Investigation and Management of Coronary Artery Disease Among Patients with Heart Failure in Ontario

by

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A thesis submitted in conformity with the requirements for the Degree of Doctor of Philosophy in Clinical Epidemiology and Health Care Research

Institute of Health Policy, Management, and Evaluation
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ABSTRACT

Background: The investigation and management of heart failure (HF) requires extensive use of healthcare resources in Ontario, Canada.

Methods: Four cohort studies using administrative databases were conducted to describe the epidemiology of HF; to assess the use of cardiac imaging and coronary revascularization; and to determine the significance of non-obstructive coronary artery disease on clinical outcomes.

Results: The incidence rate of HF decreased 32% from 380 new cases (95% CI, 376-384) per 100,000 individuals in 2002 to 256 (95% CI, 254-259) per 100,000 in 2016 ($P < 0.001$). The prevalence rate decreased from 2408 cases (95% CI, 2398-2417) per 100,000 in 2002 to 1979 (95% CI, 1972-1987) per 100,000 in 2016 ($P < .001$). Echocardiography was the most used cardiac imaging modality increasing from 386 tests (95% CI, 373-398) per 1000 HF patients in 2002 to 513 (95% CI, 501-526) per 1000 in 2011. After the initiation of an accreditation program in 2012, there was an immediate reduction in the use of echocardiography (-59.5 tests per 1000, P <.001). The use of percutaneous coronary intervention increased 100% from 13 procedures (95% CI, 11-15) per 1000 HF cases in 2002 to 26 procedures (95% CI, 22-30) per 1,000 in 2016. The use of surgical revascularization decreased 35% from 23 procedures (95% CI, 21-27) per 1000 HF cases in 2002 to 17 (95% CI, 14-21) per 1000 in 2016 ($P < .001$). Non-obstructive coronary artery disease was associated with an increased rate of cardiovascular death (HR 1.82; 95% CI; 1.27-2.62; p = 0.001) and death of any cause (HR 1.18; 95% CI 1.05-1.33; p = 0.005) in comparison to individuals with normal coronary arteries.

Conclusions: Over a 15-year period, the overall incidence and prevalence of HF declined significantly. Rest echocardiography remained the most used cardiac imaging modality with a marked decline in utilization after a quality improvement initiative. There was an increase in use of percutaneous coronary intervention counterbalanced by a decline in surgical revascularization. Among HF patients, the presence of non-obstructive coronary artery disease was independently associated with an increased rate of death in comparison to individuals with normal coronary arteries.

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1 CHAPTER 1: INTRODUCTION AND OBJECTIVES

1.1 Background

1.1.1 Public Health Burden of Heart Failure

Heart failure (HF) is a major public health problem responsible for significant morbidity, mortality, and health resources utilization. HF affects over 600 thousand individuals in Canada, 6.2 million in the United States, and over 28 million worldwide [1-3]. HF contributes to over 1 million hospitalizations and is the underlying cause in almost 100,000 deaths in Canada and the United States annually [2]. Consequently, HF has an enormous economic impact. In Canada, the direct annual costs associated with the management of HF has been estimated at US$ 2.8 billion dollars while in the United States the total costs were estimated at US$ 31 billion in 2012 and are projected to increase to US$ 70 billion in 2030 [4,5].

1.1.2 Evaluation of the Heart Failure Patient

HF is a progressive clinical syndrome resulting from cardiac disorders that impair the ability of the ventricles to fill with or eject blood [6]. In the setting of newly diagnosed HF, the assessment of patients with HF requires two major steps in addition to complete history, physical examination, and biomarkers testing: (i) objective assessment of left ventricular (LV) function; and (ii) investigation of the etiology of HF.

1.1.2.1 Assessment of Left Ventricular Function

Assessment of LV function by determining the ejection fraction (EF) is the cornerstone of HF diagnosis. The EF, which has been shown to be a powerful predictor of adverse cardiovascular outcomes [7], allows differentiation between HF patients with preserved EF versus reduced EF [8], and it defines the indication of pharmacological and device therapies or the need for valve replacement in patients with valvular disease [9]. Indeed, EF measurement is a class I recommendation according to guidelines and a determinant of quality of care [6,10,11]. The preferred diagnostic test for measuring LV function is a 2-dimensional transthoracic echocardiogram coupled with Doppler flow studies due to its widespread availability and safety profile [12]. However, several cardiac imaging modalities can be used such as magnetic resonance imaging, or coronary computed tomography angiography, which have been recognized as having a number of advantages over echocardiography including their increased accuracy for EF measurement, better anatomical resolution, visualization of coronary anatomy, and ability to characterize the myocardium according to perfusion, viability, fibrosis, and metabolism [13-18].

1.1.2.2 Investigation of the Etiology of Heart Failure

Evaluation of the etiology of HF is another important initial step in the investigation of patients with HF. Among the multitude of causes of HF, coronary artery disease (CAD) is identified as the underlying etiology in approximately 60% of cases [19-21]. Other causes, such as valvular disease, hypertension, diabetes mellitus, obesity, infections, inflammation, toxins, congenital heart disease, endocrine, and genetic disorders account for the other causes of the disease [22]. Identification of the specific condition leading to HF can be challenging, as overlap between multiple causes often occur in the same individual. Hence, the general approach has been to distinguish between an ischemic versus non-ischemic etiology. While a binary definition of the etiology is an oversimplification of a complex issue, the rationale for this approach is supported by observations that individuals with ischemic HF are at high risk for adverse cardiac events and death compared to those with non-ischemic causes [22-24], and secondary preventive measures and coronary revascularization in selected cases contributes to improved survival [25,26].

1.1.3 Ischemic Heart Failure

The presence of CAD may lead to the development of HF based on two main pathogenetic mechanisms: (i) loss of cardiomyocytes; and (ii) adaptation of the myocardium to ischemia leading to acontractile myocardium that is not irreversibly lost [27-31]. A plausible biological theory, that has supported clinical practice for the past decades, is that coronary revascularization could be used to salvage viable myocardium in addition to protecting ischemic myocardium. Evidence from over 100 nonrandomized studies has demonstrated that the distinction between scarred and viable myocardium with cardiac imaging could identify patients who were most likely to obtain benefits from a strategy of coronary revascularization as a complement to medical therapy [32-36].

1.1.3.1 Cardiac Imaging in Ischemic Heart Failure

Over the years, several approaches were developed to evaluate the presence of viable myocardium. Early techniques included nitrate administration, inotropic agents, provoked extrasystoles, and exercise during ventriculography to assess improvement in regional ventricular activity [37-42]. In contemporary practice, detection of myocardial viability employs techniques such as stress echocardiography, single-photon emission computed tomography, positron emission tomography, and cardiovascular magnetic resonance imaging. Each modality uses different viewpoints to assess viability including myocardial wall thickness, contractile reserve, myocyte cellular integrity, and metabolism [43]. The norm for individuals with ischemic HF is to undergo a multimodality cardiac imaging investigation to determine the extent and severity of CAD and to characterize the myocardium for a potential coronary revascularization. Recent contradictory findings from substudies of a randomized clinical trial have challenged the value of identifying myocardium at risk, either ischemic or viable, to improve clinical outcomes. This evidence has shown that presence of viable myocardium is associated with improvement in LV function, irrespective of treatment, but the presence of myocardial viability did not identify patients who have a survival benefit from revascularization with CABG surgery compared to medical therapy [44-47]. There was, however, an improvement in secondary outcomes of death or cardiovascular hospitalization for those with demonstrated ischemic LV systolic dysfunction who were amenable to surgical revascularization [25]. Given these findings, most health professionals likely employ a varied choice of information obtained from anatomical and functional testing which can only be obtained with diverse cardiac imaging techniques.

1.1.3.2 Treatment Considerations for Ischemic Heart Failure

Along the broad spectrum of severity of CAD in ischemic HF, the decision to recommend coronary revascularization was always unambiguous in patients with severe angina or left main coronary artery disease. However, many patients fell into a gray zone without clear evidence for benefit from revascularization. For those individuals, non-invasive cardiac testing has traditionally been used to assess the amount of hibernating, ischemic, and scarred myocardium and define the need for a revascularization [6,33,48]. Recently, the Surgical Treatment for Ischemic Heart Failure (STICH) trial revealed that CABG, among those individuals with ischemic HF but without severe angina and left main disease, was associated with a reduction in the hazard of death of any cause and cardiovascular death, addressing an important gap related to the management of ischemic HF [25,26]. An alternative to surgical revascularization, often considered in the population with ischemic HF, is percutaneous coronary intervention (PCI). Randomized controlled trials, such as the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, and a meta-analysis of observational studies have suggested that PCI can increase survival among patients with LV dysfunction. However, there is no definitive evidence to show the superiority of either PCI or CABG among those with ischemic HF when compared head to head [49,50].

1.2 Study Rationale

Despite the debate about the best approach related to the use of cardiac imaging and whether the parameters obtained with cardiac imaging add value to the management of HF, or if CABG should be considered the first-line therapy among individuals with ischemic HF, the patterns of clinical practice in the population with HF have not been characterized. It is also unknown whether the binary categorization of individuals with HF according to underlying disease etiology is still relevant to clinical practice. Traditionally, the distinction between ischemic and non-ischemic HF was based on the anatomic degree of luminal obstruction. Those with obstructive CAD in 2 or more epicardial coronary vessels were classified as ischemic while individuals with 1-vessel obstructive CAD or non-obstructive CAD would be defined as non-ischemic or as bystander disease [51]. However, there is increasing recognition that non-obstructive disease is part of a risk continuum of CAD and is associated with increased risk of adverse health outcomes.

Studies describing the use of cardiac imaging tests, coronary revascularization procedures, and associated costs have been limited to analyses of the last few months of life [52-57] or to periods of hospital admission [58-61], offering no information about cases that would represent the full spectrum of severity of HF, including incident cases in the outpatient setting. It also has not been ascertained if changes have occurred in the investigation of individuals with HF over time considering the development of new therapeutic agents and the publication of landmark clinical trials. Considering the escalating costs of healthcare services of patients with HF and the importance of the largest subgroup of individuals with ischemic heart disease, there is a need for population-based, real-world studies to examine the use of valuable resources for the investigation and management of HF in Ontario, Canada. Thus, we aimed to develop two research projects to gain a better understanding on the delivery of cardiovascular care to patients with HF at the provincial level and a third project to examine the prognostic significance of the anatomical burden of CAD which is an universal issue for patients with HF irrespective of jurisdiction .

1.3 Study Objectives

Project 1:

To describe the frequency of heart failure among adults and to examine changes in the natural history of the disease between 2002 and 2016 in Ontario.

Project 2:

To assess the delivery of care among patients with heart failure examining the use of different non-invasive and invasive cardiac imaging modalities and coronary revascularization procedures in Ontario.

Project 3:

To determine the importance of non-obstructive coronary artery disease on clinical outcomes in a contemporary cohort of patients with heart failure and depressed ejection fraction.

2 CHAPTER 2: EPIDEMIOLOGY OF HEART FAILURE IN ONTARIO

2.1 Introduction

Heart failure (HF) has been defined as the "cardiovascular epidemic of the 21st century" [62,63]. The term 'epidemic' was used originally to describe acute infectious diseases but the word is increasingly being utilized to label non-communicable conditions that occur with high prevalence such as diabetes, depression, obesity, and HF [64-66]. Despite the popularity of the term among health professionals, policy makers, and the news media to refer to any condition based on its significance as a public health problem, the term seems to be used often in a vague sense without scientific precision. According to the Dictionary of Epidemiology, epidemic is "the occurrence in a community or region of cases of an illness, specific health-related behavior, or other health-related events clearly in excess of normal expectancy"[67].

The number of cases of a disease such as HF represents the proportion of a population affected at a certain time (i.e., prevalence). In a steady-state, the prevalence is influenced by the rate at which new cases are being added to the population (i.e., incidence) and the average duration of the disease (i.e., survival after the diagnosis) [68]. The relationship among these three parameters can be described mathematically as:

$$P = IR * \text{average duration}$$

where P is the prevalence, IR is the incidence rate, and average duration is the average time that individuals live with the disease until death or cure. If the incidence of a disease remains constant, treatments that improve prognosis and expand the duration of the disease will increase prevalence. If the average duration remains constant, preventive measures that reduce the incidence of the disease will decrease prevalence. If the incidence and the average duration change in opposite directions with the same magnitude, then prevalence remains constant.

Examination of the existing literature about the parameters that determine the prevalence of HF reveals conflicting data. Studies have reported that the incidence of HF is increasing [69,70], decreasing [71-75], or stable over time [76,77]. Meanwhile, studies examining the average duration of disease have shown that patients with HF have experienced survival gains [69,71,78-80], but others have demonstrated no significant improvements in survival despite the therapeutic advances for the management of HF in the past decades [72,81].

Comparison between these studies is problematic given the wide range of methodologies employed including different study designs and case definitions used to identify individuals with HF varying from self-reported diagnosis of HF, criteria based on a combination of signs and symptoms, echocardiographic thresholds, to combination of medical codes using administrative databases. In addition, previous reports have used different metrics to describe the frequency of HF. Some authors have described absolute number of cases, crude rates, or standardized rates with different reference populations rendering comparison between studies almost impossible. And when reporting rates, the population at risk used as the denominator for the calculation might have included the entire population at risk or restricted to specific population groups.

Based on the limitations of the existing literature, it is unclear if Ontario is facing an epidemic of HF. To address this gap in knowledge, we designed a study to assess trends in the incidence and prevalence of HF across the whole spectrum of acute and chronic care to capture the full burden of HF among adults in the province. Delineating the respective responsibility of the incidence and prevalence is essential to understand the significance of HF at the population level and to design policies and strategies to prevent and manage this condition.

2.2 Methods

2.2.1 Data Sources

This population-based study used a repeated cross-sectional design and employed administrative health care databases from Ontario, Canada. Individuals with a diagnosis of HF were identified using the Ontario HF Cohort, a database of all HF patients, which is created from the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD), the Ontario Health Insurance Plan (OHIP), and the Registered Persons Database. The Ontario HF database defines a diagnosis of HF if a patient has either 1 documented admission with HF in any diagnostic field in the discharge abstract or 1 outpatient claim for HF followed by at least 1 additional outpatient claim within 1 year (codes used to identify HF listed on **Appendix 2.1**). Therefore, the definition relies on data sources that could identify patients with HF in the outpatient and inpatient settings. The date of hospital admission or the first outpatient visit represented the date of diagnosis, whichever occurred first. This identification method is based on a validated algorithm with 84.8% sensitivity and 97.0% specificity [82].

2.2.2 Study Cohort

Having identified all eligible patients with HF, we excluded those age < 20 or > 105 years old, non-Ontario residents, or an invalid diagnosis date. The upper age limit excluded implausible ages. We assembled two study cohorts of: (i) prevalent cases, and (ii) incident cases between April 1, 2002 to March 31, 2017. To create the prevalent cohort, we started the identification of HF claims in April 1, 1997 to ascertain those individuals who had been diagnosed with HF before 2002 and were alive during the study period. A patient was defined as prevalent HF if they were alive at the start of the fiscal year and had a prior diagnosis of HF or met criteria for the diagnosis of HF during that year until the fiscal year in which the patient moved away from the province or died. Thus, a patient could be included in multiple annual cohorts of prevalent cases. Incident cases were defined as those who met criteria for HF and did not have a prior diagnosis of HF after scanning all health records in the previous 5 years. An incident case was included only in the fiscal year that the patient received the diagnosis. Therefore, the incident cohort constituted a subgroup of the prevalent cohort. Follow-up was performed through March 31, 2018 for the incident cohort.

2.2.3 Statistical Analysis

For each fiscal year, we calculated the age- and sex-standardized incidence and prevalence of HF for the overall population aged 20 years or older. In addition, we calculated the sex-specific (i.e., female and male) and age-specific incidence and prevalence according to four age groups (i.e., 20 to < 65 years, 65 to <75 years, 75 to <85 year, and ≥ 85 years). All rates were directly standardized using the 1991 Canadian population as the reference population and presented with exact 95% confidence intervals (CI) calculated using the gamma distribution [83]. Rates were reported per 100,000 individuals. To identify significant changes over time, we fit linear regression models with fiscal year as the independent variable and the number of cases or the rate as the dependent variable. The presence of autocorrelation was examined using the Durbin-Watson test. If first-order autocorrelation was detected, the Prais-Winsten estimator was used for adjustment of the estimates. We examined survival probabilities for incident patients diagnosed in 2002, 2009, and 2016 using the Kaplan-Meier estimate [84]. A 2-sided p-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (Cary, NC).

2.3 Results

2.3.1 Study Cohorts

The cohort of prevalent cases included 882,355 unique individuals and the cohort of incident cases included 555,603 unique individuals identified among the general population over 20 years of age in Ontario between April 1, 2002 and March 31, 2017. Prevalent cases included in multiple annual cohorts had a median age of 76 years (IQR: 66, 83) and 50.1% were female. Incident cases had a median age of 76 years (IQR: 66, 84) and 49.8% were female.

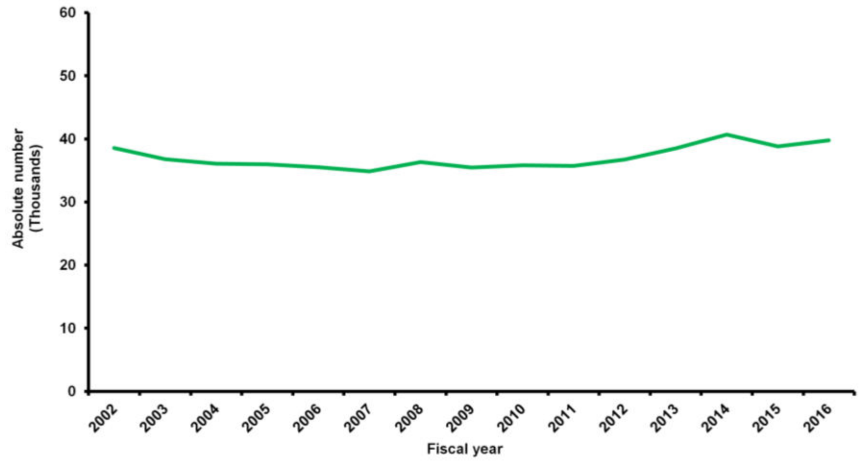
2.3.2 Incidence

2.3.2.1 Overall Population

The annual number of incident cases of HF was stable during the study period, ranging from 38,560 in 2002 to 39,754 in 2016 ($P = 0.209$). The age- and sex- standardized incidence rate decreased 32% from 380 new cases (95% CI, 376-384) per 100,000 individuals in 2002 to 256 (95% CI, 254-259) per 100,000 in 2016 ($P < 0.001$). A flattening of the decline was observed around 2012 (**Figure 2.1**).

Figure 2.1. (a) Trends in the number of new cases and (b) age- sex- adjusted incidence rate of heart failure for the overall population in Ontario, 2002-2016.

(a)



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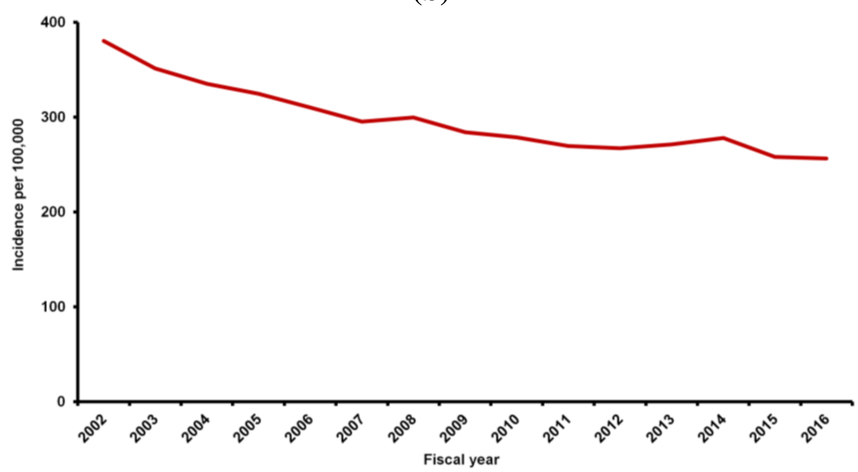
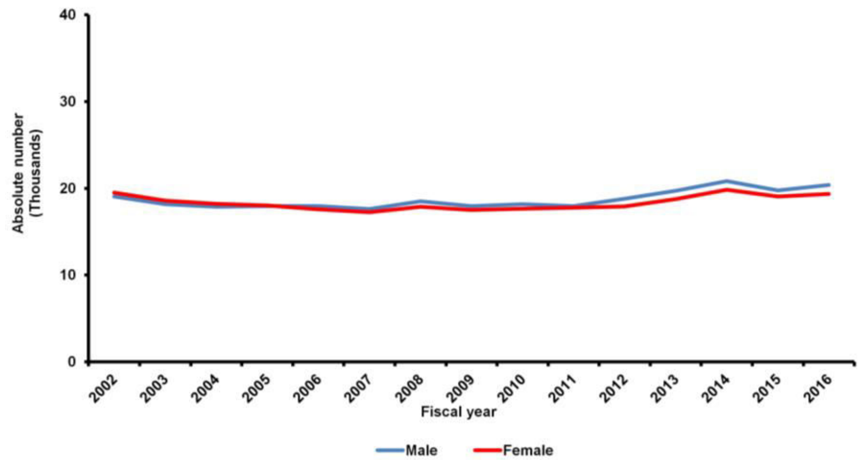


2.3.2.2 According to Sex

The annual number of incident cases of HF remained steady among women ranging from 19,500 in 2002 to 19,372 in 2016 ($P = 0.66$). Among men, a modest increase of 7% in the number of new cases of HF from 19,060 in 2002 to 20,382 in 2016 was observed ($P = 0.05$). The sex-specific incidence rate declined in both women and men. Among women, the incidence decreased 32% from 326 new cases (95% CI, 321-330) per 100,000 in 2002 to 220 (95% CI, 216-223) per 100,000 in 2016 ($P < 0.001$). Meanwhile among men, the sex-specific incidence rate declined 33% from 454 new cases (95% CI, 447-460) per 100,000 individuals in 2002 to 304 (95% CI, 299-308) per 100,000 in 2016 ($P < 0.001$) (**Figure 2.2**).

