	0.78-0.97	0.012	
	3	0.84	0.67-1.04	0.11	
Proximal LAD + one or more Cx & RCA	2	0.93	0.84-1.03	0.20	Ref = Left Main disease
TVD without proximal LAD	3	0.92	0.71-1.18	0.52	
SVD of proximal LAD	4	0.96	0.81-1.14	0.68	
1 or 2 vessel disease or none of the above	5	1.05	0.91-1.20	0.47	
Disease location	Missing	1.20	0.77-1.85	0.40	
In-Hospital Outcomes					
AMI		0.84	0.63-1.12	0.25	
Stroke		1.39	0.94-2.06	0.09	
Dialysis		1.27	0.98-1.64	0.06	
Outcome before referral date					
All-cause readmission (excluding readmissions for AMI, Stroke or repeat revascularization)		1.22	1.06-1.41	0.004	

Legend - Ref: reference group for the variable

CCS: Canadian Cardiovascular Society Class; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; HTN: hypertension; LVEF: left ventricular ejection fraction; previous MI: previous myocardial infarction (any MI within 15 years prior to index CABG); PCI: percutaneous coronary intervention; TVD: triple vessel disease; SVD: single vessel disease; LAD: left anterior descending artery; RCA: right coronary artery; Cx: circumflex ; AMI: acute myocardial infarction

Table 4b: Multivariable Cox proportional hazards model for Secondary Outcome (All-cause mortality)

Variable		**Hazard Ratio**	**95% Hazard confidence limits**	**P-value**	
CR Group		**0.76**	**0.68-0.84**	**<0.0001**	
Age		1.08	1.07-1.08	<0.0001	
Sex	Female	0.93	0.82-1.05	0.27	Ref = Male
BMI	25-30	0.96	0.85-1.08	0.50	Ref = BMI <25
	31-35	1.20	1.04-1.38	0.01	
	>35	1.40	1.13-1.73	0.001	
	Missing	0.82	0.66-1.02	0.07	
Income quintile	1	1.07	0.93-1.24	0.29	Ref = Income quintile 5
	2	1.08	0.94-1.24	0.25	
	3	1.05	0.92-1.21	0.42	
	4	1.05	0.92-1.21	0.41	
Surname-based Ethnic Group	Chinese	0.78	0.56-1.09	0.15	Ref = general population
	South Asian	1.10	0.87-1.40	0.40	
Charlson Index		1.11	0.95-1.28	0.16	
Creatinine	120-180	1.29	1.10-1.52	0.001	Ref = creatinine < 120
	>180	2.01	1.43-2.82	<0.0001	
	Missing	1.40	1.14-1.71	0.001	
CCS class	2	1.30	1.01-1.67	0.03	Ref = CCS class 1
	3	1.37	1.09-1.73	0.006	
	4	1.29	1.02-1.62	0.029	
	Missing	1.50	0.90-2.38	0.08	
LVEF grade	2	1.08	0.97-1.21	0.12	Ref = LVEF grade 1
	3	1.40	1.23-1.60	<0.0001	
	4	2.50	1.95-3.20	<0.0001	
	Missing	1.50	0.90-2.38	0.08	
HTN		1.09	0.98-1.21	0.11	
Diabetes		1.49	1.34-1.66	<0.0001	
Hyperlipidemia		0.91	0.83-1.00	0.06	
Smoking		1.18	1.07-1.30	0.0008	
PVD		1.57	1.38-1.79	<0.0001	
COPD		1.16	0.97-1.38	0.09	
CVD		1.24	1.07-1.43	0.004	
Redo CABG		1.10	0.86-1.40	0.43	
Previous PCI		0.92	0.76-1.12	0.43	
Previous MI		1.16	0.98-1.36	0.07	
Previous MI within 30 days		0.87	0.69-0.94	0.006	
Number of grafts based on OHIP billing		0.96	0.91-1.01	0.15	
Episode length of stay (LOS)		1.01	1.01-1.02	<0.0001	

Arterial graft	0	1.04	0.88-1.23	0.59	Ref = Single arterial graft
	2	0.83	0.79-0.96	0.010	
	3	0.90	0.69-1.19	0.49	
Proximal LAD + one or more Cx & RCA	2	0.86	0.76-0.96	0.010	Ref = Left Main disease
TVD without proximal LAD	3	0.92	0.68-1.23	0.58	
SVD of proximal LAD	4	0.95	0.77-1.17	0.66	
1 or 2 vessel disease or none of the above	5	0.95	0.81-1.11	0.54	
Disease location	Missing	1.02	0.63-1.66	0.91	
In-Hospital Outcomes					
AMI		0.91	0.67-1.24	0.57	
Stroke		1.53	1.10-2.33	0.044	
Dialysis		1.35	1.01-1.81	0.042	
Outcomes before referral date					
All-cause readmission (excluding readmissions for AMI, Stroke or repeat revascularization)		1.40	1.20-1.64	<0.0001	
AMI		1.40	0.76-2.56	0.27	
Stroke		5.89	3.26-10.67	<0.0001	
Repeat revascularization		0.33	0.04-2.45	0.28	

Legend - Ref: reference group for the variable

CCS: Canadian Cardiovascular Society Class; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; HTN: hypertension; LVEF: left ventricular ejection fraction; previous MI: previous myocardial infarction (any MI within 15 years prior to index CABG); PCI: percutaneous coronary intervention; TVD: triple vessel disease; SVD: single vessel disease; LAD: left anterior descending artery; RCA: right coronary artery; Cx: circumflex; AMI: acute myocardial infarction

Table 5a: *[Adjusted]* Time to event analysis for Freedom from MACCE

Freedom from MACCE for CR group compared to No-CR group	Hazard ratio: **0.83, 95% CI (0.75– 0.91)** Adjusted p-value for Cox proportional hazards model = <.0001		
Freedom from MACCE	**CR group**	**No-CR group**	
	% (95 CI)	% (95 CI)	HR (95%CI)
5yr	86.1% (85.1-87.1)	83.6% (82.3-85.0)	0.71(0.60-0.83)
10yr	69.9% (68.6-71.3)	65.4% (63.4-67.6)	0.80(0.72-0.89)
15yr	51.0% (49.3-52.6)	45.2% (42.7-47.9)	0.80(0.74-0.86)
20yr	27.1% (24.7-29.8)	21.9% (19.2-25.1)	0.83(0.77-0.89)

Legend - CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions

MACCE is defined by all-cause mortality, myocardial infarction, stroke, or repeat revascularization. The data is the table are the adjusted Kaplan -Meier estimates with the 95% confidence interval (CI). HR=hazard ratio.

Table 5b: *[Adjusted]* Time to event analysis for Freedom from all-cause mortality

Freedom from All-cause Mortality for CR group compared to No-CR group	Hazard ratio: **0.76, 95% CI (0.68– 0.84)** Adjusted p-value for Cox proportional hazards model = <.0001		
Freedom from All-cause Mortality	**CR Group**	**No-CR group**	
	% (95 CI)	% (95 CI)	HR (95%CI)
5yr	94.9% (94.4-95.5)	93.5% (92.7-94.3)	0.56(0.44-0.73)
10yr	84.0% (83.0-85.0)	80.1% (78.6-81.7)	0.75(0.66-0.85)
15yr	66.3% (64.9-67.8)	60.1% (57.9-62.4)	0.77(0.71-0.83)
20yr	38.2% (35.8-40.8)	31.4% (28.5-34.6)	0.78 (0.72-0.83)

Legend - CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions

The data is the table are the adjusted Kaplan -Meier estimates with the 95% confidence interval (CI). HR=hazard ratio.