Figure 2.2. (a) Trends in the number of new cases and (b) age- sex- adjusted incidence rate of heart failure according to sex in Ontario, 2002-2016.

(a)



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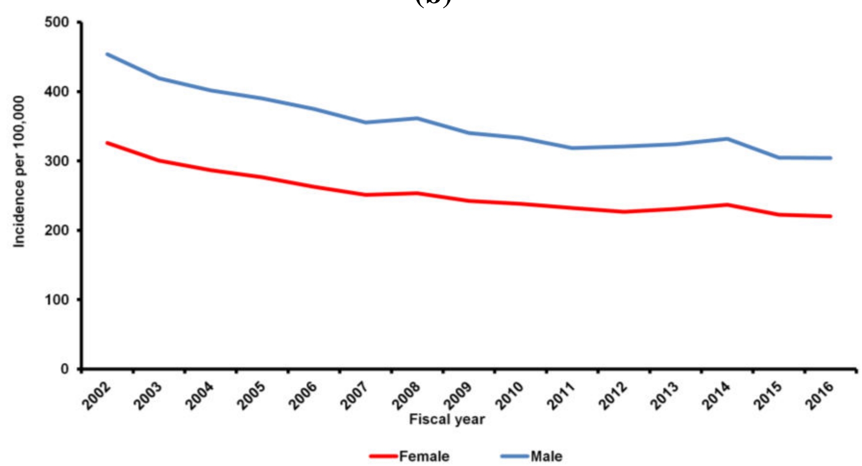
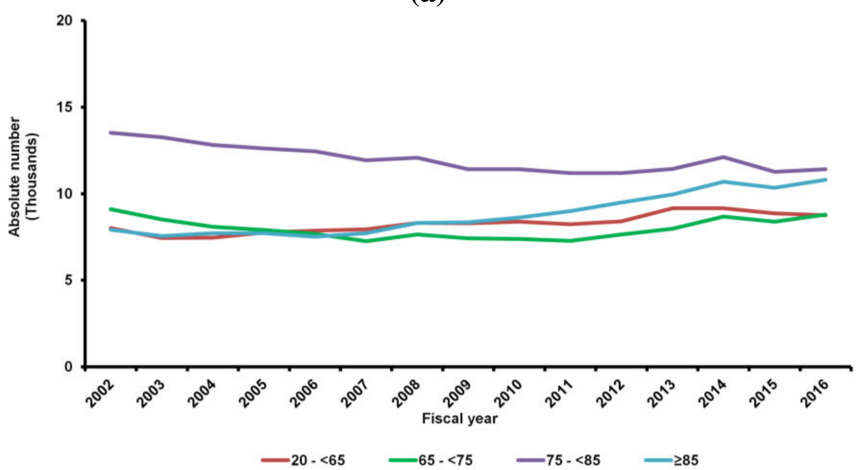


2.3.2.3 According to Age Groups

The annual number of new cases of HF increased in individuals younger than 65 years of age and in those older than 85 years of age: from 8,011 in 2002 to 8,751 in 2016 (P <.001) among the former and from 7,931 in 2002 to 10,797 in 2016 (P <.001) among the latter. The number of new cases remained steady among individuals with age between 65 and 75 years ranging from 9,100 in 2002 to 8,789 in 2016 (P = 0.85) and the number of cases decreased from 13,578 in 2002 to 11,417 in 2016 (P = 0.001) among those with age between 75 and 85 years. The age-specific incidence of HF declined in the elderly and very elderly. Among individuals age 65-75, the incidence declined 38% from 1098 new cases (95% CI, 1075-1121) per 100,000 individuals in 2002 to 686 cases (95% CI, 672-701) per 100,000 in 2016 (P <.001). Among those aged 75-85 years, the incidence decreased 36% from 2604 new cases (95% CI, 2560-2649) per 100,000 individuals in 2002 to 1661 cases (95% CI, 1630-1691) per 100,000 in 2016 (P < .001). The incidence declined 33% over time in those older than 85 years of age from 5437 new cases (95% CI, 5308-5568) per 100,000 individuals in 2002 to 3599 cases (95% CI, 3528-3670) per 100,000 in 2016 (P < .001). However, the age-specific incidence rate of HF remained stable among those younger than 65 years of age ranging between 107 new cases (95% CI, 104-109) per 100,000 individuals in 2002 and 101 cases (95% CI, 99-103) per 100,000 in 2016 (P = 0.282) (**Figure 2.3**).

Figure 2.3. (a) Trends in the number of new cases and (b) age- sex- adjusted incidence rate of heart failure according to age groups in Ontario, 2002-2016.

(a)



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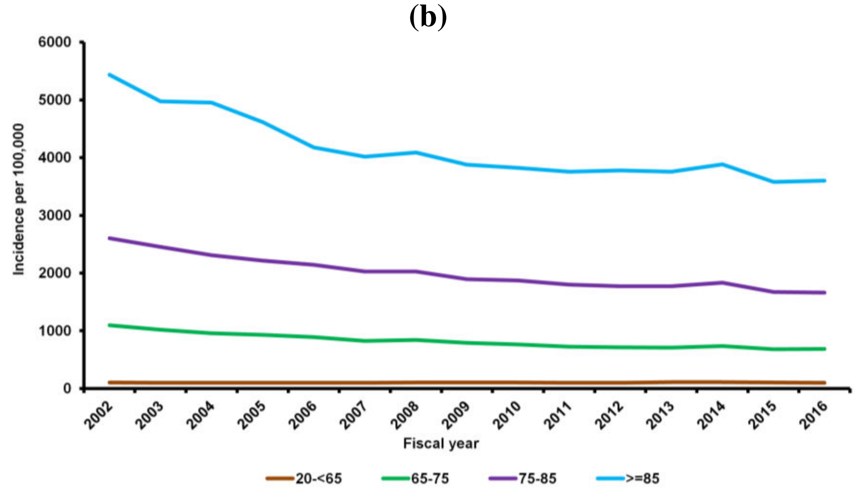


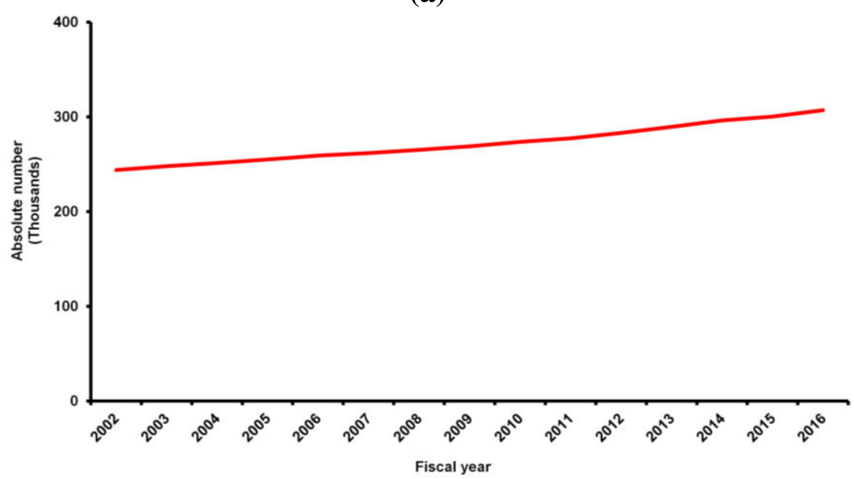
2.3.3 Prevalence

2.3.3.1 Overall Population

From 2002 to 2016, the number of prevalent cases increased by 26% from 243,882 to 307,023 ($P < .001$) while the age- and sex- standardized prevalence decreased from 2408 cases (95% CI, 2398-2417) per 100,000 individuals in 2002 to 1979 (95% CI, 1972-1987) per 100,000 in 2016 ($P < .001$) (**Figure 2.4**).

Figure 2.4. (a) Trends in the total number of cases and (b) age- sex- adjusted prevalence rate of heart failure for the overall population in Ontario, 2002-2016.

(a)



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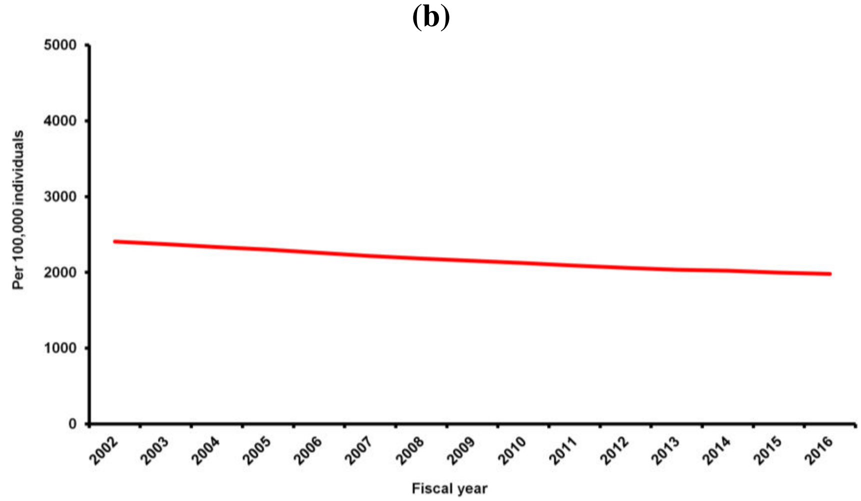
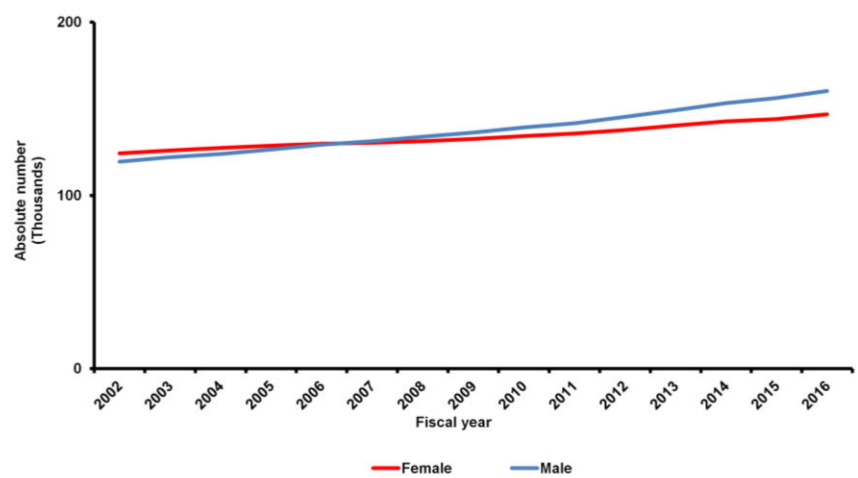


2.3.3.2 According to Sex

The total number of cases of HF increased 18% among females from 124,338 cases in 2002 to 146,749 in 2016 ($P < .001$). Among men, the total number of cases increased by 34% from 119,544 in 2002 to 160,274 in 2016 ($P < .001$). The sex-specific prevalence rate decreased 20% from 2070 cases of HF (95% CI, 2058-2082) per 100,000 individuals in 2002 to 1661 cases (95% CI, 1652-1670) per 100,000 in 2016 ($P < .001$) among women. However, among men, the sex-specific prevalence decreased 16% from 2843 cases (95% CI, 2827-2859) per 100,000 individuals in 2002 to 2395 cases (95% CI, 2383-2407) per 100,000 in 2016 ($P < .001$) (**Figure 2.5**).

Figure 2.5. (a) Trends in the total number of cases and (b) age- sex- adjusted prevalence rate of heart failure according to sex in Ontario, 2002-2016.

(a)



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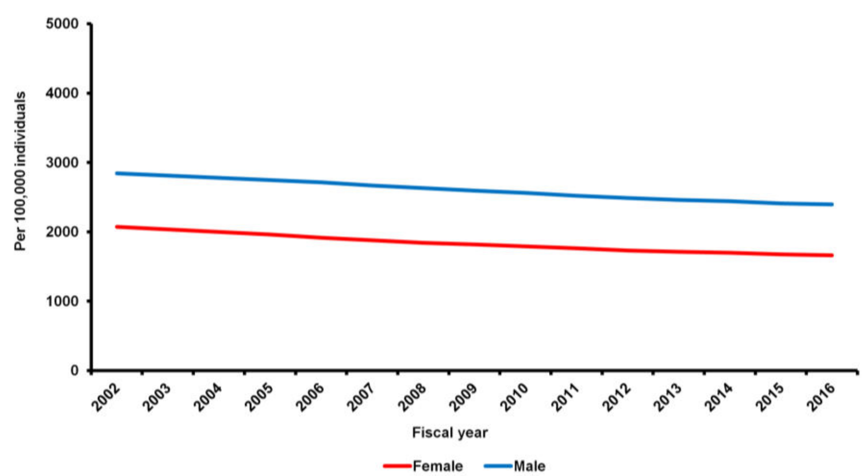
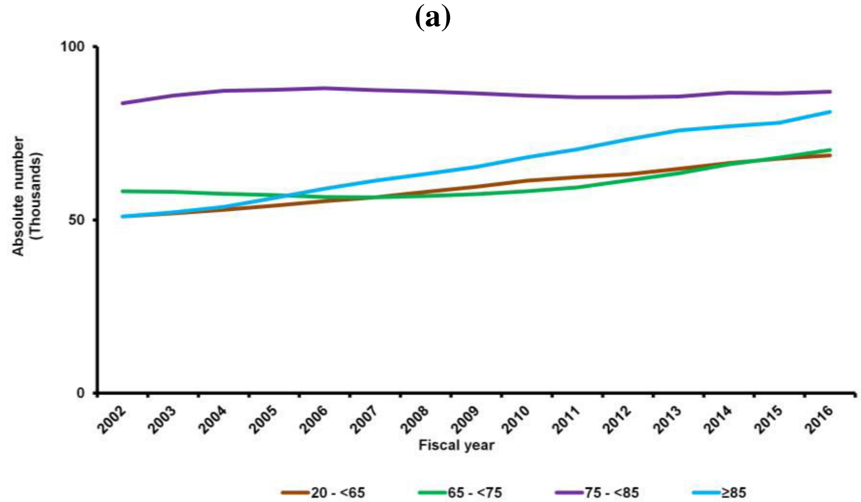


2.3.3.3 According to Age Groups

The annual number of total cases of HF increased among three of the four age groups examined. Among those younger than 65 years of age, the number of cases increased 34% from 50,976 in 2002 to 68,628 in 2016 ($P < .001$) while among individuals aged 85 years or more the total number of cases of HF increased 60% from 50,958 to 81,173 in 2016 ($P < .001$). Meanwhile, the total number of cases increased 20% from 58,291 in 2002 to 70,224 in 2016 in those with age between 65 and 75 years of age ($P = .001$) and remained stable in the group with age 75 to 85 ranging from 83,657 in 2002 to 86,998 in 2016 ($P = .39$). The age-specific prevalence of HF increased 16% among the group younger than 65 years of age from 681 cases (95% CI, 675-687) per 100,000 in 2002 to 792 (95% CI, 786-798) per 100,000 in 2016 ($P < .001$). The age-specific prevalence decreased among the other three groups examined. In those with age between 65 and 75 years, the prevalence decreased 30% from 5040 cases (95% CI, 4982-5097) per 100,000 in 2002 to 3494 (95% CI, 3453-3534) per 100,000 in 2016 ($P < .001$). In those with age from 75 to 85 years, the prevalence decreased 28% from 12,083 cases (95% CI, 11,973-12,194) per 100,000 in 2002 to 8699 cases (95% CI, 8614-8784) per 100,000 in 2016 ($P < .001$). In those older than 85 years, the prevalence decreased 38% from 19,128 cases (95% CI, 18,807-19,452) per 100,000 in 2002 to 11,854 (95% CI, 11,662-12,042) per 100,000 in 2016 ($P < .001$) (**Figure 2.6**).

Figure 2.6. (a) Trends in the total number of cases and (b) age- sex- adjusted prevalence rate of heart failure according to age groups in Ontario, 2002-2016.

(a)



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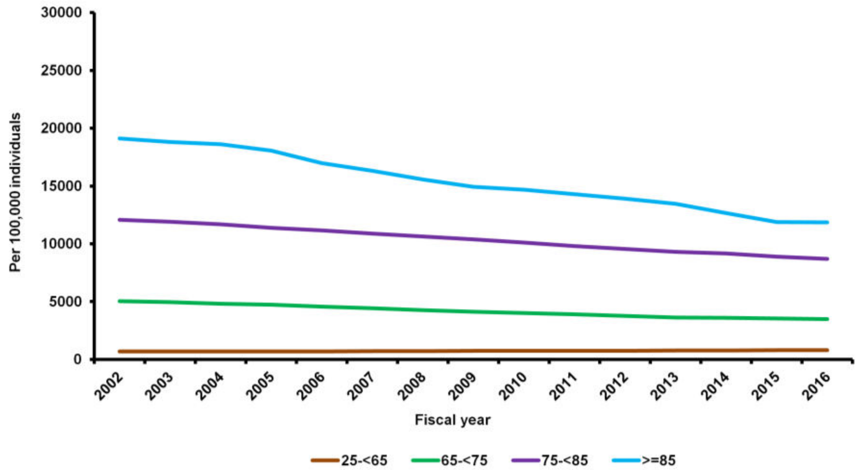
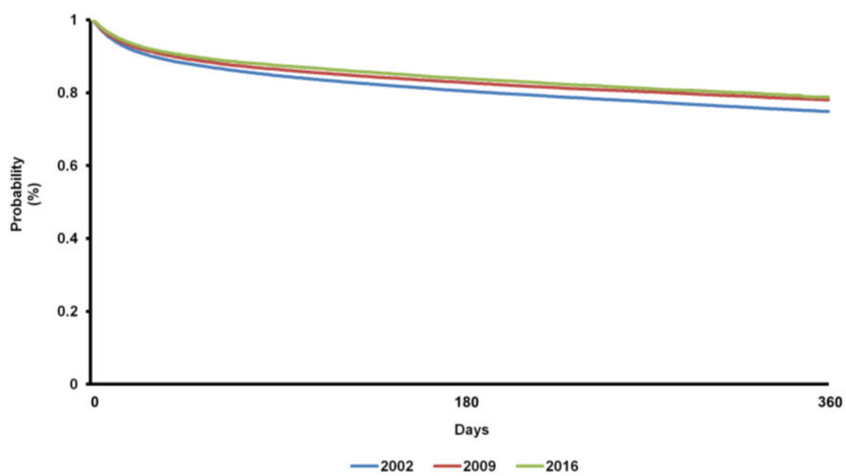


2.3.4 Survival After Diagnosis of Heart Failure

Among incident cases of HF diagnosed in 2002, the overall 30-day, 1-year, and 5-year mortality rate was 9.9%, 25.2%, and 51.3% respectively. Patients diagnosed in 2009 had a 30-day, 1-year, and 5-year mortality rate of 8.9%, 22%, and 46.2%. Meanwhile, those diagnosed in 2016 had a 30-day mortality rate of 8.2% and a 1-year mortality rate of 21.2% (**Figure 2.7**).

Figure 2.7. Survival curves for death of any cause for incident cases of heart failure diagnosed in 2002, 2009, and 2016.



2.4 Discussion

In this study of more than 800,000 individuals with HF identified using administrative databases, we reported statistically significant changes in the epidemiology of HF in Ontario over a period of 15 years. We detected that the annual number of new cases was stable with approximately 40,000 individuals receiving a diagnosis of HF every year. However, the total number of cases increased 26% during the study period with more than 300,000 individuals living with HF in 2016, in part due to better survival of those affected. When examining outcomes during follow-up, we observed a modest gain in survival. Patients diagnosed in 2002 had a 1-year mortality rate of 25% while those individuals diagnosed in 2016 had a 21% mortality rate. Analysis of adjusted rates demonstrated a decline of 32% in the incidence of HF between 2002 and 2016. Meanwhile, the prevalence rate showed a declining trend affecting approximately 2000 individuals per 100,000.

Examination of number of cases and adjusted rates according to sex and age groups revealed some intriguing trends. The number of new cases of HF increased among individuals younger than 65 years and among those older than 85 years of age. The growth in these two groups was compensated by a reduction in the number of new cases among individuals with age between 65 and 75 years. The increase in the number of prevalent cases was larger in men than in women rising by 34% in the former and 18% in the latter Since 2006, there is a predominance of cases of HF among men although women outnumber men specially among older age groups [85]. The number of prevalent cases of HF increased by 60% among individuals older than 85 years of age and 34% in the group younger than 65 years. Meanwhile, the age-specific rates indicated that the incidence declined in the elderly but remained unchanged in the group younger than 65 years of age. And the age-specific prevalence of HF increased among this age group while the prevalence declined in the other three groups.

Despite frequent references to an epidemic of HF, to answer if there is indeed an epidemic of the disease in the province, one needs to define the research question being asked, the perspective which will be used to analyze the data, and the type of metric employed to summarize the occurrence of the disease. These nuances require careful use of epidemiological terms to avoid confusion when reporting the frequency of HF in the population. Health planners and administrators will be interested in the absolute number of individuals, which is a simple count, to assess the need for services or treatment facilities and allocating resources for a population. As the number of prevalent cases is rising, it could be argued that there is an epidemic of resource utilization considering that HF is a chronic disease and patients are living longer with the disease after the diagnosis [86,87]. Health professionals on the front lines may also be interested in the number of cases. When organizing their practice, it is important to understand the caseload and the inflow of new cases. In this scenario, health professionals could make the case that their workload is increasing since individuals with HF are living longer with the disease and consequently requiring care for extended periods of time. A health professional could also build the case that the important changes detected in the profile of patients are leading to an epidemic of HF among younger adults (i.e., ≤65 years of age).

In other contexts, the number of cases alone is of little value without relating it to the size of the population. That is particularly important if policy makers and health professionals want to understand how meaningful a certain condition is for a population, to make comparisons between different regions or points in time, to estimate the risk of developing a disease over a period of time, or to elaborate or assess health promotion and disease prevention strategies. In all those scenarios, rates will be preferred over the absolute number of cases. The incidence rate will convey information about the risk of developing the disease whereas prevalence will indicate how widespread the disease is. With this perspective in mind, our data, based on an analysis of adjusted rates, represents good news for the population in Ontario. The incidence rate is declining indicating that the proportion of the population in Ontario at risk who develop HF is decreasing year after year. Furthermore, the overall prevalence rate is stable suggesting that the populational importance of HF is not increasing. However, examination of the age-specific rates demonstrated that the good news does not extend to all age groups. Among individuals younger than 65 years of age, the incidence rate did not decline, and the prevalence rate increased.

While the exact reasons for the observed trends were not explored in this study, the changes probably reflect a combination of factors. The decline in the incidence of HF has been attributed primarily to improvements in acute cardiac care and secondary prevention after an acute coronary syndrome [88]. Consistent improvements in timely therapy for the treatment of acute coronary events have been shown to decrease the severity of myocardial infarction and the risk of developing HF later in life [73,89-93]. Progress in primary prevention with better control of cardiovascular risk factors can also explain, in part, the decline in the incidence of HF. Despite the rise in obesity and diabetes, several reports have indicated better awareness, diagnosis, and control of cholesterol, blood pressure, diabetes, and smoking over time [2]. The observed increase in the number of patients with HF younger than 65 years of age might be related to the declines in mortality of infants with congenital heart disease (CHD) attributable, in part, to marked progress and advancements in guideline-directed medical therapy and surgical treatment which has allowed infants with CHD to survive to adulthood [94]. It is estimated that adults with CHD now outnumber children with CHD [95]. This shift of CHD from childhood to adulthood also increases the probability of developing HF which grows progressively with age [96].

Our study has limitations that deserve consideration. First, administrative databases do not contain clinical information such as the left ventricular ejection fraction. Therefore, it was not possible to explore changes in the epidemiology according to the type of HF (i.e., HF with reduced ejection fraction vs. preserved ejection fraction). Second, while we can speculate that the proportion of patients with HF and CHD as the underlying cause has increased and the proportion of patients with HF with coronary artery disease as the etiology decreased over time, in the absence of clinical information, we cannot determine this conclusively. Third, measuring disease frequency in populations requires standardized criteria that can be used on a large scale for ascertainment of cases of HF. While some have argued that clinical diagnostic criteria such as the Framingham or the European Society of Cardiology criteria should be used to identify patients with HF [97,98], administrative databases allow for long-term evaluation of large number of patients diagnosed with HF. Furthermore, the use of a validated algorithm with high sensitivity and specificity allowed the identification of patients with HF in the general population with reliability.

2.5 Conclusions

There have been changes in the epidemiology of HF in Ontario over the past 15 years. The existence of an epidemic of HF is supported depending on the metric examined. Although the number of new cases diagnosed annually has been stable with approximately 40,000 new cases of HF diagnosed every year, the total number of cases has increased progressively with more than 300,000 patients living with HF in the province in 2016 due to better survival after diagnosis. The analysis of adjusted rates demonstrated a major decline in the incidence of HF and a decrease in the prevalence. The subgroup of individuals with HF younger than 65 years of age seem to depart from the findings for the overall population. This age group has experienced an increase in both the number of new cases and total cases. Furthermore, the incidence rate has remained constant while the prevalence rate has increased in contrast to other age groups.

3 CHAPTER 3: TRENDS IN THE USE OF CARDIAC IMAGING AMONG PATIENTS WITH HEART FAILURE

3.1 Abstract

Importance: Cardiac imaging is a component of the provision of medical care for heart failure that has experienced a broad expansion in the past decades. However, there is a paucity of studies examining the patterns of utilization of cardiac imaging modalities in real-world clinical practice.

Objectives: To investigate temporal trends in the utilization and costs of cardiac imaging for the investigation of heart failure and to examine the association between an accreditation program and the utilization of echocardiography.

Design, Setting, and Participants: Repeated cross-sectional study based on population-based administrative databases in Ontario, Canada of individuals with heart failure identified using a validated algorithm based on hospital admissions and ambulatory physician claims between April 1, 2002, and March 31, 2017.

Main outcomes, and Measures: Age/sex-adjusted utilization rate and costs for cardiac imaging including rest and stress echocardiography, myocardial perfusion scintigraphy, invasive coronary angiography, computed tomography, magnetic resonance, and positron emission tomography.

Results: We identified 882,355 adults with prevalent heart failure (median age, 76 years; 50.1% female). There was a marked increase in the utilization rate of rest echocardiography from 386 tests (95% CI, 373-398) per 1000 heart failure patients in 2002 to 513 (95% CI, 501-526) per 1000 in 2011. Coinciding with the initiation of an accreditation program for echocardiography in 2012, there was an immediate reduction in the utilization rate (-59.5 tests per thousand, $P < .001$) which was followed by a plateau in subsequent years. At the same time, there was a reduction in the use of myocardial perfusion scintigraphy and invasive coronary angiography (10.8% and 11.2% relative decrease, respectively, from 2011 to 2016) and incorporation into practice of newer modalities after becoming publicly insured health services.

Conclusions and Relevance: Rest echocardiography remains the most used technique for imaging heart failure patients, exceeding the utilization and cost spent on other modalities. Stabilization in the utilization of traditional imaging modalities coincided temporally with the emergence of advanced techniques and province-wide quality improvement policy initiatives.

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3.2 Introduction

Heart failure (HF) is a major public health problem. In Canada, the direct annual costs associated with the management of HF has been estimated at US$2.8 billion dollars while in the United States the total costs were estimated at US$31 billion in 2012 and are projected to increase to $70 billion in 2030 [4,5]. Cardiac imaging is a growing component of the provision of medical care to individuals with HF [99]. Although an echocardiogram is still the foundational imaging technique in the investigation of HF [6], the armamentarium of diagnostic tools has expanded in recent years. Access to other cardiac imaging modalities is now considered essential because of their utility in identifying underlying aetiologies [100], risk stratification, and selection of therapies [6].

The observed expansion of services has placed greater scrutiny on cardiac imaging [101]. While there is an understanding that as individuals live longer with HF, the need for cardiac imaging increases, there have been concerns about excessive volume without justification of procedural use. In Ontario, Canada, cardiac imaging has been an area of interest for policymakers and several initiatives have been implemented in the past decade to contain the utilization of cardiac imaging. These include fee cuts, mandatory prior authorization by an expert panel, and an accreditation program for the provision of echocardiography [102].

Attesting to the importance of cardiac imaging in HF, several publications have provided advice for the use of cardiac imaging in the investigation of this condition [6,103]. However, there is a paucity of studies examining the patterns of utilization of different modalities in real-world clinical practice and whether policy reforms are achieving their goal of containing the utilization of cardiac imaging. Therefore, our primary objective was to investigate temporal trends in the utilization and costs of cardiac imaging among patients with HF in the context of a system providing universal healthcare coverage. Our secondary objectives were to examine whether an accreditation program for the provision of echocardiography was associated with temporal changes in the utilization of this modality.

3.3 Methods

3.3.1 Data Sources

This population-based study used administrative health care data from Ontario, Canada. A repeated cross-sectional design was employed and followed the STROBE reporting guidelines for cross-sectional studies [104]. All residents of Ontario qualify for health care services from a single-payer system. A unique, encoded identifier permitted linkage across administrative databases. Individuals with a diagnosis of HF were identified using the Ontario HF database, a database of all HF patients, which is created from the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD; in-hospital outcomes), the Ontario Health Insurance Plan (OHIP; physician claims), and the Registered Persons Database (demographics and vital status). The Ontario HF database defines a diagnosis of HF if a patient has either 1 documented admission with HF in any diagnostic field in the discharge abstract or 1 outpatient claim for HF followed by at least 1 additional outpatient claim within 1 year. The date of hospital admission or the first outpatient visit represented the date of diagnosis, whichever occurred first. This identification method is based on a validated algorithm with 84.8% sensitivity and 97.0% specificity [82]. 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.[105]

3.3.2 Study Cohorts

Having identified all eligible patients with HF, we excluded those age < 20 or > 105 years old, non-Ontario residents, or an invalid diagnosis date. We assembled two study cohorts of: (i) prevalent cases, and (ii) incident cases between April 1, 2002 to March 31, 2017. To create the prevalent cohort, we started the identification of HF claims in April 1, 1997 to ascertain those individuals who had been diagnosed with HF before 2002 and were alive during the study period. A patient was defined as prevalent HF if they were alive at the start of the fiscal year and had a prior diagnosis of HF or met criteria for the diagnosis of HF during that year until the fiscal year in which the patient moved away from the province or died. Thus, a patient could be included in multiple annual cohorts of prevalent cases. Incident cases were defined as those who met criteria for HF and did not have a prior diagnosis of HF after scanning all health records in the previous 5 years. An incident case was included only in the fiscal year that the patient received the diagnosis.

3.3.3 Cardiac Imaging Modalities

We examined the utilization of rest and stress echocardiography, myocardial perfusion scintigraphy (MPS), and invasive coronary angiography (ICA) which were referred to as 'traditional' modalities. Additionally, we examined the utilization of coronary computed tomography angiography (CCTA), cardiac magnetic resonance imaging (CMRI), and cardiac positron emission tomography (CPET) which were referred to as 'advanced' modalities. Recommendations for cardiac imaging tests for patients with HF according to the American Heart Association/American College of Cardiology guidelines are listed in **Appendix 3.1**. Information regarding receipt of non-invasive testing was obtained from the OHIP database, while ICA was identified using the CIHI-DAD and CIHI Same-Day Surgery database (CIHI-SDS), which have been shown to have high coding accuracy when compared to a province-wide clinical registry as the gold standard [106]. Any diagnostic service with multiple claims on the same day was counted only once to avoid duplicate claims. This procedure has been used previously when examining utilization of health resources based on administrative databases [107].

3.3.4 Codes Used to Identify Cardiac Imaging Testing

We used the codes for the professional components of claims in the OHIP database to identify cardiac imaging testing. Codes used to identify rest echocardiography, MPS, CMRI, CPET, CCTA, and stress echocardiography are listed in **Appendix 3.2**. CPET, CCTA, and stress echocardiography became publicly insured health services in Ontario starting on October 1, 2009, April 1, 2011, and September 1, 2011 respectively [108-111].

3.3.5 Costs

The analysis was conducted from the perspective of a health insurance payer. To estimate the costs associated with cardiac imaging over time, we calculated the annual costs for each modality indexing the costs to 2015 by using the fees from the OHIP reimbursement 2015 Schedule of Benefits [112]. All costs were reported in Canadian dollars [113]. To estimate the cost of each modality, we included an average total cost and we also calculated the average cost of cardiac imaging per each prevalent case of HF over time.

3.3.6 Statistical Analysis

3.3.6.1 Descriptive Analysis

A descriptive analysis was performed comparing baseline characteristics between prevalent patients in the fiscal year of 2002 and in 2016. Continuous variables were expressed as median (25^{th}, 75^{th} percentiles) and compared with the Kruskal-Wallis test. Categorical variables were expressed as the absolute number (proportion) and compared using the χ^2 statistic.

3.3.6.2 Calculation of Prevalence, Incidence, and Procedure Utilization Rate

For each fiscal year, we calculated the age- and sex-standardized prevalence and incidence of HF and the utilization rate of cardiac imaging among prevalent patients. The prevalence rate was reported as a percentage, and the incidence rate was reported per 100,000 individuals, and the utilization rate was reported per 1,000 HF patients. All rates were directly standardized using the 1991 Canadian population as the reference population and presented with exact 95% confidence intervals (CI) calculated using the gamma distribution [83]. To identify significant changes over time, we fit linear regression models with fiscal year as the independent variable and the age- and sex- adjusted rate as the dependent variable. The presence of auto-correlation was examined using the Durbin-Watson test. If first-order auto-correlation was detected, the Prais-Winsten estimator was used for adjustment. As additional analyses, we examined the utilization rate of cardiac imaging stratified according to urban or rural residence as previously described [114] and among the incident cohort.

3.3.6.3 Analysis of Effect of an Accreditation Program on Temporal Changes

To examine changes in the utilization rate before and after the initiation of an accreditation program for the provision of echocardiography, segmented linear regression was used [115]. The 2012 fiscal year was defined as the change point for this analysis.

3.3.6.4 Analysis of Time Interval between Repeated Echocardiograms

To explore if there was a decrease in the rate of receiving a repeat echocardiogram over time, the Andersen-Gill (AG) model was used in the subset of individuals who received at least one echocardiogram during the study period [116]. The AG model is a regression model for the analysis of recurrent events in which an individual can contribute to the risk set with as many echocardiograms as long as the patient is under observation [86]. Once a patient received an echocardiogram (described below as the previous echocardiogram), the new outcome was the time to next echocardiogram. Once a patient had a next echocardiogram, this became the 'previous echocardiogram'. The model was adjusted for age, sex, and year the patient received the previous echocardiogram. A hazard ratio (HR) < 1 for the variable 'year the patients received the previous echocardiogram' would mean that the rate of a repeated echocardiogram decreased with each additional year. Dependence of repeated events within the same subject was accounted for using robust standard errors [117]. Results were expressed as HR and 95% Wald confidence interval. A 2-sided p-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (Cary, NC).

3.4 Results

3.4.1 Study Cohorts

The cohort of prevalent cases included 882,355 unique individuals with a median age of 76 years (IQR: 66-83, 50.1% female) while the cohort of incident cases included 555,603 unique individuals with a median age of 76 years (IQR: 66-84, 49.8% female). The baseline characteristics of prevalent cases of patients with HF in 2002 and 2016 are presented in **Table 3.1**.

Table 3.1. Comparison of baseline characteristics between prevalent patients in the fiscal years of 2002 and 2016.

Variable	2002 (N=243,882)	2016 (N=307,023)	P-value
Age, yrs., median (25^{th}-75^{th})	76 (67-83)	76 (66-85)	<.001
Female sex, n (%)	124,624 (51.1)	146, 757 (47.8)	<.001
Rural residence, n (%)	42,680 (17.5)	40,527 (13.2)	<.001
Medical history, n (%)			
Atrial fibrillation/flutter	51,460 (21.1)	68,159 (22.2)	<.001
Cancer	20,974 (8.6)	27,325 (8.9)	<.001
Chronic kidney disease	24,632 (10.1)	62,326 (20.3)	<.001
COPD	46,338 (19.0)	44,211 (14.4)	<.001
Dementia	17,803 (7.3)	31,009 (10.1)	<.001
Depression	16,096 (6.6)	17,807 (5.8)	<.001
Diabetes	64,629 (26.5)	104,080 (33.9)	<.001
Hypertension	135,355 (55.5)	168,862 (55.0)	<.001
Liver cirrhosis	3,171 (1.3)	6,755 (2.2)	<.001
Previous AMI	37,556 (15.4)	30,702 (10.0)	<.001
Previous HF hospitalization	99,016 (40.6)	91,800 (29.9)	<.001
Peripheral vascular disease	24,632 (10.1)	14,737 (4.8)	<.001
Stroke	35,363 (14.5)	29,474 (9.6)	<.001

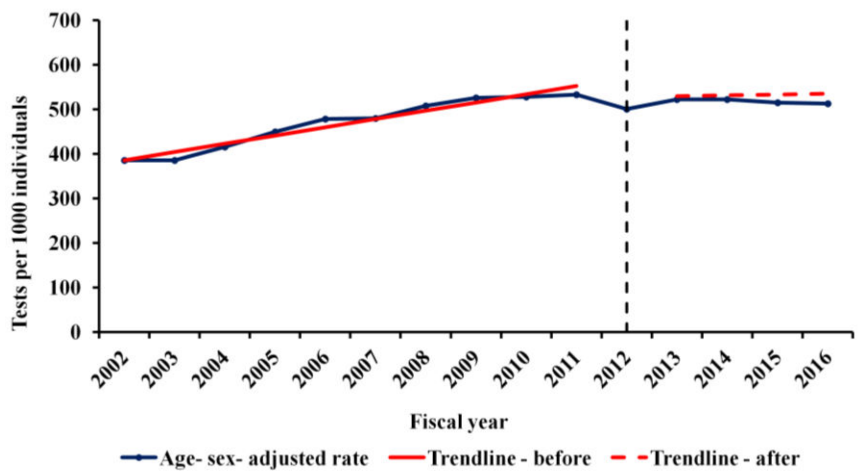
AMI: acute myocardial infarction; COPD: chronic obstructive pulmonary disease; HF: heart failure; N: number; yrs.: years of age.

3.4.2 Utilization of Cardiac Imaging

3.4.2.1 Rest Echocardiography

The absolute number of rest echocardiograms increased from 63,362 tests in 2002 to 129,009 tests in 2016. The age- and sex- standardized rate of utilization of echocardiography increased 25% from 386 tests (95% CI, 373-398) per 1000 HF patients in 2002 to 513 (95% CI, 501-526) per 1000 in 2016 (P = .001). Visual inspection of the data revealed that after reaching a peak in 2011, there was a small reduction in the utilization of echocardiography in 2012, followed by a plateau in subsequent years (**Figure 3.1**).

Figure 3.1. Temporal changes in the utilization of transthoracic echocardiography among individuals with heart failure following the publication of standards for the provision of echocardiography in Ontario.



The vertical dashed line represents the fiscal year when the document for the provision of echocardiography was published.