Table 6: *[Adjusted]* Sub-distribution HR for AMI, Stroke, and repeat revascularization (PCI or CABG) with death as a competing risk at 20 years follow-up

	CR group	**No-CR group**	**Sub-distribution HR (95%CI)**	**P-value**
Variable	N = 3,685	N = 1,315		
AMI	529	243	0.84 (0.71-1.01)	0.06
Stroke	267	140	0.76 (0.60-0.96)	0.02
Repeat revascularization (PCI or CABG)	579	216	0.90 (0.75-1.07)	0.24

Legend - CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions

AMI – acute myocardial infarction

Table 7: Cumulative incidence for non-fatal events adjusted for Death as a competing risk

	CR Group	**No-CR Group**
	% (95 CI)	% (95 CI)
Cumulative incidence 5yr AMI	0.5 (0.3-0.7)	1.9 (1.2-2.7)
Cumulative incidence 10yr AMI	3.3 (2.8-3.9)	6.0 (4.8-7.3)
Cumulative incidence 15yr AMI	9.5 (8.5-10.6)	13.7 (11.8-15.8)
Cumulative incidence 20yr AMI	21.5 (19.6-23.4)	24.3 (21.5-27.3)
Cumulative incidence 5yr stroke	0.4 (0.2-0.6)	1.1(0.6-1.8)
Cumulative incidence 10yr stroke	2.1 (1.7-2.6)	4.2 (3.2-5.4)
Cumulative incidence 15yr stroke	5.6 (4.9-6.5)	8.7 (7.1-10.4)
Cumulative incidence 20yr stroke	10.3 (9.0-11.8)	14.1 (11.8-16-5)
Cumulative incidence 5yr repeat revascularization	0.2 (0.1-0.4)	0.6 (0.3-1.2)
Cumulative incidence 10yr repeat revascularization	2.4 (1.9-2.9)	3.2 (2.3-4.3)
Cumulative incidence 15yr repeat revascularization	9.2 (8.2-10.3)	10.5 (8.8-12.4)
Cumulative incidence 20yr repeat revascularization	23.0 (21.2-24.9)	22.0 (19.3-24.7)

Legend - CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions

AMI – acute myocardial infarction

Table 8: Baseline characteristics based on the level of Cardiac rehab participation [High, Medium, Low and No participation]

Variable	value	**High - > 67%**	**Mid - 33 - 67%**	**low - < 33%**	**No-CR group** – *(intake only - 0% attendance)*	**p-value**
		N=1,974	N=1,210	N=501	N=1,315	
Age	Mean ± SD	63.8 ± 9.3	61.4 ± 9.8	60.6 ±10.0	64.0 ± 10.5	<0.001
Sex	F	275 (13.9%)	197 (16.3%)	80 (16.0%)	270 (20.5%)	<0.001
	M	1,699 (86.1%)	1,013 (83.7%)	421 (84.0%)	1,045 (79.5%)	
BMI	<25	533 (27.0%)	273 (22.6%)	119 (23.8%)	313 (23.8%)	<0.001
	25-30	1,003 (50.8%)	571 (47.2%)	219 (43.7%)	463 (35.2%)	
	31-35	331 (16.8%)	251 (20.7%)	120 (24.0%)	264 (20.1%)	
	>35	83 (4.2%)	97 (8.0%)	35 (7.0%)	88 (6.7%)	
	missing	24 (1.2%)	18 (1.5%)	8 (1.6%)	187 (14.2%)	
Income Quintile	1	266 (13.5%)	219 (18.1%)	109 (21.8%)	286 (21.7%)	<0.001
	2	318 (16.1%)	204 (16.9%)	94 (18.8%)	282 (21.4%)	
	3	361 (18.3%)	195 (16.1%)	84 (16.8%)	242 (18.4%)	
	4	357 (18.1%)	247 (20.4%)	85 (17.0%)	251 (19.1%)	
	5	672 (34.0%)	345 (28.5%)	129 (25.7%)	254 (19.3%)	
Surname-based Ethnic Group	Chinese	58 (2.9%)	25 (2.1%)	9 (1.8%)	39 (3.0%)	0.03
	General population	1,844 (93.4%)	1,118 (92.4%)	466 (93.0%)	1,201 (91.3%)	
	South Asian	72 (3.6%)	67 (5.5%)	26 (5.2%)	75 (5.7%)	
Charlson Index	Mean ± SD	0.8 ± 0.7	0.9 ± 0.7	0.9 ± 0.7	1.0 ± 0.7	<0.001
Creatinine	<120	1,778 (90.1%)	1,090 (90.1%)	444 (88.6%)	1,140 (86.7%)	0.03
	120-180	115 (5.8%)	68 (5.6%)	39 (7.8%)	91 (6.9%)	
	>180	15 (0.8%)	13 (1.1%)	4-8	23 (1.7%)	
	missing	66 (3.3%)	39 (3.2%)	13 (2.6%)	61 (4.6%)	
CCS class	0	4-8	5-9	1-5	6-10	0.36
	1	138 (7.0%)	64 (5.3%)	26 (5.2%)	82 (6.2%)	
	2	305 (15.5%)	197 (16.3%)	77 (15.4%)	179 (13.6%)	
	3	555 (28.1%)	346 (28.6%)	144 (28.7%)	345 (26.2%)	
	4	964 (48.8%)	596 (49.3%)	249 (49.7%)	698 (53.1%)	
	missing	4-8	1-5	1-5		

LVEF grade	1	974 (49.3%)	588 (48.6%)	208 (41.5%)	563 (42.8%)	<0.001
	2	671 (34.0%)	407 (33.6%)	191 (38.1%)	474 (36.0%)	
	3	279 (14.1%)	182 (15.0%)	81 (16.2%)	224 (17.0%)	
	4	37 (1.9%)	28 (2.3%)	12 (2.4%)	41 (3.1%)	
	missing	13 (0.7%)	4-8	6-10	13 (1.0%)	
HTN		1,354 (68.6%)	802 (66.3%)	346 (69.1%)	986 (75.0%)	<0.001
Diabetes		563 (28.5%)	399 (33.0%)	197 (39.3%)	521 (39.6%)	<0.001
Hyperlipidemia		1,314 (66.6%)	802 (66.3%)	344 (68.7%)	882 (67.1%)	0.79
Smoking		1,114 (56.4%)	706 (58.3%)	316 (63.1%)	798 (60.7%)	0.01
PVD		185 (9.4%)	119 (9.8%)	58 (11.6%)	179 (13.6%)	<0.001
COPD		103 (5.2%)	61 (5.0%)	28 (5.6%)	86 (6.5%)	0.32
CVD		151 (7.6%)	80 (6.6%)	40 (8.0%)	122 (9.3%)	0.09
Redo CABG		45 (2.3%)	34 (2.8%)	17 (3.4%)	47 (3.6%)	0.14
Previous PCI		119 (6.0%)	78 (6.4%)	46 (9.2%)	104 (7.9%)	0.03
Previous MI		691 (35.0%)	428 (35.4%)	180 (35.9%)	534 (40.6%)	0.007
Previous MI within 30 days		404 (20.5%)	218 (18.0%)	97 (19.4%)	225 (17.1%)	0.08
Graft number based on OHIP billing	Mean ± SD	3.3 ± 0.9	3.3 ± 0.9	3.2 ± 0.9	3.1 ± 0.9	0.002
Graft number based on OHIP billing	0	49 (2.5%)	28 (2.3%)	13 (2.6%)	33 (2.5%)	0.07
	1	50 (2.5%)	25 (2.1%)	6-10	38 (2.9%)	
	2	256 (13.0%)	169 (14.0%)	78 (15.6%)	216 (16.4%)	
	3	804 (40.7%)	469 (38.8%)	199 (39.7%)	551 (41.9%)	
	4	624 (31.6%)	402 (33.2%)	165 (32.9%)	391 (29.7%)	
	5	177 (9.0%)	111 (9.2%)	35 (7.0%)	80 (6.1%)	
	6	14 (0.7%)	4-8	1-5	6 (0.5%)	
Episode length of stay (LOS) Arterial graft	Mean ± SD	8.9 ± 5.6	9.3 ± 6.8	9.1 ± 6.2	10.2 ± 7.7	<0.001
	0	117 (5.9%)	87 (7.2%)	36 (7.2%)	106 (8.1%)	0.01
	1	1,337 (67.7%)	802 (66.3%)	317 (63.3%)	899 (68.4%)	
	2	404 (20.5%)	263 (21.7%)	129 (25.7%)	252 (19.2%)	
	3	116 (5.9%)	58 (4.8%)	19 (3.8%)	58 (4.4%)	
Left main	1	435 (22.0%)	262 (21.7%)	126 (25.1%)	304 (23.1%)	0.52
Proximal LAD + one or more Cx & RCA	2	1,047 (53.0%)	625 (51.7%)	246 (49.1%)	689 (52.4%)	
TVD without proximal LAD	3	63 (3.2%)	41 (3.4%)	22 (4.4%)	56 (4.3%)	
SVD of proximal LAD	4	162 (8.2%)	99 (8.2%)	35 (7.0%)	83 (6.3%)	
1 or 2 vessel disease or none of the above	5	254 (12.9%)	174 (14.4%)	69 (13.8%)	171 (13.0%)	
Disease location	missing	13 (0.7%)	7-11	1-5	12 (0.9%)	

Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% **-** 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%)

CCS: Canadian Cardiovascular Society Class; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; HTN: hypertension; LVEF: left ventricular ejection fraction; previous MI: previous myocardial infarction (any MI within 15 years prior to index CABG); previous MI within 30 days: indicates any myocardial infarction within 30 days prior to index coronary artery bypass graft (CABG);PCI: percutaneous coronary intervention; TVD: triple vessel disease; SVD: single vessel disease; LAD: left anterior descending artery; RCA: right coronary artery; Cx: circumflex, St. Diff: standardized difference (less than 0.1 is negligible).

As per ICES policy, all cells with fewer than 5 events were presented as a range to avoid patient identification.

Table 9a: *[Crude]* In – hospital outcomes based on the level of cardiac rehab participation [High, Medium, Low and No participation] - (*after surgery – before discharge)*

	High - > 67%	**Mid - 33 - 67%**	**low - < 33%**	**No-CR group –** *(intake only - 0% attendance)*	**p-value**
	N=1,974	N=1,210	N=501	N=1,315	
AMI	41 (2.1%)	25 (2.1%)	12 (2.4%)	18 (1.4%)	0.37
Stroke	13 (0.7%)	12 (1.0%)	1-5	10 (0.8%)	0.78
Dialysis	39 (2.0%)	32 (2.6%)	16 (3.2%)	44 (3.3%)	0.08

Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% - 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%)

AMI: acute myocardial infarction. As per ICES policy, all cells with fewer than 5 events were presented as a range to avoid patient identification.

Table 9b: *[Crude]* Outcomes between discharge – referral date based on the level of cardiac rehab participation [High, Medium, Low and No participation]

	High - > 67%	**Mid - 33 - 67%**	**low - < 33%**	**No-CR group –** *(intake only – 0% attendance)*	**p-value**
	N=1,974	N=1,210	N=501	N=1,315	
All-cause readmission (excluding readmissions for AMI, Stroke or repeat revascularization)	123 (6.2%)	71 (5.9%)	34 (6.8%)	124 (9.4%)	0.001
AMI	8-12	9 (0.7%)	1-5	8 (0.6%)	0.39
Stroke	6 (0.3%)	1-5	1-5	1-5	0.86
PCI	6 (0.3%)	1-5	1-5	8 (0.6%)	0.12
CABG	1-5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.67

Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% - 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%)

AMI: *acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft*

As per ICES policy, all cells with fewer than 5 events were presented as a range to avoid patient identification.

Table 10: Baseline characteristics of the CR group and No-CR group (with imputations for missing variables)

Variable	Value	Yes	No	Standardized difference	p-value
		N=3,685	N=1,315		
Age	Mean ± SD	62.61 ± 9.69	64.08 ± 10.51	0.14	<.001
Sex	F	552 (15.0%)	270 (20.5%)	0.15	<.001
	M	3,133 (85.0%)	1,045 (79.5%)	0.15	
BMI	Missing	1 (0.0%)	0 (0.0%)	0.02	<.001
	<25	928 (25.2%)	353 (26.8%)	0.04	
	25-30	1,819 (49.4%)	552 (42.0%)	0.15	
	31-35	718 (19.5%)	313 (23.8%)	0.10	
	>35	219 (5.9%)	97 (7.4%)	0.06	
Income Quintile	1	594 (16.1%)	286 (21.7%)	0.14	<.001
	2	616 (16.7%)	282 (21.4%)	0.12	
	3	640 (17.4%)	242 (18.4%)	0.03	
	4	689 (18.7%)	251 (19.1%)	0.01	
	5	1,146 (31.1%)	254 (19.3%)	0.27	
Surname-based Ethnic Group	Chinese	92 (2.5%)	39 (3.0%)	0.03	0.126
	General population	3,428 (93.0%)	1,201 (91.3%)	0.06	
	South Asian	165 (4.5%)	75 (5.7%)	0.06	
Charlson Index	Mean ± SD	0.91 ± 0.74	1.02 ± 0.71	0.16	<.001
Creatinine	Missing	1 (0.0%)	0 (0.0%)	0.02	0.300
	<120	3,449 (93.6%)	1,216 (92.5%)	0.04	
	>120	235 (6.4%)	99 (7.5%)	0.05	
CCS class	Missing	1 (0.0%)	0 (0.0%)	0.02	0.074
	0	17 (0.5%)	9 (0.7%)	0.03	
	1	228 (6.2%)	82 (6.2%)	0.00	
	2	580 (15.7%)	179 (13.6%)	0.06	
	3	1,050 (28.5%)	347 (26.4%)	0.05	
	4	1,809 (49.1%)	698 (53.1%)	0.08	
LVEF grade	Missing	1 (0.0%)	0 (0.0%)	0.02	<.001
	1	1,776 (48.2%)	567 (43.1%)	0.10	
	2	1,283 (34.8%)	481 (36.6%)	0.04	
	3	547 (14.8%)	225 (17.1%)	0.06	
	4	78 (2.1%)	42 (3.2%)	0.07	
HTN		2,502 (67.9%)	986 (75.0%)	0.16	<.001
Diabetes		1,159 (31.5%)	521 (39.6%)	0.17	<.001
Hyperlipidemia		2,460 (66.8%)	882 (67.1%)	0.01	0.835