Segmented regression analysis revealed that the utilization of echocardiography had a significant annually increasing trend of 18.5 tests per 1000 from 2002 to 2011. The start of the accreditation program for echocardiography in 2012 was associated with a decrease of 59.5 tests per 1000 (P

<.001) immediately following the publication and an annual 16.8 tests per 1000 (*P* = .002) decline in the utilization of echocardiography compared to the level and trend before 2012, respectively (**Table 3.2**). The repeated-events Cox regression analysis revealed that there was a slight decrease in the time for a repeated echocardiogram (HR 1.033; 95% CI 1.032-1.034; P <.001) with each increase in year according to the year that the echocardiogram was received.

Table 3.2. Results for the segmented linear regression analysis examining the age- sex-standardized utilization rate of rest echocardiography before and after 2012.

Parameter	Coefficient	Standard error	t value	*P*-value
Intercept	367.5	8.6	42.78	<.001
Annual change before accreditation	18.5	1.4	13.36	<.001
Immediate change after accreditation	-59.5	13.0	-4.58	<.001
Additional annual change after accreditation	-16.8	4.2	-3.99	0.002

3.4.2.2 Stress Echocardiography

The absolute number of stress echocardiograms increased from 1,804 tests in 2011 to 5,555 tests in 2016. The age- and sex- standardized rate of utilization of stress echocardiography increased from 10 tests (95% CI, 8-11) per 1000 HF patients in 2011 to 25 (95% CI, 23-28) per 1000 in 2016 in individuals with HF (*P* = 0.03) (**Figure 3.2**). Stress echocardiograms represented less than 5% of the total number of echocardiograms performed in 2016.

3.4.2.3 Myocardial Perfusion Scintigraphy

The absolute number of MPS increased from 15,176 tests in 2002 to 27,038 tests in 2016. The age- and sex- standardized rate of utilization of MPS remained stable from 2002 to 2011, ranging from 79 tests (95% CI, 75-84) per 1000 HF individuals to 80 (95% CI, 76-84) per 1000. Starting in 2012, there was a decline in the rate of utilization of MPS decreasing to 70 tests (95% CI, 66-73) per 1000 and remaining stable thereafter (*P* = .008) (**Figure 3.2**).

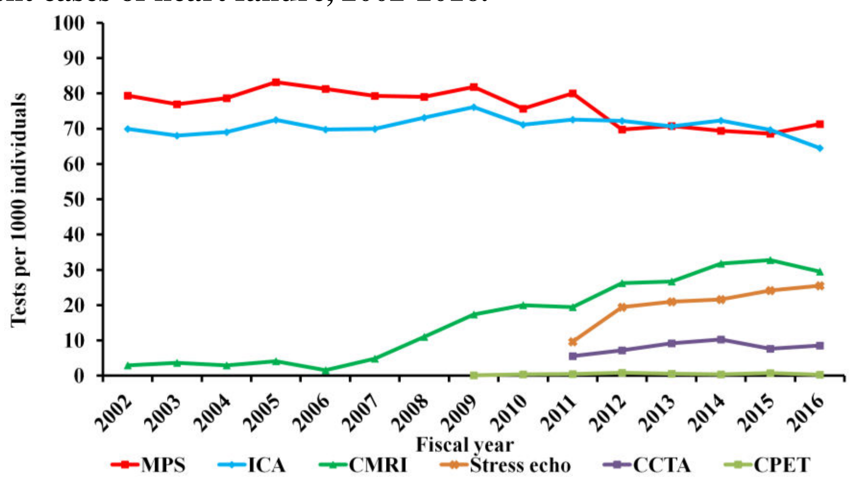
3.4.2.4 Invasive Coronary Angiography

The absolute number of ICA increased from 11,976 tests in 2002 to 20,436 tests in 2016. The age- and sex- standardized utilization rate of ICA has been stable along the observation period fluctuating around 70 tests per 1000 HF individuals but declining in the last two years of the study to 64 tests (95% CI, 61-68) per 1000 individuals ($P = 0.7$) (**Figure 3.2**).

3.4.2.5 Advanced Cardiac Imaging

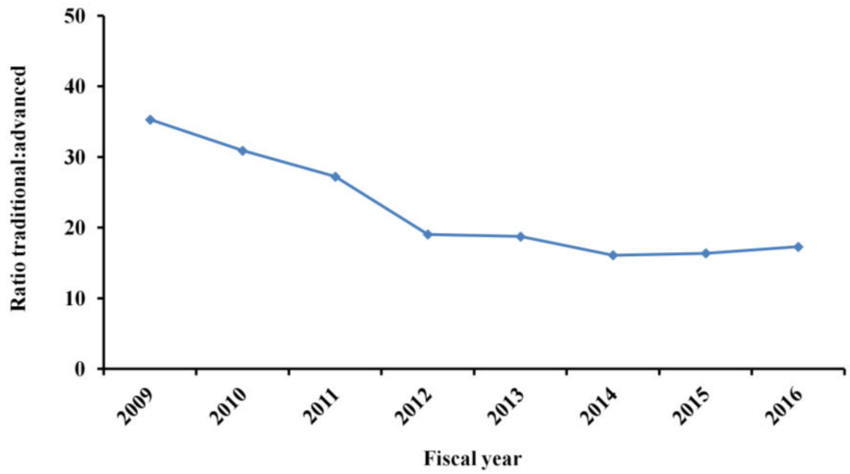
The absolute number of CCTA increased from 681 tests in 2011 to 1,760 tests in 2016. The age- and sex- standardized rate of utilization of CCTA per 1000 patients ranged from 6 (95% CI, 4-7) in 2011 to 9 (95% CI, 7-10) in 2016 ($P = 0.3$). The absolute number of CMRI increased from 93 tests in 2002 to 1,862 tests in 2016. The age- and sex- standardized rate of utilization of CMRI per 1000 patients increased from 3 tests per 1000 HF individuals (95% CI, 2-5) in 2002 to 30 per 1000 (95% CI, 26-33) in 2016 ($P < .001$). The absolute number of CPET increased from 35 tests in 2009 to 129 tests in 2016. The age- and sex- standardized rate of utilization of CPET per 1000 patients ranged from 0.1 test (95% CI, 0.08-0.2) per 1000 patients in 2009 to 0.4 (95% CI, 0.2-0.5) per 1000 in 2016 ($P = 0.4$) (**Figure 3.2**). With the availability of advanced cardiac imaging starting in 2009, there was a decline in the ratio of traditional to advanced imaging procedures over time (**Figure 3.3**).

Figure 3.2. Age- and sex- standardized utilization of other cardiac imaging modalities among prevalent cases of heart failure, 2002-2016.



CCTA: coronary computed tomography angiography; CMRI: cardiac magnetic resonance; CPET: cardiac positron emission tomography; ICA: invasive coronary angiography; MPS: myocardial perfusion scintigraphy; stress echo: stress echocardiography.

Figure 3.3. Traditional to advanced cardiac imaging modalities ratio, 2009-2016.

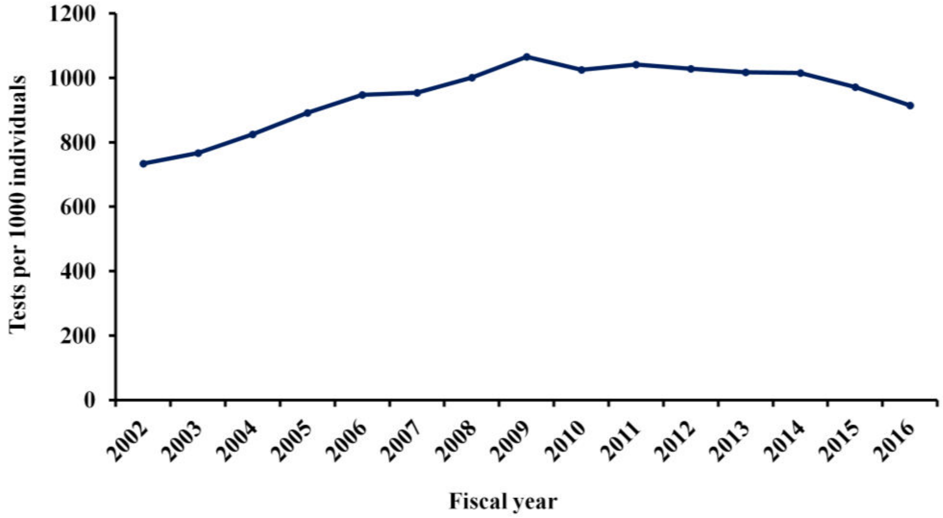


3.4.3 Utilization of Cardiac Imaging According to Rurality and Among the Incident Heart Failure Cohort

The utilization rate of cardiac imaging among incident cases of HF, especially echocardiography and ICA, was higher in the year in which patients were diagnosed with HF compared to the prevalent cohort. However, temporal trends in the incident HF cohort were similar to that observed among prevalent cases (**Figure 3.4**). When examining the utilization of cardiac imaging according to urban or rural residence, individuals with HF living in rural areas had lower utilization of rest and stress echocardiography and CMRI but other imaging tests were similar irrespective of geography, particularly in recent years of study (**Figure 3.5**).

Figure 3.4. Age- and sex- utilization of (a) rest echocardiography and (b) other cardiac imaging modalities among individuals with incident heart failure, 2002-2016.

(a)



(b)

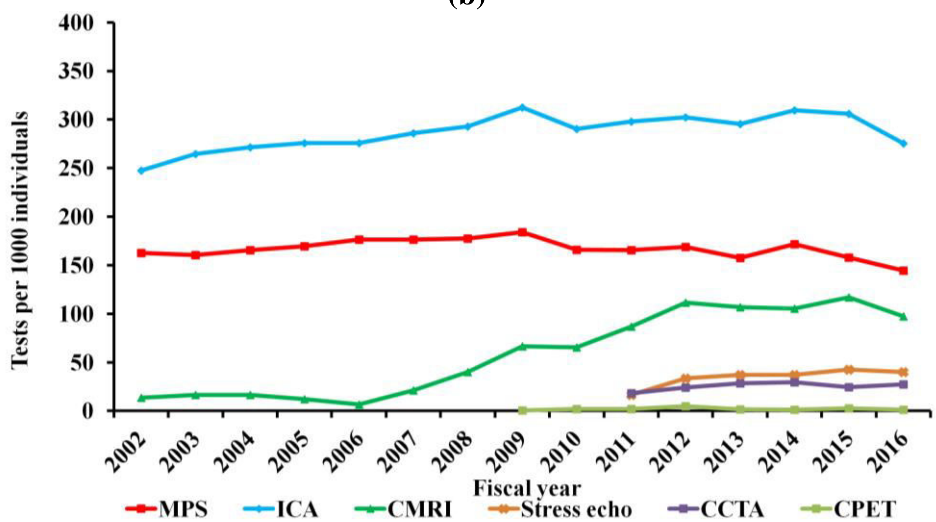
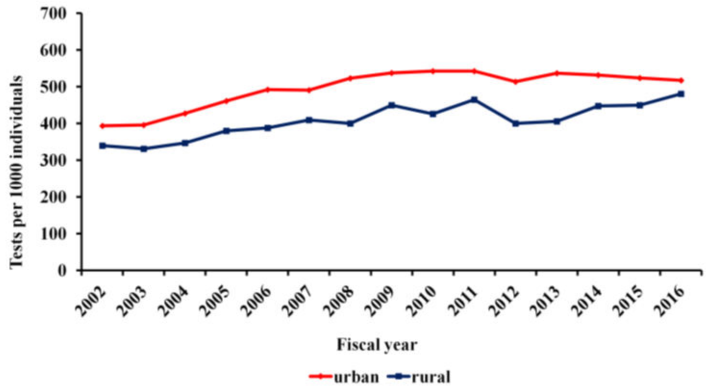
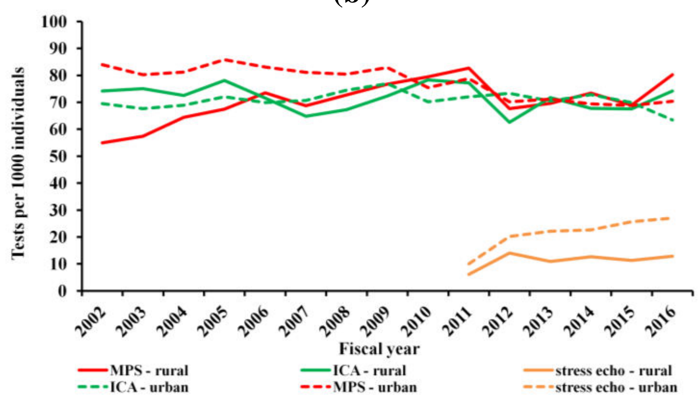


Figure 3.5. Age- and sex- utilization of (a) rest echocardiography, (b) traditional cardiac imaging modalities, and (c) advanced cardiac imaging modalities among prevalent cases of heart failure according to the place of living, 2002-2016.

(a)

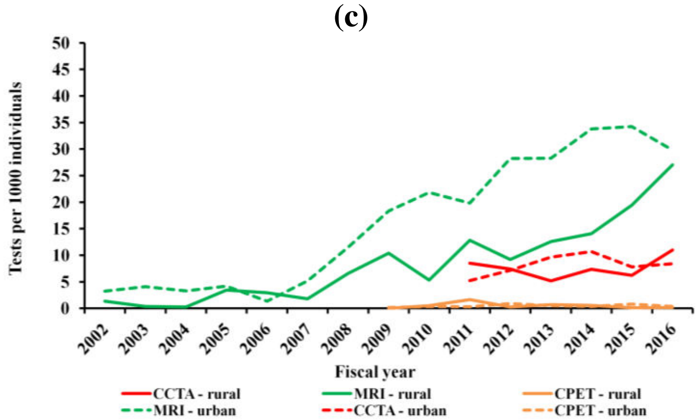


(b)



ICA: invasive coronary angiography; MPS: myocardial perfusion scintigraphy; stress echo: stress echocardiography.

(c)



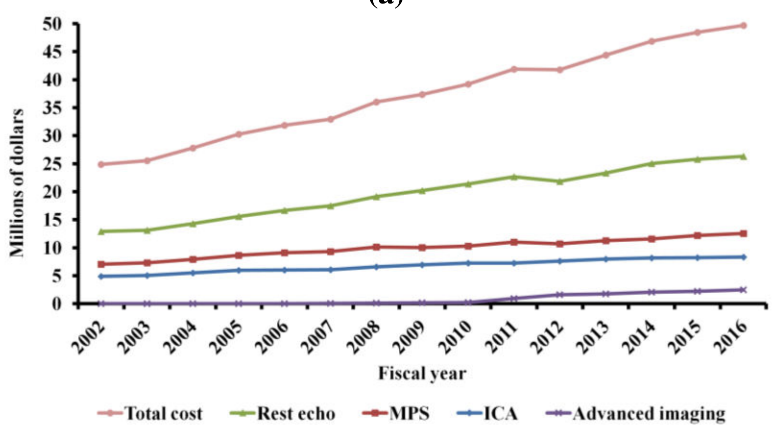
CCTA: cardiac coronary tomography angiography; CPET: cardiac positron emission tomography; MRI: magnetic resonance imaging.

3.4.4 Costs

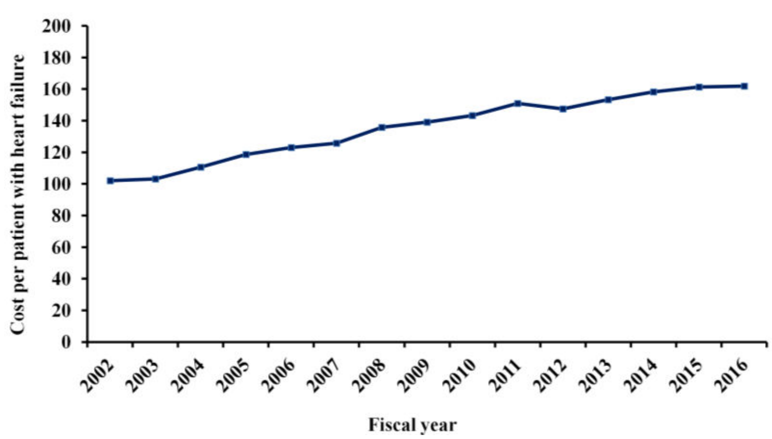
Annual expenditures for cardiac imaging in the investigation of HF increased by nearly 2-fold from CAN$ 24.8 million in 2002 to CAN$ 49.6 million in 2016. Rest echocardiography was responsible for approximately 53% of the total spent on cardiac imaging in 2016. The modalities that incurred the second and third highest costs were MPS and ICA which were responsible for 25% and 17% of all costs, respectively. Advanced modalities CCTA, CMRI, stress echocardiography, and CPET were responsible for 5% of all expenses from cardiac imaging in 2016. The average cost of cardiac imaging per patient with HF increased from CAN$102 dollars to CAN$162 in 2016. However, the average cost stabilized in the last two years of the observed time period (**Figure 3.6**).

Figure 3.6. (a) Overall costs and (b) costs per capita associated to cardiac imaging in the investigation of patients with heart failure, 2002-2016.

(a)



(b)



3.5 Discussion

This study examined the utilization of cardiac imaging among individuals with a diagnosis of HF during a 15-year period in the largest province in Canada. Our data revealed two complementary perspectives that need to be dissected in order to understand the role played by those resources in daily practice. From a clinical perspective, based on the analysis of adjusted rates, we observed that regardless of potential advantages of advanced imaging modalities, the investigation of HF is still based on a triad of traditional modalities that includes rest echocardiography, MPS, and ICA. And among those traditional modalities, rest echocardiography remains the most utilized test by far exceeding that of any other imaging technique.

Further, we observed some intriguing trends in our data: the utilization of rest echocardiography experienced a rapid growth between 2002 and 2011, which was vastly disproportional to the occurrence of HF in the population. While the incidence rate of HF has decreased significantly and the prevalence has remained relatively stable, the adjusted utilization of rest echocardiography increased by almost 40% during the same period. However, after 2011, we observed that the utilization of rest echocardiography leveled off to an approximately 0% growth while MPS experienced a decrease. Those temporal trends were virtually identical among the incident cohort. Meanwhile, while individuals with HF living in rural areas had lower rates of rest and stress echocardiography and CMRI compared to those living in urban areas, trends in other imaging modalities were similar irrespective of region residence.

Another perspective offered by our study was the healthcare system point-of-view. We observed that the number of exams and the costs for all modalities have experienced an escalation over time. Our data demonstrated that rest echocardiography was responsible for more than half of all expenditures from cardiac imaging in 2016. Meanwhile, advanced modalities were responsible for only 5% of the total costs. The high utilization of echocardiography amongst all modalities may be explained, because echocardiograms are non-invasive and there is a perception among health professionals that the price per unit is low compared to other imaging techniques [118]. Meanwhile, scanners for advanced technologies are restricted to major centers and are not available for the average patient with HF in the province [119]. Interestingly, among advanced technologies, CPET had the lowest utilization of all. CPET is distinct in comparison to other modalities since it requires mandatory prior authorization by a panel composed of radiologists and cardiologists in order to be insured under OHIP [120].

In Ontario, several initiatives that could explain the observed trends have been considered and implemented to control the utilization of cardiac imaging. For instance, the provincial government proposed a plan in 2012 to reduce the physician fee for rest echocardiography by 50% in cases of self-referral. Although this plan was never implemented, it started a discussion about appropriateness of testing [121,122]. Also, in 2012, an agency responsible for regulating cardiac care in the province, CorHealth, published standards for the provision of echocardiography establishing requirements regarding equipment, facilities, and personnel involved in echocardiographic examinations. The document also defined indications in which would be appropriate to perform the exam and set a process that echocardiography laboratories must follow to achieve the standards and get accredited [102]. A finding of our study was that this accreditation program was followed by an immediate reduction in the utilization of echocardiography and later by a stabilization in the use of this modality suggesting that the program was effective to control the use of echocardiography in the province. However, the analysis of repeated exams demonstrated that there was a decrease in the time to repeat echocardiography, but the magnitude of change was small. It is not possible to determine the impact of the accreditation program over the use of stress echocardiography since this modality only became publicly available in 2011.

The pressure to restrain unnecessary testing comes also from physicians who have promulgated appropriate use criteria (AUC) and the 'Choosing Wisely Canada' Campaign to guide and educate health professionals and patients about overuse of diagnostic imaging [103,123-126]. Besides those organized efforts, it should be noted that the stabilization and reduction in the utilization of traditional modalities coincided temporally with the start in coverage under OHIP of advanced imaging. The adoption of new technologies is another factor that could explain the observed temporal changes.