Smoking		2,136 (58.0%)	798 (60.7%)	0.06	0.086
PVD		362 (9.8%)	179 (13.6%)	0.12	<.001
COPD		192 (5.2%)	86 (6.5%)	0.06	0.071
CVD		271 (7.4%)	122 (9.3%)	0.07	0.026
Redo		96 (2.6%)	47 (3.6%)	0.06	0.070
Previous PCI		243 (6.6%)	104 (7.9%)	0.05	0.107
Previous MI		1,299 (35.3%)	534 (40.6%)	0.11	<.001
Previous MI within 30days		719 (19.5%)	225 (17.1%)	0.06	0.056
episode LOS	Median (IQR)	7.0 (6-10)	8.0 (6-12)	0.16	<.001
Number of grafts based on OHIP billing	0	90 (2.4%)	33 (2.5%)	0.00	<.001
	1	83 (2.3%)	38 (2.9%)	0.04	
	2	503 (13.6%)	216 (16.4%)	0.08	
	3	1,472 (39.9%)	551 (41.9%)	0.04	
	4	1,191 (32.3%)	391 (29.7%)	0.06	
	5	323 (8.8%)	80 (6.1%)	0.10	
	6	23 (0.6%)	6 (0.5%)	0.02	
Arterial graft	0	240 (6.5%)	106 (8.1%)	0.06	0.007
	1	2,456 (66.6%)	899 (68.4%)	0.04	
	2	796 (21.6%)	252 (19.2%)	0.06	
	3	193 (5.2%)	58 (4.4%)	0.04	
Disease location	Missing	1 (0.0%)	0 (0.0%)	0.02	0.230
Left main	1	825 (22.4%)	306 (23.3%)	0.02	
Proximal LAD + one or more Cx & RCA	2	1,926 (52.3%)	694 (52.8%)	0.01	
TVD without prox LAD	3	135 (3.7%)	60 (4.6%)	0.05	
SVD of prox LAD	4	301 (8.2%)	84 (6.4%)	0.07	
1 or 2 vessel disease or none of the above	5	497 (13.5%)	171 (13.0%)	0.01	

Legend - CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions
CCS: Canadian Cardiovascular Society Class; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; HTN: hypertension; LVEF: left ventricular ejection fraction; previous MI: previous myocardial infarction (any MI within 15 years prior to index CABG); previous MI within 30 days: indicates any myocardial infarction within 30 days prior to index coronary artery bypass graft (CABG); PCI: percutaneous coronary intervention; TVD: triple vessel disease; SVD: single vessel disease; LAD: left anterior descending artery; RCA: right coronary artery; Cx: circumflex, St. Diff: standardized difference (less than 0.1 is negligible).

Figure legends

Figure 1. Cohort creation diagram
***Legend* -** ICES number (IKN) is a unique, confidential ICES number assigned to each person for successful linkage across data sets, CABG: coronary artery bypass graft, CIHI: Canadian Institute for Health Information Discharge Abstract Database

Figure 2a. Crude Kaplan-Meier curve for 20-year freedom from MACCE for the CR vs No-CR groups.
***Legend* -** CR group – patients who were referred and attended at least one session.
No-CR group – patients who were referred but did not attend any sessions
Freedom from Major Adverse Cardiac and Cerebrovascular events (MACCE). MACCE indicates Major Adverse Cardiac and Cerebrovascular Events. MACCE is defined as a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization.
MACCE was lower in patients who attended CR compared to those who did not attend.

Figure 2b. Adjusted Kaplan-Meier curve for 20-year freedom from MACCE for the CR vs No-CR groups.
Legend - CR group – patients who were referred and attended at least one session.
No-CR group – patients who were referred but did not attend any sessions
Freedom from major adverse cardiac and cerebrovascular events (MACCE). MACCE is defined as a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization. The shaded area represents the 95% confidence interval.
MACCE was lower in patients who attended CR compared to those who did not attend.

Figure 3a. Crude Kaplan-Meier curve for 20-year freedom from all-cause mortality for the CR vs No-CR groups.
***Legend* -** CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions
Freedom from all-cause mortality.
Overall survival was higher in the CR group as compared to the No-CR group.

Figure 3b. Adjusted Kaplan-Meier curve for 20-year freedom from all-cause mortality for the CR vs No-CR groups.
***Legend* -** CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions
Freedom from all-cause mortality. The shaded area represents the 95% confidence interval.
Overall survival was higher in the CR group as compared to the No-CR group.

Figure 4a. Cumulative incidence for stroke in CR vs No-CR with death as a competing risk.
***Legend* -** CR group – patients who were referred and attended at least one session. No-CR group – patients who were referred but did not attend any sessions. The shaded area represents the 95% confidence interval.
When adjusted for Death as a competing risk, attendance of CR post isolated CABG was associated with a significant decrease in Stroke during the follow-up period.

Figure 4b. Cumulative incidence for AMI in CR vs No-CR with death as a competing risk.
Legend **-** CR group – patients who were referred and attended at least one session. No-CR group – patients who were referred but did not attend any sessions. The shaded area represents the 95% confidence interval.
When adjusted for Death as a competing risk, attendance of CR post isolated CABG was not associated with a significant decrease in AMI during the follow-up period although the adjusted hazard ratio favoured the CR group.

Figure 4c. Cumulative incidence for repeat revascularization (PCI or CABG) in CR vs No-CR with death as a competing risk.
Legend **-** CR group – patients who were referred and attended at least one session. No-CR group – patients who were referred but did not attend any sessions. The shaded area represents the 95% confidence interval.
When adjusted for Death as a competing risk, attendance of CR post isolated CABG was not associated with a significant decrease in repeat revascularization during the follow-up period although the adjusted hazard ratio favoured the CR group.

Figure 5a . Forest plot - showing stepwise comparison between levels of CR attendance, High vs Mid, Mid vs Low and Low vs No-CR for the primary outcome (MACCE).
Legend **-** MACCE indicates Major Adverse Cardiac and Cerebrovascular Events. MACCE is defined above.
(High attendance was defined as attended > 67% of CR sessions, Mid attendance 33% - 67%, Low attendance <33%, and No-attendance 0% of CR sessions).
There was a stepwise graded response, for mid-level and high-level of attendance but there was no CR effect with low attendance.

Figure 5b . Forest plot – showing stepwise comparison between levels of CR attendance, High vs Mid, Mid vs Low and Low vs No-CR for the secondary outcome (all-cause mortality).
Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance 33% - 67%, Low attendance <33%, and No-attendance 0% of CR sessions).
There was no CR effect for low-level of attendance, but a stepwise graded response for mid-level and high-level of attendance.

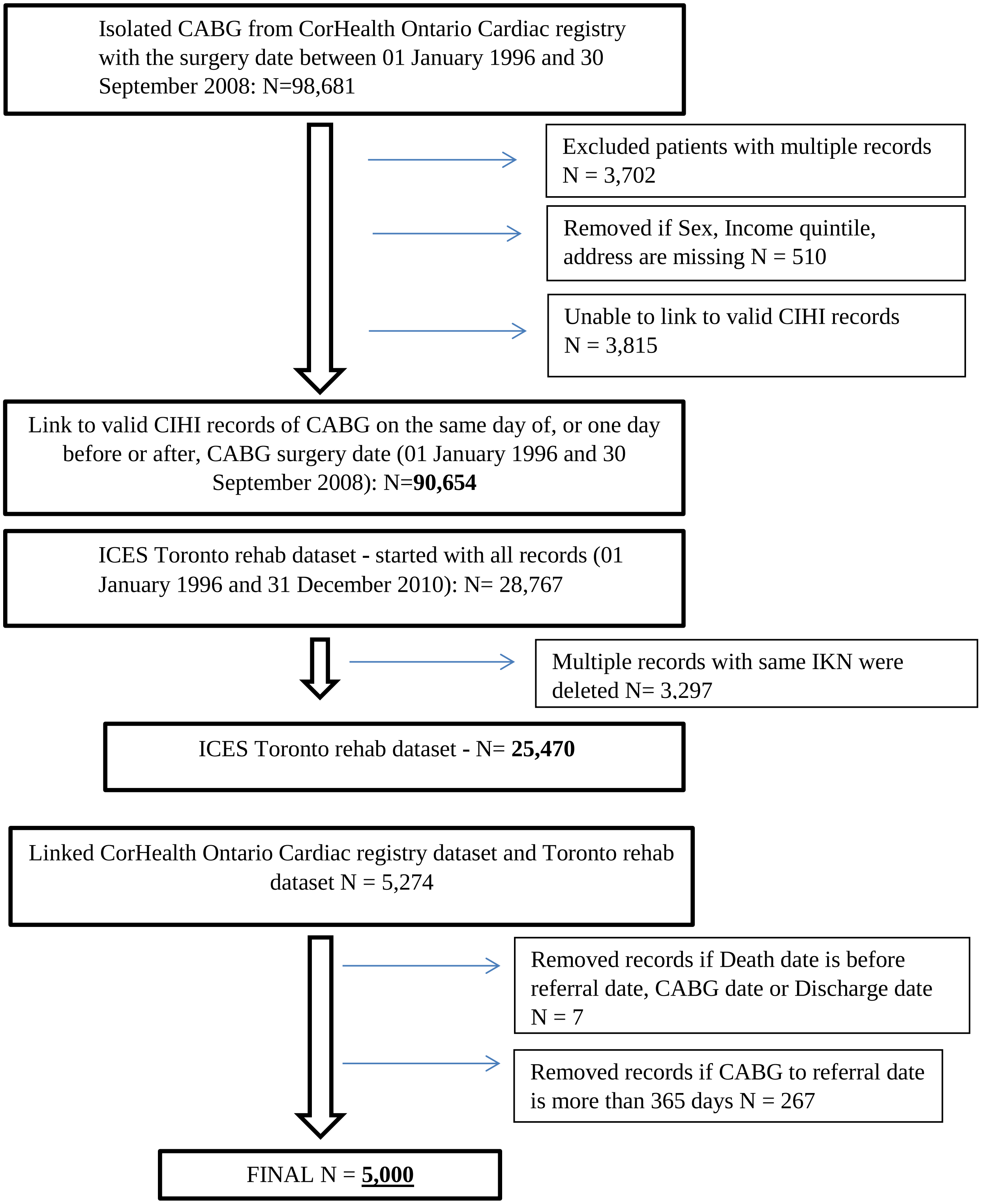
Figure 6a. Adjusted Kaplan-Meier curve for 20year freedom from MACCE for groups: High CR vs No-CR group, Mid CR vs No-CR, Low CR vs No-CR, High CR vs Low CR and Mid CR vs Low CR.
Legend **-** Freedom from major adverse cardiac and cerebrovascular events (MACCE). MACCE indicates Major Adverse Cardiac and Cerebrovascular events. MACCE is defined as a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization. Scale is adjusted to highlight Time zero= referral date up to 20 years. HR = hazard ratio (95% confidence interval (CI)). The shaded area represents the 95% confidence interval. (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% - 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%).
Patients with high level of attendance had better freedom from MACCE than non-attendees.

Figure 6b. Adjusted Kaplan-Meier curve for 20year freedom from all-cause mortality for groups: High CR vs No-CR group, Mid CR vs No-CR, Low CR vs No-CR, High CR vs Low CR and Mid CR vs Low CR.

Legend - Freedom from all-cause mortality. Scale is adjusted to highlight Time zero= referral date up to 20 years. HR = hazard ratio (95% confidence interval (CI)). The shaded area represents the 95% confidence interval. (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% - 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%).

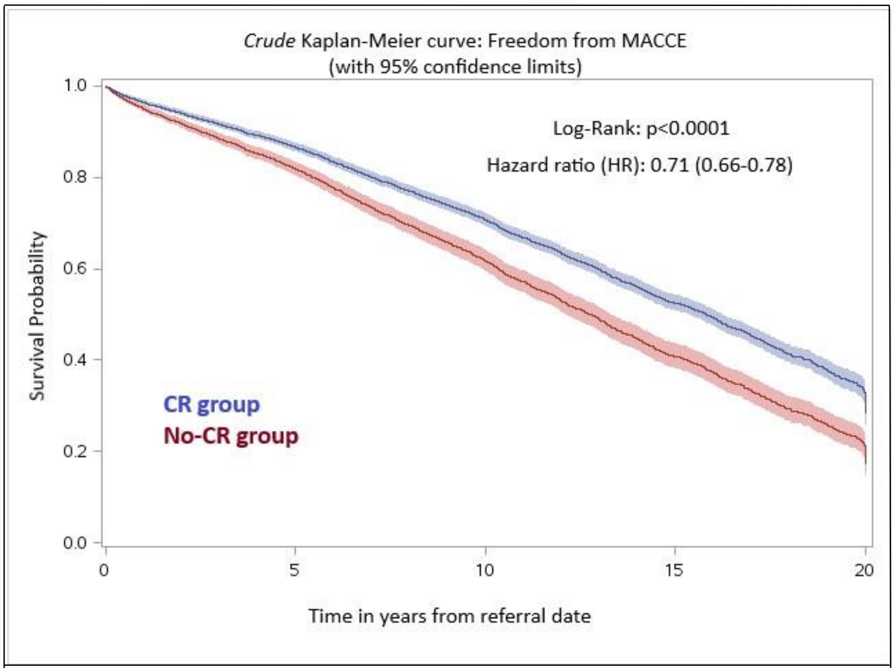
Overall survival was higher in patients with high level of attendance as compared to No-CR group.

Figure 1. Cohort creation diagram



Legend*: ICES number (IKN) is a unique, confidential ICES number assigned to each person for successful linkage across data sets, CABG: coronary artery bypass graft, CIHI: Canadian Institute for Health Information Discharge Abstract Database*

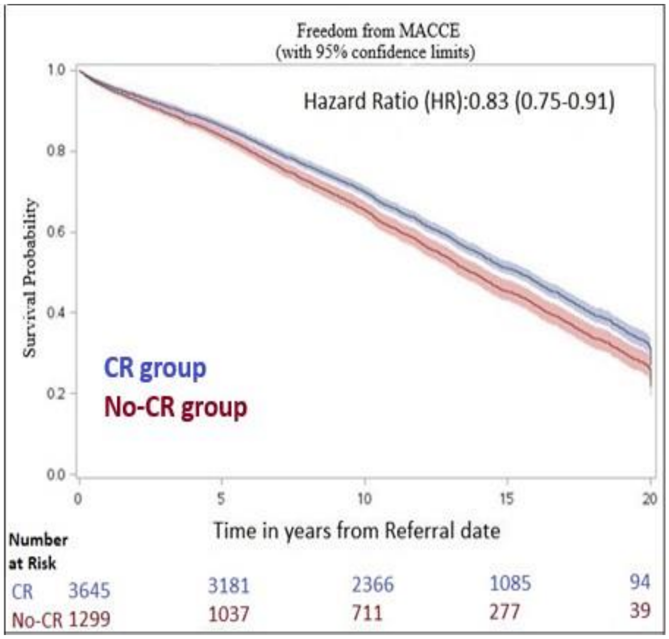
Figure 2a. Crude Kaplan-Meier curve for 20-year freedom from MACCE for the CR vs No-CR groups.



Legend - CR group – patients who were referred and attended at least one session.
No-CR group – patients who were referred but did not attend any sessions
Freedom from Major Adverse Cardiac and Cerebrovascular events (MACCE). MACCE indicates Major Adverse Cardiac and Cerebrovascular Events. MACCE is defined as a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization.

MACCE was lower in patients who attended CR compared to those who did not attend.