The observed trends may guide policy makers as they develop future imaging-related policies. First, CPET was the modality with the lowest utilization of all techniques. While this may be related to the few indications which are insured and the lack of province-wide capacity to perform the exam, it is also possible that it may be the consequence of the need for mandatory prior authorization. The disadvantages of this requirement are the negative effects on timeliness of diagnosis which may be harmful to patients. Second, any research that aims to examine the consequences of policies implemented to restrain the increase of a specific modality should consider the overall picture for the management of the condition under investigation. In the scenario of HF, the isolated analysis of rest echocardiography could lead to the notion that quality improvement initiatives are controlling the utilization of that modality, while in fact one cannot conclusively rule out that the observed trends may be the consequence of substituting traditional modalities for advanced techniques as suggested by the ratio of traditional to advanced modalities over time. Consequently, the net effect may not necessarily be a reduction of the number of tests and costs.

Our study should be interpreted in the context of its limitations. First, OHIP does not capture a small proportion (<5%) of outpatient physician services due to the existence of alternate payment plans. Nor does it identify some of the cardiac tests performed in inpatient settings since the costs may be absorbed by hospital global budgets and the claims not submitted to OHIP [127].Considering the systemic pressure to reduce hospitalizations and length of stay for patients admitted to hospital with HF, there is the possibility that tests which were being performed in-hospital are now being done in the outpatient setting explaining the increase in the number of tests being performed along the time. Despite the above, this study provides the best population estimates related to the utilization of cardiac imaging among HF patients in daily practice. Second, there are several potential reasons that could explain the stabilization and decline in the utilization of rest echocardiography, MPS and ICA starting in 2011. Our study did not allow us to tease out the impact of each individual initiative on the observed trends. Third, economic impact was determined by amounts billed for services provided. However, the economic impact of a technology on health care costs may be more complicated by affecting the utilization of other services either by offsetting savings or inducing costs which were not quantified. Fourth, whether the utilization rate observed for the different imaging modalities is clinically justified remains uncertain considering that administrative databases do not allow investigators to determine the reasons why tests have been ordered.

3.6 Conclusions

The investigation of HF is still based on the utilization of rest echocardiography, MPS, and ICA. Rest echocardiography remains the most used technique exceeding the utilization and total spending on any other modality, with rapid increase until 2011. After 2011, there was a decrease in the utilization of echocardiography, ICA, and MPS which coincided temporally with the emergence of advanced techniques and province-wide quality improvement initiatives to contain the use of cardiac imaging.

4 CHAPTER 4: TEMPORAL TRENDS OF CORONARY REVASCULARIZATION PRACTICE AMONG NEWLY DIAGNOSED PATIENTS WITH HEART FAILURE IN ONTARIO

4.1 Introduction

Coronary revascularization is an important consideration in the management of patients with ischemic heart failure (HF). Historically, coronary artery bypass (CABG) surgery has been the treatment of choice to improve symptoms and survival in eligible patients [128,129]. But the role of CABG was established in the 1970s and early 1980s, when surgery was virtually the only approach for the treatment of coronary artery disease (CAD). Since then, the treatment of CAD has progressed along a number of lines: percutaneous coronary intervention (PCI) has emerged as a less-invasive alternative with reduced procedural risks offering comparable outcomes to CABG [130], and effective pharmacological interventions and implanted devices have created uncertainty about the need of either CABG or PCI due to the possibility of a trivial incremental benefit when coronary revascularization is offered on top of optimal modern medical therapy [131].

Amid this uncertainty, the Surgical Treatment for Ischemic Heart Failure (STICH) study compared the long-term benefits of CABG and contemporary medical treatment in patients with ischemic HF. The first report of the trial in 2011 demonstrated no difference in the primary outcome of death from any cause between the two treatment groups [25]. Extended follow-up of the trial and a better understanding of the results, though, revealed that CABG offered an immediate mortality risk related to the procedure which was balanced by better long-term outcomes in those surviving surgery [26]. Still, this time period of 5 years between the initial communication of the results of the STICH trial and the publication of the extension of the study (STICHES) could have seen a paradigm shift in the management of ischemic HF [132,133]. The trial may have encouraged a more conservative approach with less utilization of invasive coronary angiography (ICA) and coronary revascularization similarly to what has been observed after the publication of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial among patients without HF [134,135].

As the options for the treatment of CAD and the evidence comparing alternative strategies have expanded, the standard of care for patients with ischemic HF has changed. However, up to this point, it is unknown how the utilization of ICA, CABG, and PCI in the management of HF has evolved in the past decade and whether the STICH trial was associated to any modifications in clinical practice. Therefore, our objectives were twofold: evaluate temporal trends in the invasive investigation of CAD and coronary revascularization practice in HF and to establish whether the publication of a landmark clinical trial for the management of patients with ischemic HF was associated to significant changes in coronary revascularization practice.

4.2 Methods

4.2.1 Overview

This study used a repeated cross-sectional study design to examine temporal trends in the utilization of invasive coronary angiography and coronary revascularization procedures in patients with a new diagnosis of HF.

4.2.2 Data Sources

We linked 2 administrative databases: the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) for hospital admission data and the Ontario Health Insurance Plan (OHIP) claims database for ambulatory data to identify outpatient visits with a diagnosis of HF. For CIHI-DAD, we used the diagnosis codes 428, 414.8, 422, 425, 429, 402.9 plus 428, and 404.9 plus 428 from the International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM). And the codes I50, I25.5, I40, I41, I42, I43, I11 plus I50, and I13 plus I50 for CIHI-DAD from the Tenth Revision Canadian enhanced version (ICD-10-CA). For OHIP, we used the diagnosis codes from ICD-9. We then determined patients with HF in the general population of Ontario if there was either 1 documented admission with HF at any diagnostic field in the discharge abstract or 1 outpatient claim for HF that was followed by at least 1 additional outpatient HF claim within 1 year. We based our identification method on a previously validated algorithm shown to have 84.8% sensitivity and 97.0% specificity in identifying HF in the community [82]. The date of hospital admission or the date of the first outpatient visit represented the date of diagnosis.

4.2.3 Study Cohort

Having identified all eligible patients with HF in Ontario, we created a study cohort of incident cases excluding those with age less than 20 or greater than 105 years old, patients who were not residents of Ontario, those found to have a diagnosis date after a documented date of death, those who lost OHIP eligibility, and those with a recent acute myocardial infarction (AMI). The time period studied included the fiscal years of 2002 to 2016. We used a 5-year washout period without a prior diagnosis of HF to allow the inclusion of new cases of HF. An incident case was included in the fiscal year that the patient was diagnosed. We decided to examine incident HF based on the assumption that an analysis of new cases would better reflect the current thinking about the need of invasive investigation of CAD and utilization of coronary revascularization at each year of the study period. We excluded patients with a recent AMI to eliminate patients with an acute coronary syndrome complicated by HF. While the need for ICA and a potential coronary revascularization procedure have clear indications among patients with an acute coronary syndrome, those indications are debatable for patients with chronic HF and underlying CAD [136].

4.2.4 Procedures

We examined the utilization of ICA, PCI, and isolated CABG. ICA was identified using Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) codes 489.2 to 489.8, 499.6 and 499.7 and Canadian Classification of Health Interventions (CCI) code 3.IP.10. PCI was identified using CCP codes 480.2, 480.3, and 480.9, and CCI code 1.IJ.50. CABG was identified using CCP codes 481.0 to 481.9 and CCI code 1.IJ.76. Repair of the mitral valve was identified using CCP code 471.2 and CCI code 1.HU.80 while replacement was identified using CCP codes 472.2 and 472.3 and CCI code 1.HU.90. CABG combined with valvular surgery was defined when codes for CABG and mitral surgical procedures were identified during the same hospitalization event even if not coded exactly on the same date. Isolated CABG was defined as a surgical revascularization procedure performed without mitral valvular surgery. CIHI-DAD, which was used to identify invasive cardiac services, has been shown to have high coding accuracy to identify those procedures when compared to a province-wide clinical registry as the gold standard [137].

4.2.5 Statistical Analysis

4.2.5.1 Calculation of Procedure Utilization

We calculated the utilization rate of ICA and coronary revascularization procedures which was reported per 1000 HF patients. All rates were directly standardized using the 1991 Canadian population as the reference population and presented with exact 95% confidence intervals (CI) calculated using the gamma distribution [83]. Procedures were identified within a time frame of 6 months before and after the date of diagnosis to include procedures which were performed for the initial management of the disease and might have predated when the actual diagnosis of HF was received. As additional analysis, we calculated the age- sex standardized utilization of any coronary revascularization procedure (i.e., PCI or isolated CABG) and the ratio of PCI to isolated CABG calculated as the ratio of their respective annual age- and sex- standardized utilization rates.

4.2.5.2 Analysis of Temporal Changes

To identify statistically significant changes over time, we fit linear regression models to the data with fiscal year as the independent variable and the age- sex- adjusted incidence as the dependent variables. The presence of autocorrelation was examined using the Durbin-Watson test. If first-order autocorrelation was detected, the Prais-Winsten estimator was used for adjustment. To examine temporal trends in the utilization of ICA, PCI, and CABG before and after the publication of the STICH trial, we used segmented linear regression. The first quarter of 2011, which corresponds to publication of the coronary revascularization hypothesis [25], was defined as the change point for the data. We also examined temporal trends using the publication of the COURAGE trial, in the first quarter of 2007, as a change point. We assumed that practitioners could have generalized the results of this trial for the population with HF although the results only apply to individuals with normal ventricular function. A 2-sided p-value <0.05 was considered statistically significant. Analyses were performed using SAS 9.4 (Cary, NC).

4.3 Results

4.3.1 Utilization of Invasive Coronary Angiography

Between 2002 and 2016, more than 90,000 ICA were performed among patients with a new diagnosis of HF. The number of cardiac catheterizations increased from 4114 tests in 2002 to 7272 in 2016 ($P < .001$). Visual inspection of the annual age- and sex-standardized utilization rate of ICA demonstrated an increase from 201 procedures (95% CI, 185-219) per 1,000 HF patients in 2002 to a peak of 275 procedures (95% CI, 257-294) per 1000 in 2009. After 2009, the adjusted utilization of ICA decreased to 252 tests (95% CI, 235-269) per 1000 remaining stable until the end of the study period (**Figure 4.1**). Segmented regression analysis of quarterly adjusted utilization rate of ICA revealed that there was no immediate change in the use of ICA after the publication of the COURAGE and STICH trials (coefficient 4.8, standard error (SE) 12.4, P-value 0.7 and coefficient -3.3, SE 11.6, P-value 0.7 respectively), nor additional quarterly changes in the utilization of ICA compared to the previous level and trend (coefficient -0.5, SE 1.2, *P*-value 0.6 and coefficient -2.2, SE 1.1, P-value 0.06 respectively) (**Figure 4.2 and Table 4.1**).

Figure 4.1. Annual age- and sex- standardized utilization of invasive coronary angiography among incident cases of heart failure, 2002-2016.

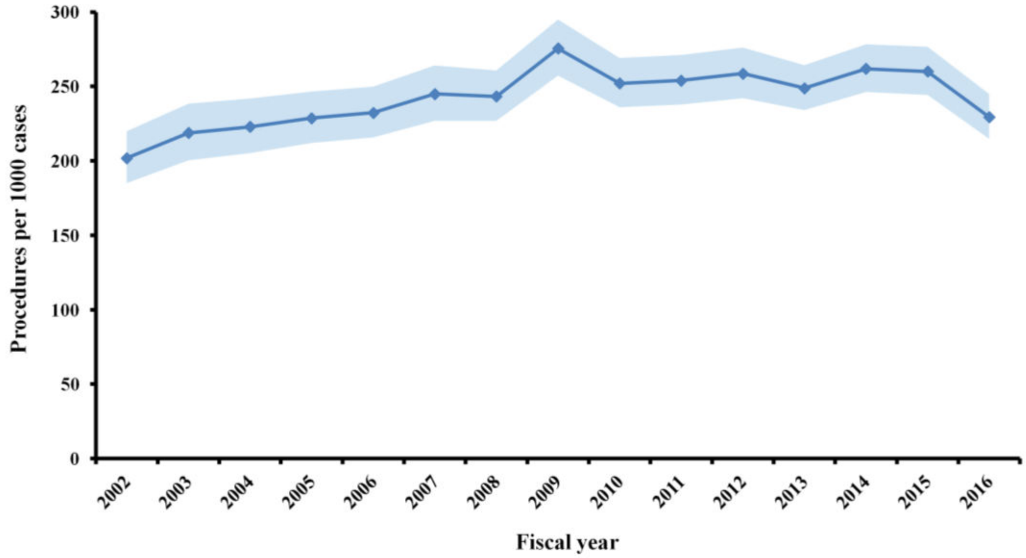
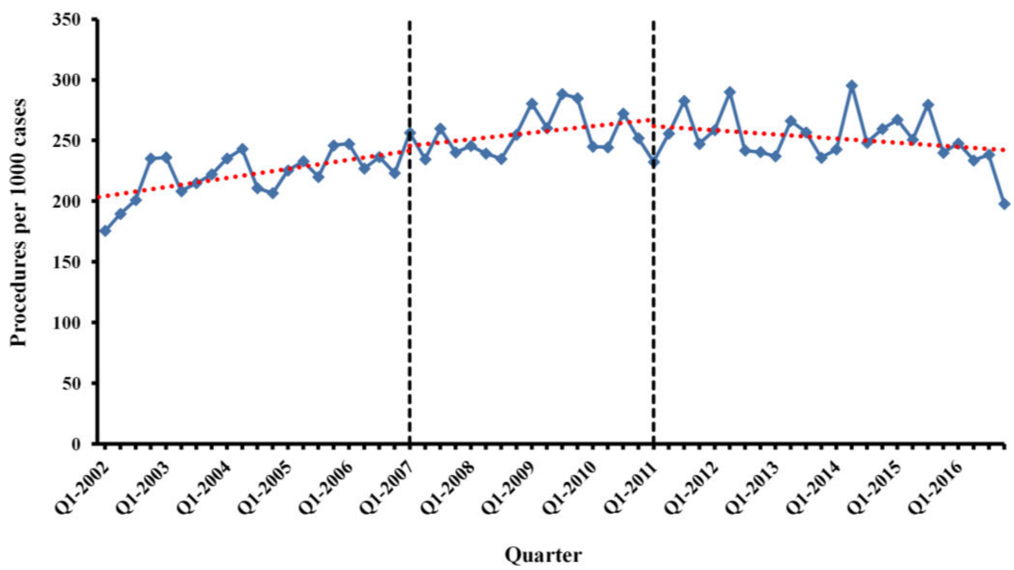


Figure 4.2. Trends in the quarterly utilization of invasive coronary angiography following the publication of the COURAGE and STICH trials.



The COURAGE trial was published in the first quarter of 2007 and the STICH trial in the first quarter of 2011.

Table 4.1. Trends in the quarterly utilization rate of invasive coronary angiography following the publication of the COURAGE and STICH trials.

Parameter	Coefficient	Standard error	t value	*P*-value
Intercept	202.3	8.5	23.8	<.001
Quarterly change before COURAGE or STICH	1.9	0.7	2.6	0.01
Publication of COURAGE trial				
Immediate change after COURAGE	4.8	12.4	0.38	0.7
Additional quarterly change after COURAGE	-0.5	1.2	-0.43	0.6
Publication of STICH trial				
Immediate change after STICH	-3.3	11.6	-0.29	0.7
Additional quarterly change after STICH	-2.2	1.1	-1.96	0.06

4.3.2 Utilization of Percutaneous Coronary Intervention

During the study period, approximately 15,600 PCI were performed among patients with a new diagnosis of HF. The absolute number of PCI increased from 554 interventions in 2002 to 1,283 in 2016 ($P < .001$). The age- sex- standardized rate of PCI increased 100% during the study period with a progressive rise from 13 procedures (95% CI, 11-15) per 1000 new HF cases in 2002 to 33 procedures (95% CI, 29-36) per 1,000 in 2014 ($P < .001$) followed by a decline to 26 procedures (22-30) per 1,000 in 2015 and 2016 (**Figure 4.3**). When examining the utilization of PCI as a quarterly rate, no significant immediate or additional quarterly changes were observed in the utilization of PCI following the publication of the COURAGE and STICH trials according to the segmented regression analysis (**Figure 4.4 and Table 4.2**).

Figure 4.3. Annual age- and sex- standardized utilization of percutaneous coronary intervention among incident cases of heart failure, 2002-2016.

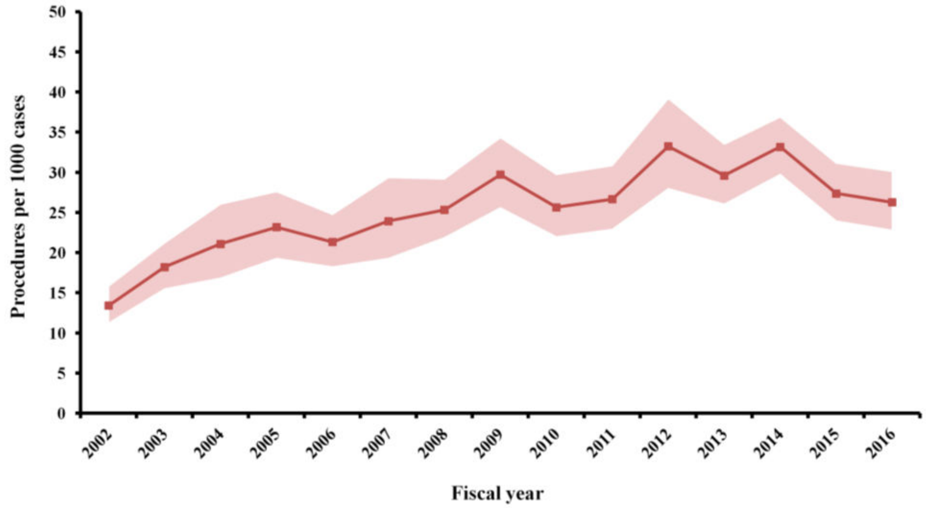
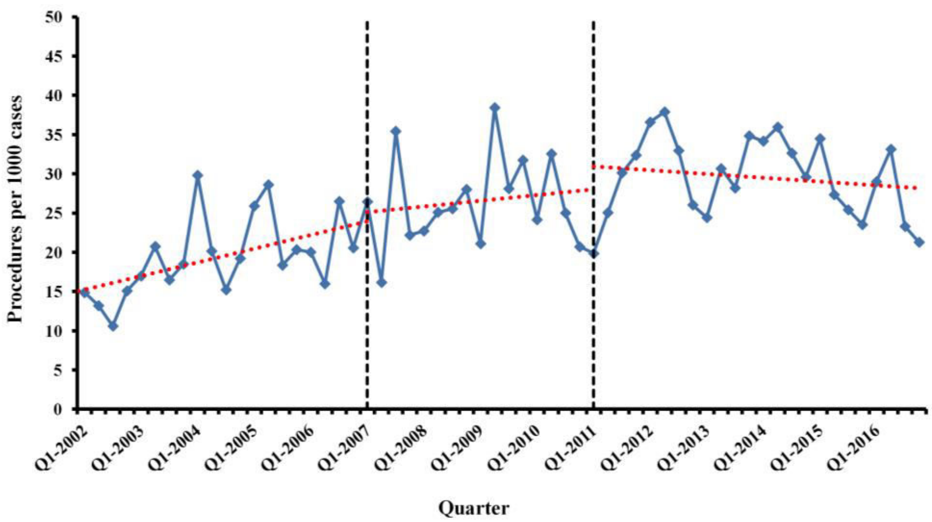


Figure 4.4. Trends in the quarterly utilization of percutaneous coronary intervention following the publication of the COURAGE and STICH trials.



The COURAGE trial was published in the first quarter of 2007 and the STICH trial in the first quarter of 2011

Table 4.2. Trends in the quarterly utilization rate of percutaneous coronary intervention following the publication of the COURAGE and STICH trials.

Parameter	Coefficient	Standard error	t value	*P*-value
Intercept	14.8	2.4	6.2	<.001
Quarterly change before COURAGE or STICH	0.4	0.2	2.2	0.03
Publication of COURAGE trial				
Immediate change after COURAGE	1.4	3.5	0.40	0.7
Additional quarterly change after COURAGE	-0.3	0.3	-0.73	0.5
Publication of STICH trial				
Immediate change after STICH	3.2	3.3	0.98	0.3
Additional quarterly change after STICH	-0.3	0.3	-0.96	0.3

4.3.3 Utilization of Isolated Coronary Artery Bypass Graft Surgery

From 2002 to 2016, more than 15,000 CABG surgeries without associated valvular procedures were performed. The absolute number of isolated CABG decreased from 1061 surgeries conducted in 2002 to 937 CABG surgeries in 2016 ($P = 0.01$). The annual age- and sex-standardized use of CABG decreased 35% from 23 procedures (95% CI, 21-27) per 1000 new HF cases in 2002 to 17 (95% CI, 14-21) per 1000 in 2016 ($P < .001$) (**Figure 4.5**). The publication of the COURAGE and STICH trials were not associated with significant immediate changes in the quarterly utilization rate of isolated CABG (coefficient -0.5, SE 2.1, P-value 0.8 and coefficient -1.1, SE 1.9, P-value 0.5 respectively). Nor it was associated with additional quarterly changes in the use of isolated CABG (coefficient 0.01, SE 0.2, P-value 0.9 and coefficient 0.2, SE 0.2, P-value 0.3 respectively) (**Figure 4.6 and Table 4.3**).

Figure 4.5. Annual age- and sex- standardized utilization of isolated coronary artery bypass surgery among incident cases of heart failure, 2002-2016.

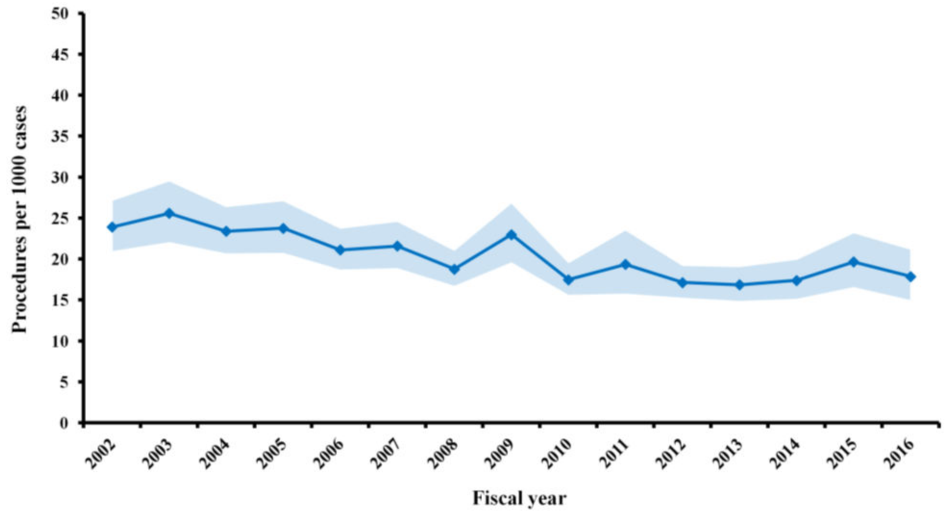
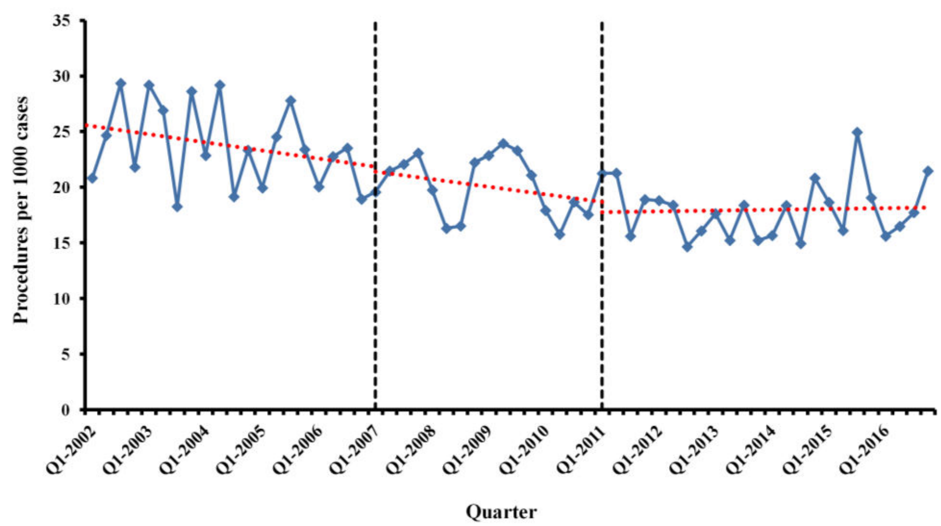


Figure 4.6. Trends in the quarterly utilization of isolated coronary artery bypass surgery following the publication of the COURAGE and STICH trials.



The COURAGE trial was published in the first quarter of 2007 and the STICH trial in the first quarter of 2011.

Table 4.3. Trends in the quarterly utilization rate of isolated coronary artery bypass graft surgery following the publication of the COURAGE and STICH trials.

Parameter	Coefficient	Standard error	t value	*P*-value
Intercept	25.7	1.4	18.2	<.001
Quarterly change before COURAGE or STICH	-0.2	0.1	-1.5	0.1
Publication of COURAGE trial				
Immediate change after COURAGE	-0.5	2.1	-0.22	0.8
Additional quarterly change after COURAGE	0.01	0.2	0.06	0.9
Publication of STICH trial				
Immediate change after STICH	-1.1	1.9	-0.57	0.5
Additional quarterly change after STICH	0.2	0.2	1.00	0.3

4.3.4 Utilization of Any Type of Coronary Revascularization Procedure

The use of either PCI or isolated CABG surgery has increased from 1615 procedures in 2002 to 2220 procedures in 2016 ($P < .001$). The age- sex-adjusted use of any coronary revascularization procedure increased 19% from 37 procedures (95% CI, 33-41) per 1000 HF patients in 2002 to 44 procedures (95% CI, 40-49) per 1000 in 2016 although this difference was not statistically significant ($P = 0.05$) (**Figure 4.7**). The ratio of adjusted PCI to CABG rates was 0.6 in 2002 increasing to 1.5 in 2016 after reaching a maximum value of 1.9 in 2012. In 2005, the ratio was equal to 1 and after that there was a preponderance in the utilization of PCI over CABG as the favored modality for revascularization (**Figure 4.8**).

Figure 4.7. Annual age- and sex- standardized utilization of any coronary revascularization procedure among incident cases of heart failure, 2002-2016.

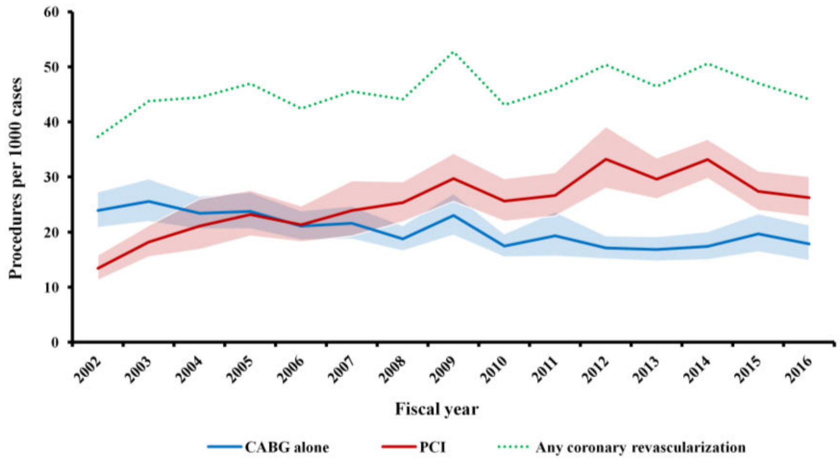
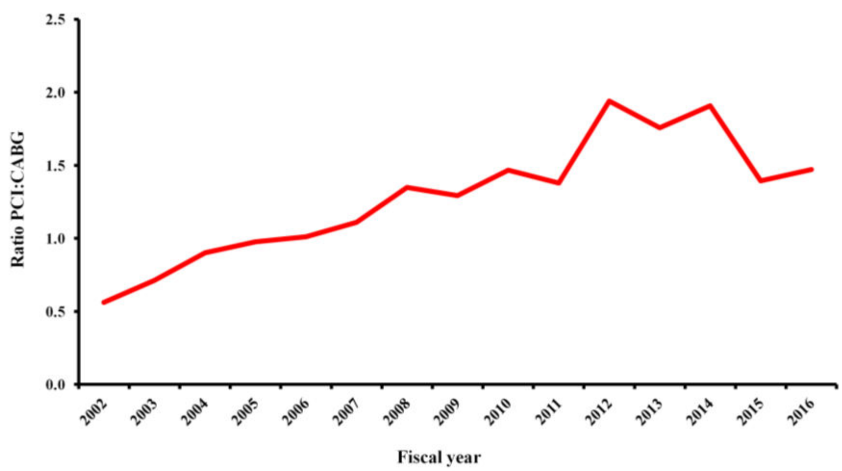


Figure 4.8. PCI to isolated CABG ratio.



4.4 Discussion

In this 15-year analysis of individuals newly diagnosed with chronic HF in Ontario, we observed that the use of ICA for the investigation of CAD increased between 2002 and 2009 when it reached a peak remaining stable after that until 2016. The plateau in the utilization of ICA after 2009 coincided temporarily with the availability of newer non-invasive modalities for the assessment of CAD which became publicly insured health services in the province [138]. Another finding of our study was the detection of an increase in the utilization rate of PCI accompanied by a simultaneous decline in the use of isolated CABG during the study period. Until 2005, CABG was the preferred coronary revascularization modality for the management of ischemic

HF but after 2005, PCI became the most used technique. Despite the impressive increase in the use of PCI, there was no apparent net increase in the utilization rate of revascularization procedures suggesting that PCI replaced CABG and was being used for patients who in the past underwent surgical revascularization. Similarly to previous studies conducted among the general population, we noticed a decline in the utilization of both CABG and PCI in the last two years of follow-up [139-141].

Our study also revealed that the publication of the STICH trial and the COURAGE trial were not associated with significant changes in the rate of utilization of ICA, PCI, or CABG among patients with HF. We assumed that the findings of both trials could have encouraged clinicians to feel less compelled to order ICA and manage more HF patients with medical therapy alone. The publication of the STICH trial in 2011, which detected no significant difference in the primary outcome between medical therapy alone and medical therapy plus CABG, was followed by controversy [142-145]. The discussion was polarized between those who believed that CABG was superior to medical therapy alone despite the results of the study and those who contended that the perceived benefit of CABG originated from previous studies that predated modern medical therapy and not supported by a modern clinical trial [132]. When the findings of the STICH trial were examined in light of the COURAGE trial, which demonstrated that revascularization with PCI did not reduce the risk of cardiovascular events among patients with stable CAD and normal left ventricular function, there were enough arguments to support a more conservative approach in the management of patients with ischemic HF. While the publication of the COURAGE trial was associated to meaningful declines in the volume of PCI performed in the United States [134,135], our study revealed that the STICH trial had no impact over clinical practice. In fact, the benefit of CABG over medical therapy alone among patients with HF was later confirmed with extended follow-up of the original trial according to the STICH Extended Study (STICHES) published in 2016 [26].

Even if the controversy surrounding the interpretation of the STICH trial is now clear, the role of PCI among patients with HF is not. In theory, PCI has the potential to allow the benefits of coronary revascularization with fewer complications than CABG surgery. However, this assertion comes from observational studies and subgroups analysis of clinical trials with all the inherent limitations of this type of data and which has never been tested in a randomized study [130]. At this time, a clinical trial – the 'Revascularization for Ischaemic Ventricular Dysfunction' (REVIVED) is currently underway to compare the role of PCI against medical therapy in the management of ischemic HF with severe left ventricular dysfunction [146,147].

Our study has limitations that deserve considerations. First, in observational studies, it is impossible to infer a causal association between specific events and observed trends. We are examining the utilization of procedures occurring in a complex health system for the management of highly complex patients. As such, we made assumptions to analyze and interpret the data but factors other than those evaluated or mentioned that we are not aware may have contributed to the patterns observed. Second, administrative databases lack information about important clinical characteristics such as left ventricular systolic function, the extent of coronary artery disease (i.e., the number of vessels affected), and presence and extent of ischemia, viability, and scarring. Therefore, we are unable to calculate trends in specific subgroups (e.g., patients with severe left ventricular systolic dysfunction similar to the ones enrolled in the STICH trial), or trends in the severity and extent of CAD along the time which could explain the substitution of CABG for PCI. Despite potential limitations, this study gives us a unique perspective to understand the utilization of ICA and coronary revascularization procedures among patients with HF in daily clinical practice.

4.5 Conclusions

Over a 15-year period, the utilization of coronary revascularization procedures has remained stable among patients with HF. Despite the stability in the overall use of revascularization procedures, there was a progressive increase in PCI counterbalanced by a decline in CABG. The utilization of ICA increased between 2002 and 2009 but it has stabilized after 2009 coinciding temporally with the emergence of noninvasive cardiac imaging modalities that can visualize the coronary anatomy. The publication of the STICH trial and the COURAGE trial were not associated with significant changes in clinical practice related to the management of patients with HF and CAD.

5 CHAPTER 5: INVASIVE CORONARY ANGIOGRAPHY-BASED CLASSIFICATION SYSTEMS FOR MEASURING THE BURDEN OF CORONARY ARTERY DISEASE – A SYSTEMATIC REVIEW

5.1 Abstract

Background: Invasive coronary angiography is used to determine the presence, extent, and location of coronary artery disease. Based on its findings, health professionals determine the best management strategy across the spectrum of treatment options that may include optimal medical therapy and coronary revascularization. Therefore, it is essential to stratify patients according to levels of disease to estimate prognosis and the need and patient suitability for revascularization.

Objectives: To identify invasive coronary angiography-based classification systems of coronary artery disease through a systematic review and describe the characteristics of these systems.

Methods: MEDLINE was searched for observational studies proposing classification systems for coronary artery disease using invasive coronary angiography. Two authors independently reviewed articles to select eligible studies and performed data abstraction.

Results: Thirty studies proposing 40 classification systems published between 1960 and 2018 were included. These classifications were divided into four broad groups according to the anatomic details used: (i) number of diseased vessels (N=15), (ii) segments of coronary vessels affected (N=17), (iii) myocardium at risk (N=5), and (iv) percutaneous coronary intervention scoring systems (N=3). The anatomical features included the severity of the stenosis used to define a significant obstruction, vessels and branches considered and their importance according to blood flow and area of myocardium supplied, procedure adopted to accommodate left main disease, and lesion morphology and location in the coronary tree. Four studies comparing the prognostic performance of different classifications were identified and no clear advantage of one system over the other was detected. Of the 30 studies included, 12 studies determined that left ventricular function was independently associated with survival and a more important predictor than the burden of coronary disease measured by arteriographic indices.

Conclusions: Several classification systems have been developed over the decades to measure the burden of coronary artery disease using invasive coronary angiography. There was a progressive incorporation of anatomic details over time without any clear improvement in prognostication and prediction of adverse health outcomes. Classification systems based on the number of diseased vessels, while simple, also provide enough information to estimate prognosis and guide decision-making in clinical practice. Studies conducted to understand the natural history of coronary disease were also important to identify left ventricular function as an important predictor of outcomes.

5.2 Introduction

Invasive coronary angiography (ICA) is a common procedure. More than 1 million procedures are performed every year in the United States [148]. Known or suspected coronary artery disease (CAD) is the most common indication of ICA. Based on presence, extent, and location of CAD, health professionals determine the best management strategy across the spectrum of treatment options ranging from risk factor modification for those with no CAD in one extreme to coronary artery revascularization plus optimal medical therapy for those with more severe disease in the other extreme [149].

Decisions about the need for coronary revascularization are particularly difficult since the clinical consequences of CAD are the result of a complex interplay of anatomic and physiologic data. Despite the notion that treatment decisions should not be driven merely by the severity of coronary stenosis, the anatomic burden of CAD determined by ICA remains the main determinant of risk for assessment and management of patients with CAD [150]. Therefore, it is essential to stratify patients according to disease risk, estimating prognosis, and the need and patient suitability for a coronary revascularization procedure [149].

Up to this point though, there has been no comprehensive identification and description of classification systems used to categorize patients with CAD according to the findings of ICA. Thus, the aim of this systematic review was to gain an understanding of classification systems that have been created to measure the burden of CAD. Accordingly, the primary objective was to identify ICA-based classification systems of CAD through a systematic review and describe the characteristics of these systems. The secondary objective was to establish if any classification system had a better prognostic ability in comparison to others.

5.3 Methods

5.3.1 Overview

A systematic literature review was undertaken using principles of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines, including a comprehensive search, study selection and data extraction independently undertaken by two authors [151].

5.3.2 Search Strategy

The literature review was conducted using Medline to identify articles published between January 1, 1960 and July 30, 2018. A manual review of references from the articles chosen for full-text evaluation was performed to identify any additional relevant studies. Review articles, textbooks and published letters were also examined for potentially eligible studies. In addition, experts were contacted inquiring about their knowledge of other relevant studies. The search was performed based on different combinations of text words and MeSH terms that included "coronary catheterization", "score", "index", "criteria", and "scheme" (**Appendix 5.1**). No additional limitations related to the population, disease, or type of study were added.

5.3.3 Study Selection

Studies were selected in a two-stage process. First, citations were reviewed, and full manuscripts were obtained for all citations describing angiography-based classification systems using invasive coronary angiography. Second, full text of articles selected in the first stage were reviewed to determine eligibility for inclusion. To be included in the systematic review, published studies, including abstracts, described a theoretical or practical (i.e., actually tested in patients) classification system, score or model that grouped or organized patients with or without HF based on the burden of CAD measured by invasive coronary angiography. No restrictions on the type of outcome examined in the studies were imposed. Studies that enrolled patients with conditions other than CAD such as pulmonary embolism, rheumatic heart disease, solid organ transplantation, congenital heart disease, hypertrophic cardiomyopathy, Tako-Tsubo cardiomyopathy, auto-immune disease, and HIV were excluded. In addition, guidelines, case reports, editorials letters, and reviews were excluded. Any conflicting results during any stage of the study selection were resolved by consensus between Juarez Rosso de Braga and another author involved in the study selection for this systematic review.

5.3.4 Data Extraction and Data Presentation

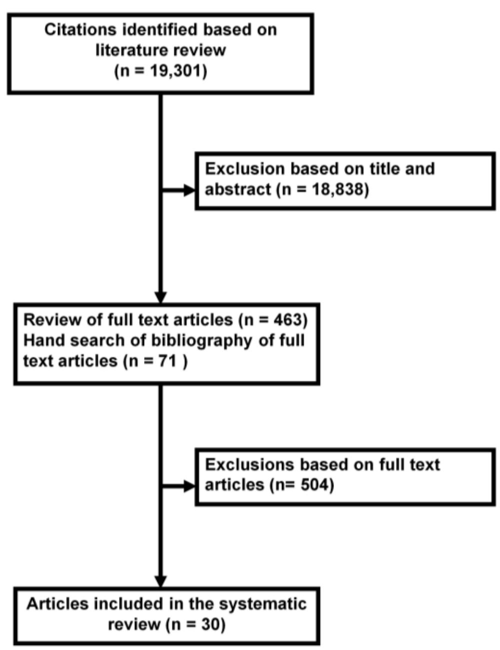
Data from each included study was abstracted into a standardized data collection form. Data extracted was compared and discrepancies were resolved by consensus as described in section 5.3.3. Information extracted from each article included: author and year of publication; characteristics of study; type of study (i.e., theoretical versus clinical); sample size and inclusion/exclusion criteria; number of patients with HF and definition of HF used in the study; features of the classification system, and procedures to use the classification. The results of the studies included in this systematic review were reported qualitatively or presented in tables.

5.4 Results

5.4.1 Search Result

A total of 19,301 citations were identified of which 463 full-text articles were reviewed in detail after excluding studies based on the title and abstract. A hand search of bibliographies of those selected articles found 71 more potential articles for inclusion (**Figure 5.1**).

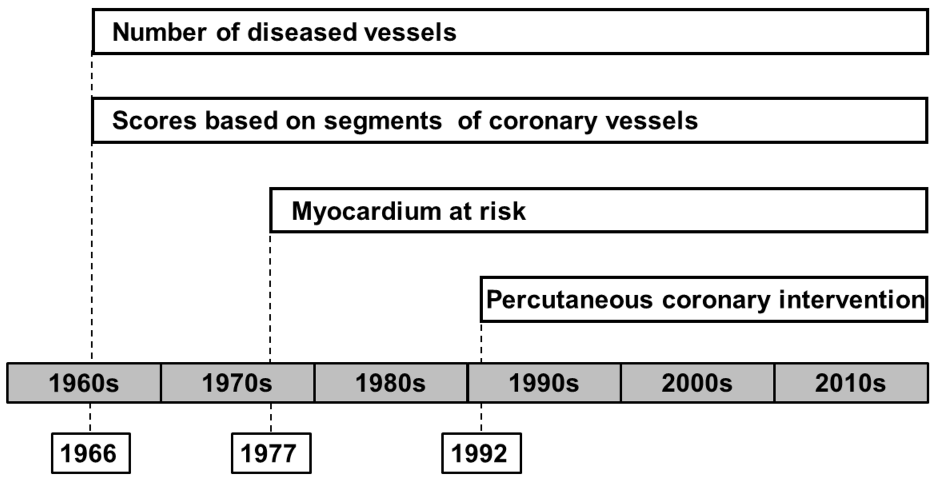
Figure 5.1. Search results.