Figure 2b: Adjusted Kaplan-Meier curve for 20-year freedom from MACCE for the CR vs No-CR groups

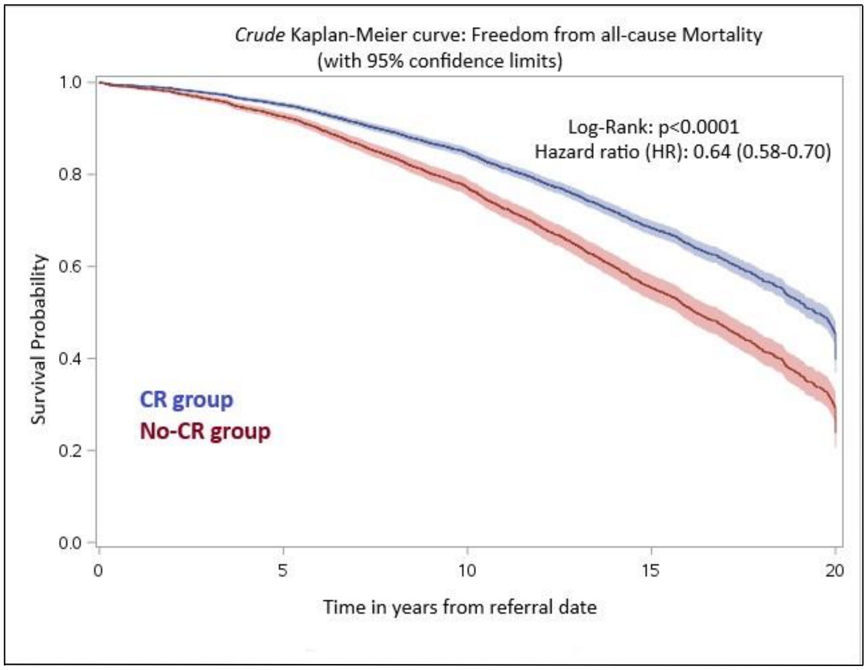


Legend: CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions

Freedom from major adverse cardiac and cerebrovascular events (MACCE). MACCE indicates Major Adverse Cardiac and Cerebrovascular Events. MACCE is defined as a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization. The shaded area represents the 95% confidence interval.

MACCE was lower in patients who attended CR compared to those who did not attend.

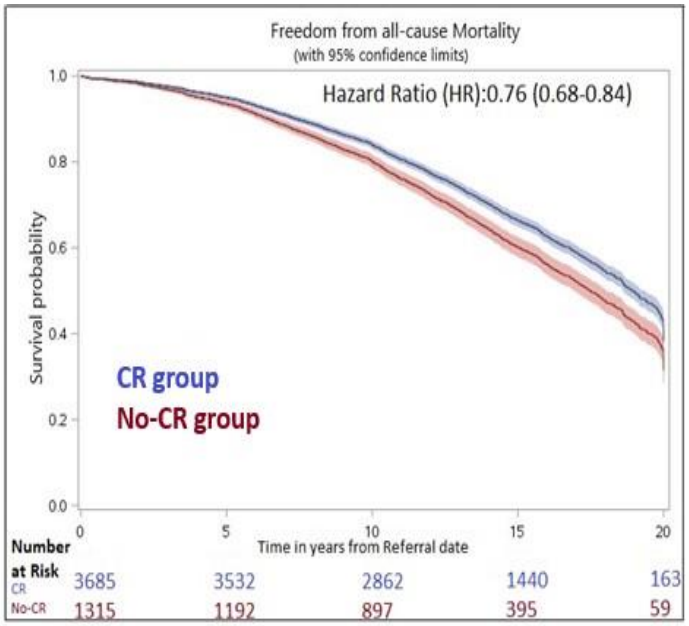
Figure 3a. Crude Kaplan-Meier curve for 20-year freedom from all-cause mortality for the CR vs No-CR groups.



Legend - CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions
Freedom from all-cause mortality.

Overall survival was higher in the CR group as compared to the No-CR group.

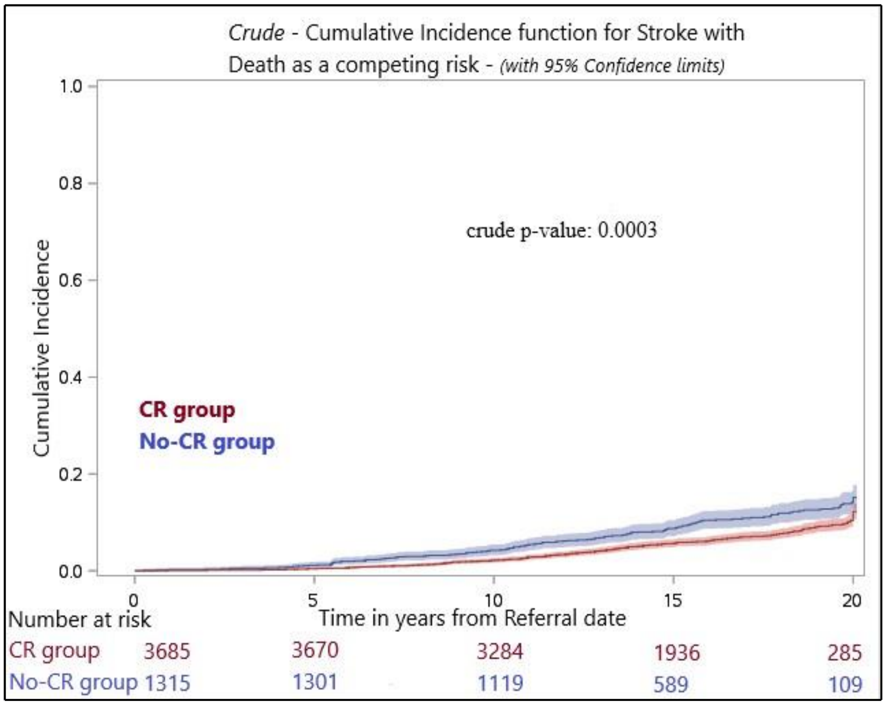
Figure 3b: Adjusted Kaplan-Meier curve for 20-year freedom from all-cause mortality for the CR vs No-CR groups



Legend*:* CR group – patients who were referred and attended at least one session
No-CR group – patients who were referred but did not attend any sessions
Freedom from all-cause mortality. The shaded area represents the 95% confidence interval.

Overall survival was higher in the CR group as compared to the No-CR group.

Figure 4a: Cumulative incidence for stroke in CR vs No-CR with death as a competing risk

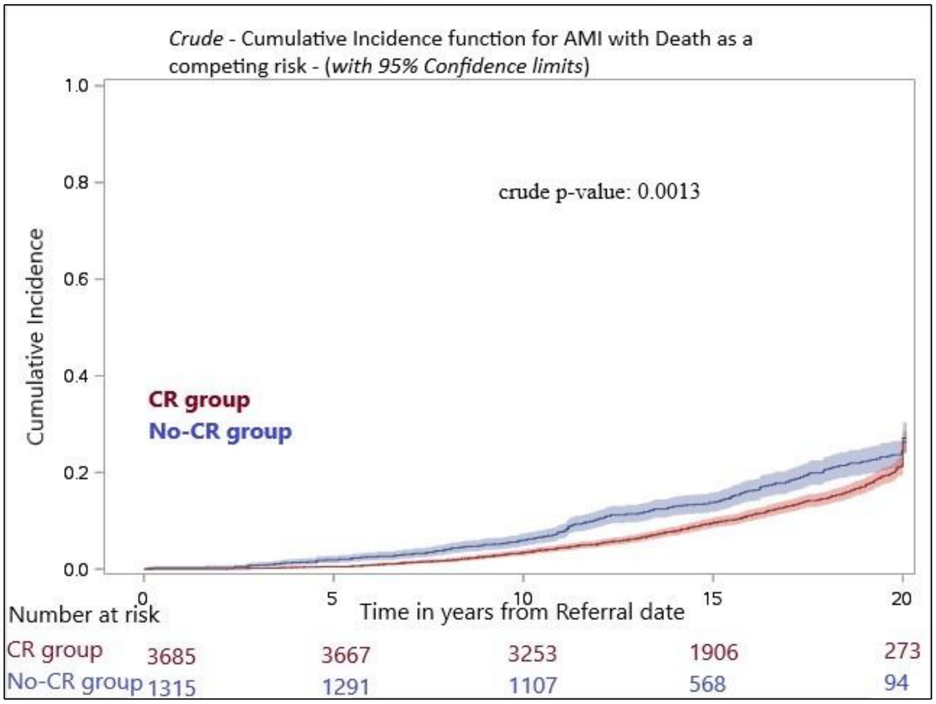


Legend - CR group and No-CR group

CR group – patients who were referred and attended at least one session. No-CR group – patients who were referred but did not attend any sessions. The shaded area represents the 95% confidence interval.

When adjusted for Death as a competing risk, attendance of CR post isolated CABG was associated with a significant decrease in Stroke during the follow-up period.

Figure 4b: Cumulative incidence for AMI in CR vs No-CR with death as a competing risk

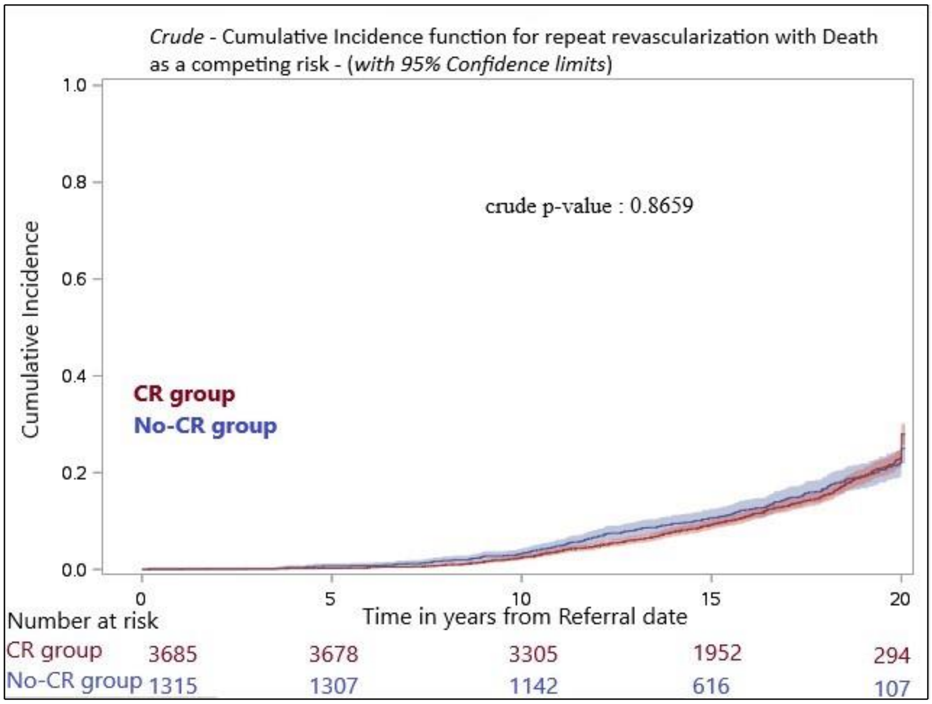


Legend - CR group and No-CR group

CR group – patients who were referred and attended at least one session. No-CR group – patients who were referred but did not attend any sessions. The shaded area represents the 95% confidence interval.

When adjusted for Death as a competing risk, attendance of CR post isolated CABG was not associated with a significant decrease in AMI during the follow-up period although the adjusted hazard ratio favoured the CR group.

Figure 4c: Cumulative incidence for repeat revascularization (PCI or CABG) in CR vs No-CR with death as a competing risk

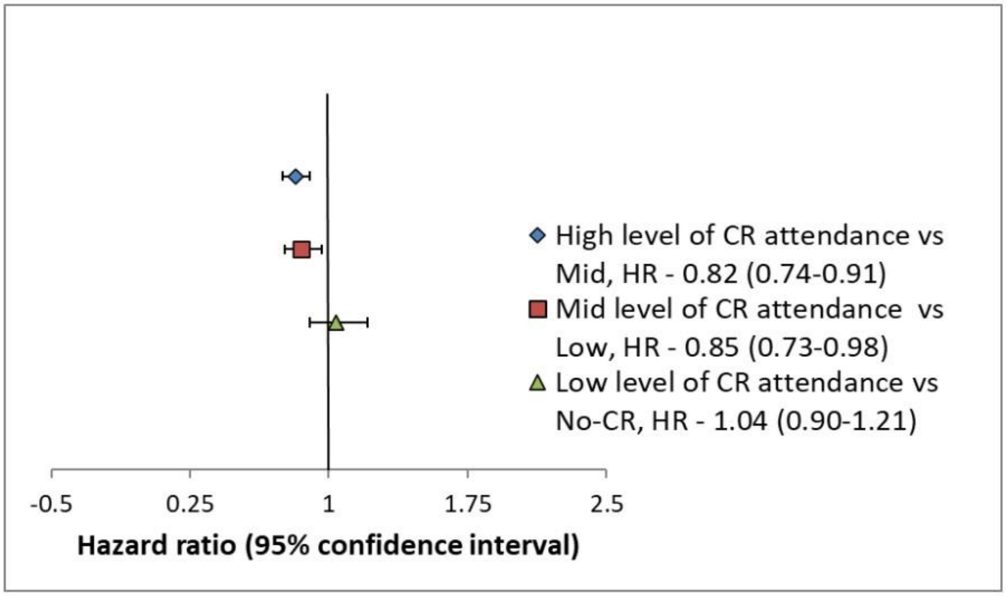


Legend - CR group and No-CR group

CR group – patients who were referred and attended at least one session. No-CR group – patients who were referred but did not attend any sessions. The shaded area represents the 95% confidence interval.

When adjusted for Death as a competing risk, attendance of CR post isolated CABG was not associated with a significant decrease in repeat revascularization during the follow-up period, although the adjusted hazard ratio favoured the CR group.

Figure 5a: Forest plot – showing stepwise comparison between levels of CR attendance, High vs Mid, Mid vs Low and Low vs No-CR for the primary outcome (MACCE)