5.4.2 Overview of Classification Systems for Coronary Anatomy

We identified 30 studies proposing 40 classification systems published between 1960 and 2018 (**Figure 5.2**). Broadly, these classification systems can be grouped in four categories according to the anatomic details used to classify patients with CAD: (i) number of diseased vessels (N=15), (ii) segments of coronary vessels affected and severity of stenosis (N=17), (iii) myocardium at risk (N=5), and (iv) percutaneous coronary intervention (PCI) scoring systems (N=3) (**Figures 5.3 and 5.4**).

Figure 5.2. Classification systems based on invasive coronary angiography.



Numbers on the bottom indicate the year that the first classification system of each category was published.

Figure 5.3. Classification systems based on invasive coronary angiography – 1966-1989.

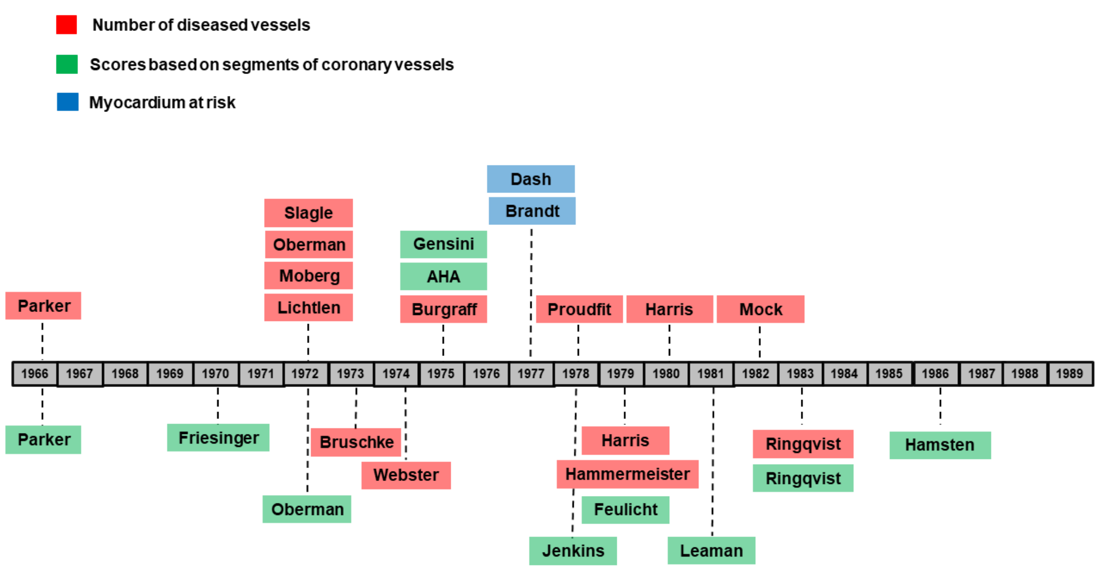
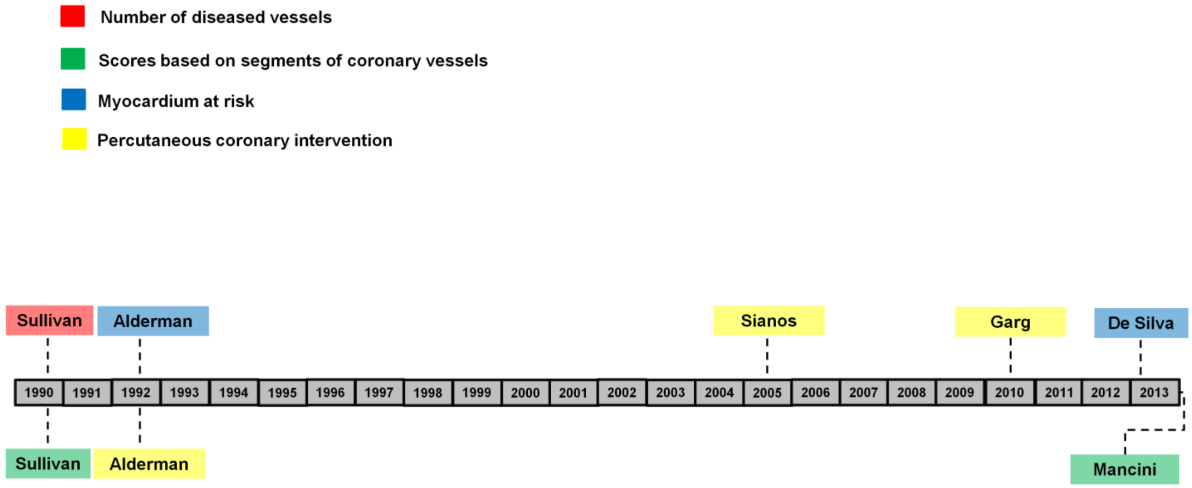


Figure 5.4. Classification systems based on invasive coronary angiography – 1990-2014.



5.4.2.1 Number of Diseased Vessels

The first approach to classify the burden of CAD was based on the number of diseased vessels (**Table 5.1**). These specifically identify the number of major native coronary arteries - left anterior descending (LAD), circumflex (Cx), and right coronary artery (RCA) that have atherosclerotic disease using a cut-off value to define obstructive CAD that is considered clinically relevant. According to the number of vessels with significant disease, patients are classified as having 1-, 2-, or 3-vessel disease. Coronary vessels with stenoses below a specified threshold are not considered to indicate CAD. In 1966, Parker *et al*. proposed the quantification of CAD based on the number of diseased vessels [152] which was followed by several authors [153-167]. A variation of this type of classification was proposed by Ringqvist *et al*. in which the analysis was restricted to the proximal portion of the coronary arteries [165]. Two main factors create differences across these classification systems: (i) how they incorporate the presence of CAD in the left main (LM) coronary artery; and (ii) the cut-off used to define significant obstructions. Some studies excluded or made no reference about how patients with LM disease were categorized [152-154,156]. Other studies considered patients with LM disease as a distinct group irrespective of the number of additional vessels with CAD [158-164], while some studies defined patients with LM disease as having 1-vessel disease [166], 2-vessel disease [155], or 2- or 3-vessel disease depending on the balance of the coronary circulation [165]. The cut-off for defining significant disease also varied among the classification systems. Some studies used a threshold of

50% [152,155,157,159,161,163], 70% [162,164-166], 75% [160,163], or 80% [154,158] for lesions in the LAD, Cx, or RCA.

5.4.2.2 Scores Based on Segments of Coronary Vessels Affected and Severity of Lesions

Although the division into 1-, 2-, and 3-vessel disease was immediately useful for classifying patients with CAD, there were concerns that a binary classification for CAD was a crude categorization. Different scores were proposed aiming to be more complete by incorporating two components: (i) instead of using a cut-off for significance with dichotomization of lesions, scores assigned numerical values for atherosclerotic lesions, with higher values for more stenotic lesions; (ii) the relative importance of primary vessels and branches of the primary vessels according to the amount of blood flow was integrated (**Table 5.2**). In those classifications, the most stenotic lesion in each vessel is graded individually and added together for a total score. Then, the score can be used alone with no distinction made across different vessels or branches [152,155,166,168-172], or the stenosis score can be used in combination with a numeric value that tried to express the importance of the vessel based on the coronary blood flow. This was done either by ranking different combinations of coronary lesions based on severity and location with higher

Table 5.1. Classification systems based on the number of diseased vessels.

Author	Year	Threshold for obstructive disease	LM
Parker	1966	≥50%	Not mentioned
Lichtlen	1972	Not mentioned	Not mentioned
Moberg	1972	≥80%	Not mentioned
Oberman	1972	≥50%	2-vessel disease
Slagle	1972	Not mentioned	Not mentioned
Bruschke	1973	≥50%	Separated group
Webster	1974	≥80%	Separated group
Burgraff	1975	≥50%	Separated group
Proudfit	1978	≥50%	Separated group
Harris	1979	≥50% and ≥75%	Separated group
Hammermeister	1979	≥70%	Separated group
Harris	1980	≥75%	Separated group
Mock	1982	≥70%	Separated group
Ringqvist	1983	≥70%	2- or 3- vessel disease
Sullivan*	1990	≥70%	1-vessel disease

* a.k.a: Sullivan Vessel classification.
LM: left main coronary artery disease.

scores for more stenotic lesions in the proximal portion of the LAD and the LM [150,165,167,173] or by multiplying each stenosis score by a weight that was proportional to the vessel size [165,174-176]. Some attempts were made to measure the proportion of the coronary circulation with angiographically detectable atheroma instead of measuring obstructive disease [166,172]. In addition, the American Heart Association (AHA) proposed a system for reporting the findings of ICA. Although this classification was a theoretical system that did not involve the calculation of a score, it nonetheless warrants discussion because its segmentation of the coronary tree into 15 portions influenced several subsequent classification systems [177].

5.4.2.3 Myocardium at Risk

The number of diseased vessels and scores based on segments and severity of lesions failed to consider the variability of importance of coronary arteries in terms of size of areas of myocardium supplied by each vessel. Different vessels supply variable areas of the left ventricular myocardium [178]. This notion generated the concept that the total amount of myocardium in jeopardy determined by CAD needed to be quantified to accurately estimate prognosis. Five classification systems based on the quantification of myocardium at risk have been proposed [179-184]. These classifications divide the left ventricle into regions according to the supply of different coronary vessels. Based on the contribution of individual vessels for a specific area and the severity of CAD, a myocardial score is calculated (**Table 5.3**).

5.4.2.4 Percutaneous Coronary Intervention Classification Systems

The increasing importance of revascularization procedures, more specifically PCI, revealed that any of the previous classification systems were insufficient to determine suitability for revascularization. When selecting a patient for intervention with either PCI or CABG, the complexity of the lesions is a factor that needs to be considered. We identified two classification systems based exclusively on angiographic details: the BARI (Bypass Angioplasty Revascularization Investigation) Myocardial Jeopardy Index and the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score [185]. In addition, we identified one classification system combining clinical information and angiographic data: the Clinical SYNTAX score which was calculated by multiplying the SYNTAX score by a measurement that would take into account age, serum creatinine, and ejection fraction [186] (**Table**

Table 5.2. Classification systems based on segments of coronary vessels affected.

Author	Year	Classification	Description
Parker	1966	-	Divides the coronary tree in LAD, Cx, and RCA. The degree of stenosis is assigned a numeric value ranging from 0 to 3. 0: normal anatomy; 1: <50%; 2: 50-99%; 3: 100%. Lesions for each artery are graded and summed to a maximum score of 9.
Friesinger	1970	Coronary Arteriographic Score	Divides the coronary tree in LAD, Cx, and RCA. The degree of stenosis is assigned a numeric value ranging from 0 to 5. 0: no abnormalities; 1: trivial irregularities; 2: 50-90%; 3: multiple stenosis 50-90%; 4: >90%; 5: total obstruction. Lesions for each artery are graded and summed to a maximum score of 15.
Oberman	1972	-	Divides the coronary tree in 7 segments: proximal and distal LAD, Cx, and RCA in addition to the LM. The degree of stenosis is assigned a numeric value ranging from 1 to 5. 1: no significant obstruction; 2: <50%; 3: 50-75%; 4: >75%; 5: complete occlusion. Lesions for each segment are graded and summed to a maximum score of 35.
AHA	1975	AHA Reporting System	Divides the coronary tree in 15 segments: LM; proximal-mid-distal RCA; PDA as a branch of RCA; proximal-mid-distal LAD; 1st and 2nd diagonal; proximal-distal Cx; OM; posterolateral; and PDA as a branch of Cx. Lesions for each segment are categorized into 0-25%; 26-50%; 51-75%; 76-90%; 90-99%; and 100%.
Gensini	1975	Cardscores	Divides the coronary tree in 15 segments similarly to the AHA classification. The degree of stenosis is assigned a numeric value ranging from 1 to 32. 1: 0-25%; 2: 26-50%; 4: 51-75%; 8: 76-90%; 16: 90-99%; 32: 100%. A multiplying factor ranging from 0.5 to 5 is assigned to each branch depending of vessel size and balance of circulation. The total score is the sum of the lesion scores adjusted for the presence of collaterals.
Jenkins	1978	Coronary Atherosclerosis Score	Divides the coronary tree in 8 proximal segments ignoring distal segments: LM, LAD, septal, diagonal, Cx, OM, RCA, and PDA. The degree of stenosis is assigned a numeric value ranging from 1 to 4. 1: <50%; 2: 50-74%; 3: 75-99%; 4: total obstruction. Lesions for each segment are graded and summed to a maximum score of 32.
Feurlicht	1979	NHCH Index	Divides the coronary tree on a schematic diagram with different paths according to the balance of the coronary circulation. The product of the fraction luminal openings of the segments on each path is calculated. The sum of these products is multiplied by a constant to generate an index between 0 and 100.
Leaman	1981	Coronary Score	Divides the coronary tree in 15 segments similarly to the AHA classification. The degree of stenosis is assigned a numeric value ranging from 1 to 5. 1: 70-89%; 3: 90-99%; 5: 100%. A multiplying factor ranging from 0 to 6 is assigned to each segment according to their contribution to myocardium perfusion on a right- or left-dominant coronary system. Lesions for each segment are graded and summed to a maximum score of 36.

Ringqvist	1983	Modified NHCH index	Uses the product of the luminal opening fractions as in the NHCH index. Before summation, each of the products is weighted by a factor determined empirically from the CASS study. The weight reflects the contribution of each branch to myocardium perfusion.
Ringqvist	1983	Proximal Arterial Segments Score	Divides the coronary tree in proximal LAD, Cx, and RCA in addition to the LM. Stenosis ≥70% in the RCA, LAD, or Cx and ≥50% in the LM are assigned a numeric value according to the combination of lesions. 1: no proximal segment diseased; 2: one proximal segment diseased, either the Cx or RCA; 3: proximal LAD diseased; 4: proximal disease in both the CX and RCA; 5: proximal disease in LAD and in CX or RCA; 6: LM disease; 7: three proximal segments diseased with or without LM disease.
Ringqvist	1983	Arterial Segments Score	Divides the coronary tree in 8 segments: LM, proximal-mid LAD, proximal-mid RCA, proximal-distal CX, and first OM. Score is calculated based on a weighted sum of stenosis in each segment. The LM and the three proximal segments are weighted most heavily.
Hamsten	1986	Atheromatosis Score	Divides the coronary tree in 15 segments similarly to the AHA classification. Atherosclerotic lesions are assigned a numeric value ranging from 0 to 3 according to the extension and 1 to 3 for plaque size. The values for extension and plaque size are then multiplied for each segment. The sum of all segmental scores is divided by the number of evaluated coronary segments.
Hamsten	1986	Stenosis Score	Divides the coronary tree in 15 segments similarly to the AHA classification. The degree of stenosis is assigned a numeric value ranging from 0 to 16. 0: normal or lesions<25%; 1: 25-50%; 2: 50-75%; 4: 75-90%; 8: 90%-99%; 16: total occlusion. The sum of all segmental stenosis scores is divided by the number of evaluated coronary segments.
Sullivan	1990	Stenosis Score	Divides the coronary tree in eight segments. The degree of stenosis is assigned a numeric value ranging from 1 to 4. 0: normal; 1: 1-49%; 2: 50-74%; 3: 75-99%; 4: total occlusion. Lesions for each segment are graded and summed to a maximum score of 32.
Sullivan	1990	Extent Score	Divides the coronary tree in LM, LAD, diagonal, septal, Cx, OM, and PDA. The proportion of each vessel involved by atheroma, identified as luminal irregularity, is multiplied by a factor for each vessel. 5: LM; 20: LAD; 10: diagonal; 5: septal; 20: Cx; 10: OM; 20: RCA; 10: PDA. The scores for each branch are summed to give a maximum score of 100.
Mark	1994	Duke CAD Prognostic Index	Ranks and weights combinations of coronary lesions. Considers the number of diseased vessels giving more weight to more stenotic lesions specially in the proximal LAD and LM.
Mancini	2014	Anatomic burden score	Ranks and weights combinations of coronary lesions. Considers the number of diseased vessels giving more weight to stenoses ≥50% in the proximal LAD and Cx

AHA: American Heart Association; CAD: coronary artery disease; CASS: Coronary Artery Surgery Study; Cx: circumflex artery; LAD: left anterior descending artery; LM: left main coronary artery; NHCH: National Heart and Chest Hospital; OM: obtuse marginal; PDA: posterior descending artery; RCA: right coronary artery.

Table 5.3. Myocardium at risk classification systems.

Author	Year	Classification	Description
Brandt	1977	Green Lane	The LV is divided in different areas and each area is given fixed values (septum: 7 units; OM: 3 units; inferior: 3 units; diagonal: 2 units). Stenosis are graded as: a: 100%; b: 90-99%; c: 75- 89%; d: 50-74%; e: <50%. Using the combination of grade of stenosis and the myocardial value, each artery is given a myocardial score. Scores are added to a maximum myocardial score of 15.
Dash	1977	Duke Jeopardy Score	Divides the coronary tree in 6 segments: LAD, diagonal, septal, Cx, OM, and PDA. Each segment with proximal stenosis >70% is assigned 2 points. Lesions for each segment are graded and summed to a maximum score of 12.
Alderman	1992	BARI	Divides the coronary tree in 29 segments. The LV is divided in 3 territories: anterior, lateral, inferoposterior. Calculates the amount of myocardium supplied by coronary vessels with stenosis ≥50%. Each terminating vessel is assigned a score of 0 to 3. From the score of each terminating vessel, the relative contribution of various arteries is used to calculate a regional score. The sum of the three regional territory scores is the global left ventricular territory score.
Graham	2001	APPROACH	The LV is divided into regions with different weights according to the percentage of myocardium supplied by a vessel or its branches. Jeopardized territories are those supplied by vessels with ≥70% stenoses or >50% for the LM. Jeopardized territories are summed for a maximum score of 100.
De Silva	2013	BCIS Myocardial Jeopardy Score	Modification of the Duke Jeopardy Score that allows classification of LM disease and graft disease after CABG. LM ≥50% is given a score of 8 points. Native coronary arteries are scored, and points are then deducted for patent grafts to these territories, where applicable. Scores are summed to a maximum of 12 points.

AHA: American Heart Association; BARI: Bypass Angioplasty Revascularization Investigation trial; BCIS: Balloon-Pump Assisted Coronary Intervention Study; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CASS: Coronary Artery Surgery Study; Cx: circumflex artery; LAD: left anterior descending artery; LM: left main coronary artery; LV: left ventricle; OM: obtuse marginal; PDA: posterior descending artery; RCA: right coronary artery.

5.4). We categorized the BARI Myocardial Jeopardy Index as either a myocardium at risk and a PCI classification system because the BARI index quantified the amount of jeopardized myocardium but it also described the location and anatomical aspects of coronary lesions according to morphological features [187,188]. The SYNTAX score is the most exhaustive classification developed to date and it is based on a series of classification systems described in previous sections: the AHA classification for the segmentation of the coronary tree [177], the Leaman score [175], the AHA lesions classification system [187,188], the total occlusion classification system [189], and classification systems for bifurcation lesions [190].

5.4.3 Importance of Left Ventricular Function

Our search did not identify any studies that developed CAD classification systems specifically for individuals with HF. But we identified two studies that examined different classifications, such as the number of diseased vessels and the CAD prognostic index, in cohorts with HF [24,191]. Although the primary objective of those studies was to create a binary definition of HF according to the underlying etiology, they have demonstrated that the severity of CAD among patients with HF, measured by arteriographic classifications, is a significant independent predictor of mortality and provides more prognostic information than a simple dichotomization into ischemic or non-ischemic HF. Even if no classification systems have been developed for HF, some of the studies reviewed were instrumental in identifying left ventricular (LV) function as a predictor of prognosis. Although the definition of HF differed across studies, which varied from a combination of symptoms, findings on chest radiography, hemodynamic measurements, and left ventricular function measured by ventriculography (**Table 5.5**), several observations were made. First, LV function was independently associated with survival irrespective of arteriographic findings [160,164,165,181,184]. Second, LV function was a more important predictor of survival than the burden of CAD measured by arteriographic indices [161,162,164]. Third, the subgroup with the highest mortality were individuals with multivessel disease and HF [155,164,192]. Fourth, a measure of LV function combined with a measure of arteriographic findings led to an improvement in the prognostic ability in comparison to arteriographic findings alone [165,192].