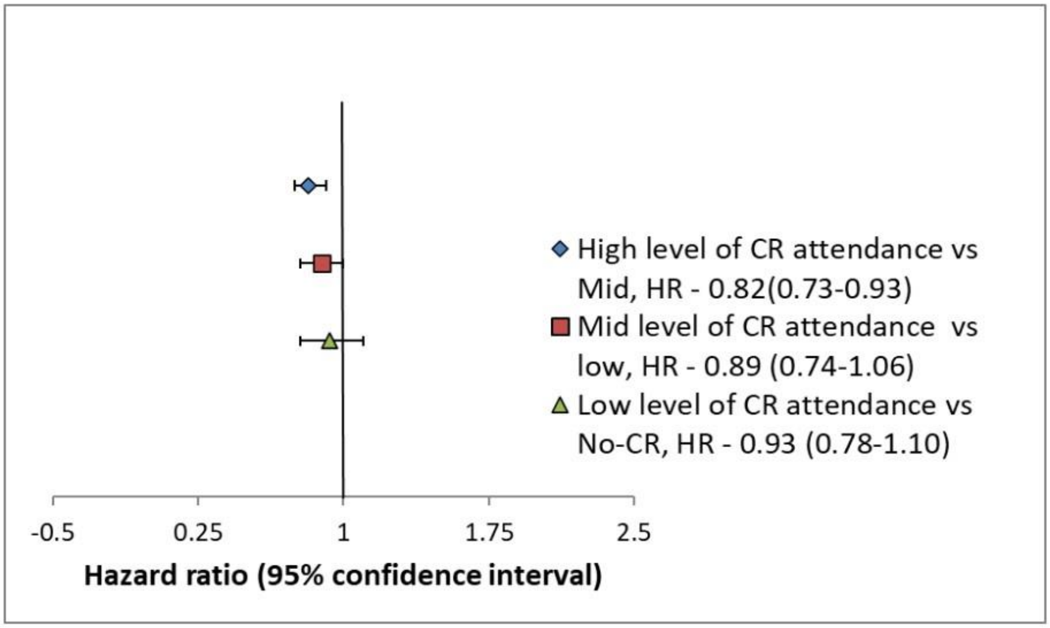


Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% **-** 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%)

MACCE indicates Major Adverse Cardiac and Cerebrovascular Events. MACCE is defined as a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization.

There was a stepwise graded response, for mid-level and high-level of attendance but there was no CR effect with low attendance.

Figure 5b: Forest plot – showing stepwise comparison between levels of CR attendance, High vs Mid, Mid vs Low and Low vs No-CR for the secondary outcome (all-cause mortality)

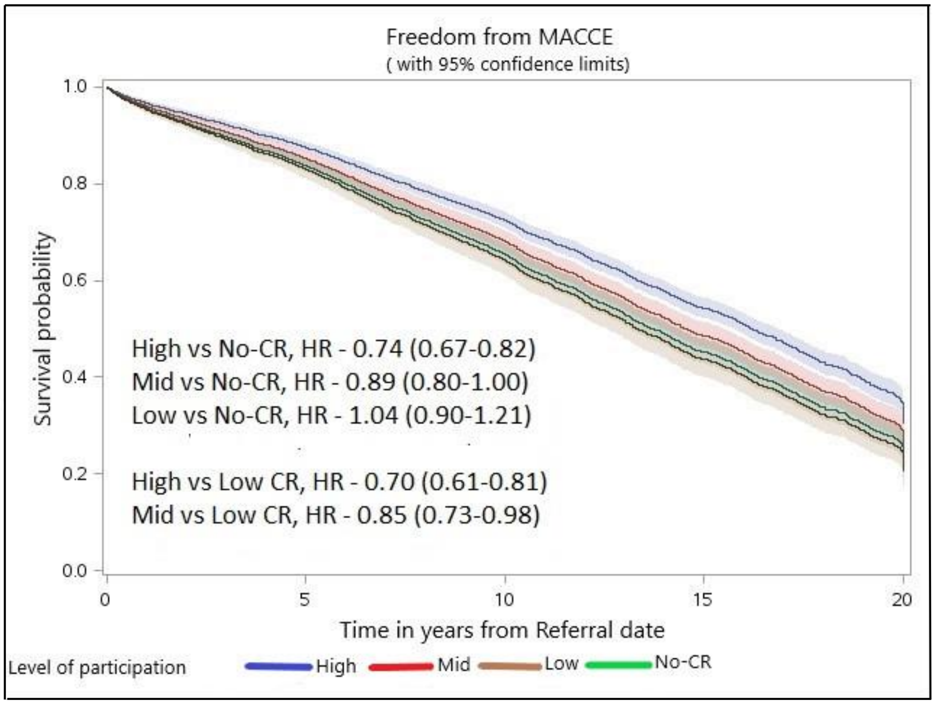


Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% - 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%)

All-cause mortality includes CV mortality and all other causes of mortality.

There was no CR effect for low-level of attendance, but a stepwise graded response for mid-level and high-level of attendance.

Figure 6a: Adjusted Kaplan-Meier curve for 20-year freedom from MACCE for groups: High CR vs No-CR group, Mid CR vs No-CR, Low CR vs No-CR, High vs Low CR and Mid vs Low CR

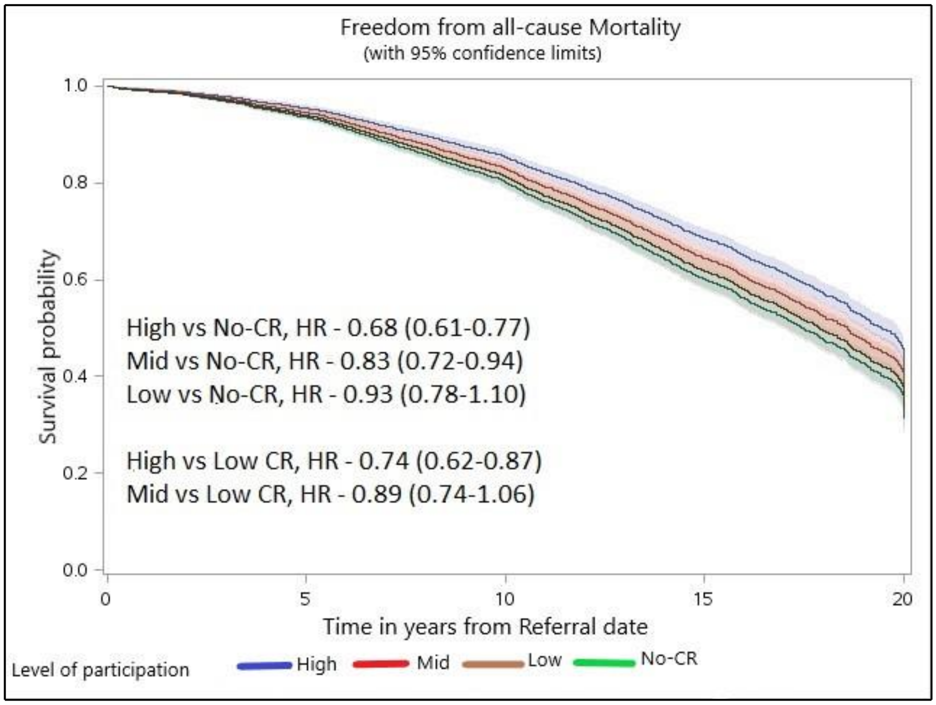


Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% - 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%)

Freedom from major adverse cardiac and cerebrovascular events (MACCE). MACCE indicates Major Adverse Cardiac and Cerebrovascular events. MACCE is defined as a composite endpoint of all-cause mortality, acute myocardial infarction (AMI), stroke or repeat revascularization. Scale is adjusted to highlight Time zero= referral date up to 20 years. HR = hazard ratio (95%CI). The shaded area represents the 95% confidence interval.

Patients with high level of attendance had better freedom from MACCE than non-attendees.

Figure 6b: Adjusted Kaplan-Meier curve for 20-year freedom from all-cause mortality for groups: High CR vs No-CR group, Mid CR vs No-CR, Low CR vs No-CR, High vs Low CR and Mid vs Low CR



Legend - (High attendance was defined as attended > 67% of CR sessions, Mid attendance attended 33% - 67% of CR sessions, Low attendance attended <33%, and No-attendance 0%)

Freedom from all-cause mortality. All-cause mortality includes CV mortality and all other causes of mortality. Scale is adjusted to highlight Time zero= referral date up to 20 years. HR = hazard ratio (95%CI). The shaded area represents the 95% confidence interval.

Overall survival was higher in patients with high level of attendance as compared to No-CR group.

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