Table 5.4. Percutaneous coronary intervention classification systems.

Author	Year	Classification	Description
Alderman	1992	BARI	Defines segments of the coronary arteries, myocardial territories, and distribution of coronary vessels (see Table 5.3). Classifies the location and anatomical aspects of coronary lesions. Each lesion determining a stenosis ≥50% or greater is uniquely identified and assigned a type according to morphological features.
Sianos	2005	SYNTAX	Divides the coronary tree in 16 segments. Each segment has a different weight and varies depending of left or right dominance. Other lesion characteristics have additive value to the score and include diameter reduction, bifurcation, trifurcation, ostial stenosis, length, calcification, diffuse disease, presence of thrombus, and tortuosity.
Garg	2010	Clinical SYNTAX	Calculated by multiplying the SYNTAX score by the modified ACEF score. The modified ACEF score is calculated using the formula age divided by ejection fraction plus 1 point for every 10 mL/min reduction in the clearance of creatinine below 60 mL/min per 1.73 m^2.

ACEF score: Age, creatinine, ejection fraction; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery.

Table 5.5. Definition of heart failure used in studies included in the systematic review.

Author	Year	Definition of Heart Failure
Oberman	1972	Symptoms of HF (dyspnea on exertion associated to orthopnea or paroxysmal nocturnal dyspnea) and heart enlargement on a chest radiography.
Bruschke	1973	Based on left heart ventricular angiography. Ventricles classified in normal; presence of localized scar tissue; diffuse scar tissue; aneurysm.
Burgraff	1975	Requirement of continuing administration of digitalis with or without diuretics on a chronic basis or; Hemodynamic data classified as normal or abnormal or; Based on left heart ventricular angiography. Ventricles classified in normal or abnormal in the presence of local hypokinesis, generalized hypokinesis, akinetic areas, or dyskinesis.
Proudfit	1978	Based on left heart ventricular angiography. Ventricles classified in normal; presence of localized scar tissue; diffuse scar tissue with or without aneurysm.
Hammermeister	1979	Based on left heart ventricular angiography. Left ventricular contraction classified as: I = normal; II = hypokinesis or akinesis involving less than 25% of the ventricular circumference; III = hypokinesis or akinesis involving 25-75% of the ventricular circumference; IV = dyskinesis; V = diffuse hypokinesis or akinesis involving more than 75% of the ventricular circumference.
Harris	1980	Based on left heart ventricular angiography. Left ventricular contraction classified as: normal or abnormal in the presence of one or more localized areas of asynergy; diffusely abnormal if there were multiple areas of asynergy producing a diffusely abnormal contraction pattern with an estimated EF<25%.
Mock	1982	Based on left heart ventricular angiograms. The ventriculogram was divided into five segments: anterobasal, anterolateral, apical, diaphragmatic and posterolateral. The systolic contraction pattern of each of the five segments was numerically scored: 1 = normal, 2 = moderate hypokinesis, 3 = severe hypokinesis, 4 = akinesis, 5 = dyskinesis and 6 = aneurysm present. The LV score was the sum of the points of these five segments. The LV score was categorized in: good LV function (score 5-11); moderate impairment of LV function (score 12-16) and poor LV function (score 17-30).
Ringqvist	1983	Based on left heart ventricular angiograms. Calculated similarly to the score used in the study by Mock et al (above).

Callif	1985	Cardiomegaly on chest radiograph or history of congestive HF or LVEF.
Bart	1997	LVEF ≤40% with or without symptoms.
Felker	2002	LVEF ≤40% and a history of symptomatic HF (NYHA class II or greater).
De Silva	2013	LVEF <50%.

EF: ejection fraction; HF: heart failure; LV: left ventricle; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Table 5.6. Comparative studies of different classification systems.

Author	Year	N	Classifications examined	Outcome	Methods and findings
Ringqvist	1983	24,959	Two classifications based on the number of diseased vessels: number of diseased vessels and number of proximal arterial segments diseased. Six scores based on segments of vessels affected and severity of stenosis: proximal arterial score, Friesinger, Gensini, NHCH, modified NHCH, and the arterial segment score.	Time to death of any cause	Comparison of the likelihood chi-square statistic obtained from the Cox PH model used to develop each classification.* Friesinger = 580; number of proximal arterial segments diseased = 614; proximal arterial score = 635; number of diseased vessels = 654; NHCH = 707; NHCH = 717; arterial segment score = 859; Gensini = 937.
Callif	1985	462	One classification based on the number of diseased vessels. One classification based on myocardium at risk: Duke Jeopardy Score.	Time to death of any cause	Comparison of the likelihood chi-square statistic obtained from the Cox PH model used for each classification. * Number of diseased vessels = 35.7; Duke Jeopardy score = 42.6.
Graham	2001	20,067	Three classifications based on myocardium at risk: BARI, Duke Jeopardy Score, and APPROACH.	Mortality at 1 year	Comparison of c-statistic obtained from the logistic regression model used for each classification. Duke = 0.740; APPROACH = 0.744; BARI = 0.745.§
Neeland	2012	3600	Three classifications based on the number of diseased vessels: one using a significance threshold of 50%, 70% and Sullivan Vessel. Six classifications based on segments of coronary vessels and severity of stenosis: Duke CAD Severity Index, Friesinger, Gensini, Jenkins, Sullivan Stenosis, and Sullivan Extent. One classification based on myocardium at risk: Duke Jeopardy Score.	Correlation between classification systems and burden of CAD measured by ICUS	All angiographic scores correlated with each other (range for Spearman coefficient [ρ] 0.79-0.98, P<.0001). All scores correlated significantly with average plaque burden and plaque area by ICUS (range ρ 0.56-0.78, P<.0001 and 0.43-0.62, P< .01, respectively).

*: The best classification is the one that maximizes the likelihood chi-square test statistic.
§: Among patient receiving medical therapy.
CAD: coronary artery disease; ICUS: intracoronary ultrasound; N: number of patients included; PH: proportional hazard.

5.4.4 Comparative Studies of Classification Systems

We identified four studies comparing classification systems (**Table 5.6**). Ringqvist et al. compared eight arteriographic classifications and found that although all had a good ability to predict survival, the Gensini classification performed better than the others [165]. In another study, Califf et al. demonstrated that the jeopardy score was slightly superior to the number of diseased vessels to estimate survival [181]. Meanwhile, Graham et al. detected that 3 of the myocardial jeopardy scores provided independent prognostic information but negligible differences in their prognostic ability [183]. Neeland et al., in the most comprehensive comparison of angiographic scoring systems, detected a strong correlation across the 10 classification systems examined with each other and with atherosclerotic plaque burden measured with intracoronary ultrasound [193]. But this study did not examine which system had better ability to estimate prognosis, but it only examined the ability of classification systems to estimate the burden of disease in the coronary vessels.

5.5 Discussion

In this systematic review of 30 studies, we identified 40 classification systems developed for measuring the extent of CAD using ICA. Our review gives a historical perspective of successive attempts to quantify CAD that began more than half a century ago. We observed that with each new attempt, the classifications became more comprehensive. Detailed analysis of classifications revealed that they differed in several anatomical features: (i) the severity of the stenosis used to define a significant obstruction; (ii) the vessels and branches considered and their segmentation; (iii) application of weights to segments of the coronary circulation according to the amount of blood flow; (iv) consideration of the area of myocardium supplied by each coronary vessel; (v) procedure adopted to accommodate LM disease; and (vi) incorporation of specific details about lesion morphology and location in the coronary tree.

Another finding of our study was that despite the evolution of ICA classification over time, it is still unclear if the progressive incorporation of anatomic information has added any value for prognostication or guiding patient treatment. The few studies that have examined this issue suggest that no classification system is superior to quantify the extent of CAD and estimate prognosis with the predictive ability being virtually the same across classifications. This evidence has important limitations: some studies are decades old, the methods used for comparing classifications did not necessarily employ current statistical and methodological standards. Conversely, newer classifications such as the SYNTAX and BARI were not compared with older classifications. Despite these limitations, the evidence supports the notion that a simple classification based on the number of diseased vessels, which does not require complicated calculations or computer software, is preferable for practical reasons than more complex systems to estimate prognosis in general among patients with CAD.

The emergence of non-invasive cardiac imaging modalities and the ability to quantify the amount of ischemic myocardium or viable myocardium eclipsed the importance of the anatomical burden of CAD determined by ICA. However, recent evidence demonstrated that the anatomic burden of CAD remains the most important factor for prognostication and decision-making. In a retrospective non-prespecified analysis of the COURAGE trial, Mancini et al. reported that the anatomic burden of CAD assessed by ICA was an independent predictor of death and myocardial infarction in contrast to the ischemic burden measured by functional testing which had no association with outcomes [150]. Similar results were detected among patients with HF and depressed LV function. A post-hoc analysis of the STICH trial showed that patients with depressed ejection fraction with 3-vessel CAD had worse survival and received greater benefit from surgical revascularization in comparison to patients with less extensive CAD [194]. Meanwhile, substudies of the STICH trial demonstrated that the presence of myocardial ischemia or viable myocardium did not identify patients with worse prognosis or those with greater potential benefit from revascularization procedures [44,195]. More recently, the ISCHEMIA trial revealed that the presence of at least moderate inducible ischemia did not identify patients with a benefit from coronary revascularization when added to optimal medical therapy on the rate of the occurrence of cardiovascular death, acute myocardial infarction, hospitalizations for unstable angina, heart failure, or resuscitated cardiac arrest among patients with stable ischemic heart disease and normal ventricular function [196].

With the availability of direct visualization of coronary atherosclerosis by noninvasive coronary computed tomography angiography (CCTA), the role of ICA as the gold standard may be challenged. CCTA is more accurate than ICA for detecting CAD since conventional angiography does not directly assess the condition of interest but only a contour of the affected vessel based on the lumen obstruction [197]. Despite this well-documented lack of objectivity, clinical practice today continues to rely on visual assessment according to ICA for the description of lesion severity. Indeed, studies that use visual assessment to describe lesion severity continue to be published in leading cardiology journals despite the well-documented problems with poor reproducibility and lack of accuracy of this methodology. It is possible that we are not close enough to retiring or replacing ICA for the majority of patients in daily practice [198].

Two questions can possibly be answered with this systematic review: whether ICA-based classification systems should be used in daily clinical practice and which classification system could be utilized in clinical practice. The answer is yes to the first question. A classification system allows comparison of different patients with different complexities of disease. This is particularly relevant to estimate prognosis and inform decision-making, for uniform discussion among health professionals, and for proper characterization of participants in clinical research. The answer to the second question may be dependent on the scenario in which the classification system is needed. In general, management options available for improving patient outcomes are not infinite and largely confined to risk factor modification for those with no CAD, optimal medical therapy for patients with CAD, and coronary revascularization in addition to medical therapy in patients with severe CAD. Given the few present management options, we may not need highly sophisticated tools to categorize CAD. It seems that except when determining the best treatment option among alternatives for coronary revascularization, with either PCI or CABG, there is no need for excessive details in order to guide therapy. In addition, when considering the comparative studies examined in this review, it seems that there are no obvious advantages of one system over the other. Therefore, for most scenarios in daily practice, a classification based on the number of diseased vessels could be used in daily practice without losing for the purposes of most types of clinical decision-making.

This systematic review is the first study specifically designed to retrieve, analyze and critically appraise existing invasive angiographic-based classification systems for CAD. We developed a broad search strategy in order to capture the largest possible number of publications on this topic.

However, our study has limitations that deserve consideration. First, it was difficult to develop a search filter for the literature review. Relevant references that we knew beforehand would need to be included in our review could not be identified at all even with different search strategies. This was particularly true for older studies. Therefore, we had to develop a search strategy that lacked specificity. While this caused the retrieval of a massive number of studies, we still acknowledge the possible existence of other classification systems that could not be located. Second, comparative studies of different classification systems are scarce and lack the methodological rigour that are required nowadays. Therefore, our recommendation about classifications based on the number of the number of diseased vessels as the optimal choice for use in clinical practice should be examined in the light of this weak evidence.

5.6 Conclusions

Several classification systems have been developed to measure the burden of coronary artery disease using invasive coronary angiography with progressive incorporation of anatomic details. There is no evidence that one system is superior to predict risk of adverse health outcomes. Classification systems based on the number of diseased vessels, although simple, provide enough information to estimate prognosis and guide decision-making in clinical practice. Studies conducted to understand the natural history of CAD were also important to identify left ventricular function as an important predictor of outcomes among individuals with CAD.

6 CHAPTER 6: IMPORTANCE OF NON-OBSTRUCTIVE CORONARY ARTERY DISEASE IN THE PROGNOSIS OF PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

6.1 Abstract

Background: Individuals with heart failure (HF) are often dichotomized in those with ischemic vs. non-ischemic HF according to the underlying etiology. This binary classification creates a heterogeneous group combining individuals with non-obstructive coronary artery disease (CAD) with those with normal coronaries under the non-ischemic label.

Objective: To examine the prognostic significance of non-obstructive CAD in patients with HF, as a distinct category apart from those with normal coronary arteries.

Methods: A cohort of individuals with heart failure and reduced ejection fraction undergoing invasive coronary angiogram was examined and linked to administrative databases for outcomes evaluation. Patients were divided into those with normal coronaries, non-obstructive disease, and obstructive disease. The primary outcome was the composite of cardiovascular (CV) death, non-fatal myocardial infarction (AMI), non-fatal stroke, or HF hospitalization.

Results: Of 12,814 individuals, 2656 (20.7%) had normal coronaries, 2254 (17.6%) had non-obstructive CAD, and 7904 (61.7%) had obstructive CAD. The risk of the primary outcome was increased in the non-obstructive group (hazard ratio (HR) 1.17, 95% confidence interval (CI) 1.04-1.32, p=0.01) relative to those with normal coronaries. Non-obstructive CAD was associated with an increased hazard of CV death (HR 1.82; 95% CI; 1.27-2.62; p = 0.001) and death of any cause (HR 1.18; 95% CI 1.05-1.33; p = 0.005). There were no significant differences in the rate of AMI, stroke, or HF hospitalization.

Conclusions: Among HF patients with reduced EF, the presence of non-obstructive CAD was independently associated with an increased hazard of the primary composite outcome and death of any cause.

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6.2 Introduction

Coronary artery disease (CAD) is the most common cause of heart failure (HF).[19] In daily practice, health professionals endeavor to identify those patients for whom the underlying etiology of HF is CAD, as opposed to non-ischemic causes. The rationale is that individuals with ischemic HF are at high risk for adverse cardiac events and death,[19,22] and could potentially be candidates for intervention and secondary preventive measures.[6]

While the binary classification (i.e., ischemic vs. non-ischemic) is widely employed, this terminology has not been without controversy. Indeed, since the description in the 1970s of an entity of cardiomyopathy caused by atherosclerosis,[199] a major point of contention has been the extent of CAD that should be present to be considered prognostically important as opposed to the mere presence of CAD that is not severe enough to impact upon prognosis or be considered etiologically responsible for the diagnosis of HF.

Classically, ischemic HF has been defined as depressed myocardial contractility in the presence of a previous acute myocardial infarction (AMI), a revascularization procedure, or significant CAD defined as a stenosis of 75% or greater in at least two epicardial vessels.[24] Alternatively, patients with no apparent CAD, or CAD in any number of epicardial vessels below the aforementioned significance threshold (i.e., non-obstructive), or obstructive disease in a single vessel, with no history of AMI or coronary revascularization, have been classified aggregately as non-ischemic.[24] Consequently, non-ischemic HF patients represent a heterogeneous group that combines non-obstructive CAD together with those who demonstrate apparently normal coronaries under the assumption that the extent of disease is not clinically important or relevant.

However, recent findings have suggested that in those without HF, the risk of adverse clinical events from non-obstructive lesions is intermediate between those with apparently normal coronaries and significant CAD.[200-202] Since HF patients exhibit a high baseline rate of mortality and morbidity, it is unknown if the presence of non-obstructive CAD is of sufficient prognostic importance to manifest upon clinical outcomes. Therefore, our primary objective was to examine the prognostic significance of non-obstructive CAD in patients with HF and reduced ejection fraction (HFrEF). As a secondary objective, we aimed to assess the association between the overall CAD burden and prognosis in HFrEF.

6.3 Methods

6.3.1 Study Design and Participants

This was a retrospective cohort study that included patients who had undergone an elective invasive coronary angiogram (ICA) because of suspected or confirmed CAD or HF between October 1, 2010, and March 31, 2015 in Ontario, Canada and had reduced left ventricular ejection fraction (EF < 35%). The CorHealth Cardiac Registry was used as the primary data source for the study. This registry, previously known as the Cardiac Care Network Registry, has been used extensively in the past.[203] Designated trained hospital personnel collected and entered into the database information about demographics, clinical presentation, comorbidities, EF, and coronary anatomy data of all individuals undergoing ICA in the province.

To assemble our study cohort, we excluded patients younger than 18 or older than 105 years of age, those with invalid health-card numbers or who were non-residents of Ontario, had an aborted ICA, had an AMI within 30 days before the date of ICA, had missing EF or EF ≥ 35%, had previous heart or lung transplantation, were being assessed as potential organ donors, had a previous coronary revascularization procedure, had been primarily referred for ICA because of valvular disease or congenital heart disease, or had clinical instability at the time of the catheterization. We excluded patients with a recent AMI to eliminate individuals with an acute coronary syndrome complicated by HF and depressed EF. For patients who underwent more than one ICA during the study period, the first procedure was considered the index and the baseline for the analysis.

6.3.2 Additional Data Sources

The study cohort created using the CorHealth Registry was linked to other administrative databases: the Ontario Health Insurance Plan (OHIP) database which contains data on physician billing for both ambulatory and hospital care, the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) for hospital admissions, the Registered Persons Database (RPDB) to determine vital status during follow-up, and the Office of the Registrar General - Death (ORGD) database to determine whether death had a cardiovascular or non-cardiovascular cause. Multiple data sources and validated algorithms combining inpatient and outpatient codes were used to determine the presence of comorbidities (**Appendix 6.1**).[204] All data sources were linked using unique encoded identifiers and analyzed at ICES.

6.3.3 Definitions

Patients were defined as having no apparent CAD in the absence of any stenoses in the coronary tree (0% stenosis and no luminal irregularities). Non-obstructive disease was defined as the presence of limited atherosclerotic disease demonstrated by a stenosis <50% (1-49%) in the left main (LM) and < 70% (1-69%) in the left anterior descending (LAD), circumflex (Cx), or right coronary artery (RCA). Obstructive CAD was defined as the presence of a stenosis ≥ 50% in the LM or ≥ 70% in the LAD, Cx, or RCA. In the registry, information on the specific coronary vessels affected is not provided for patients classified as having non-obstructive disease, while the majority of patients recorded as having obstructive CAD had information about the specific vessels affected (i.e., LM, LAD, Cx, or RCA). The CorHealth Registry records the EF measured prior to the ICA with non-invasive testing or the EF determined at the time of catheterization with left ventriculography (if performed). The registry allows information about the EF to be entered as a continuous or categorical variable. Most individuals (~75%) in the Registry had EF classified into one of four pre-specified categories: preserved (≥ 50%), mildly-reduced (35-49%), moderately-reduced (20-34%), or severely-reduced (< 20%) LVEF, while the remaining ~25% had EF recorded as a numerical value. We classified individuals with a numerical EF into one of the four LVEF categories described above. To avoid any ambiguity in the definition of depressed EF, we excluded individuals with EF 35-49%, restricting the analysis to those with moderate- or severely-reduced LVEF.

6.3.4 Main Exposure

The main exposure was the severity of CAD visualized during catheterization by the operator performing the exam. The accuracy of the coronary anatomy recorded in the CorHealth Registry has been previously validated and demonstrated very good reliability when compared to a random sample of coronary angiography procedures reviewed by cardiologists at a central laboratory.[205] For the primary analysis, patients were divided into three groups: (i) no apparent CAD; (ii) non-obstructive disease; and (iii) significant disease. In a secondary analysis, we divided patients with significant CAD, who had information about the specific vessels affected (i.e., LM, LAD, Cx, or RCA), into those with 1-, 2-, or 3-vessel disease, representing the number of major coronary arteries with a significant obstruction. Patients with LM disease were classified as a distinct category irrespective of the number of additional diseased vessels.

6.3.5 Outcomes

The primary outcome was the composite of cardiovascular (CV) death, hospitalizations with a primary diagnosis of AMI, HF, or ischemic stroke. Secondary outcomes included the individual components of the composite outcome and death from any cause. Hospitalizations caused by an AMI were identified using the International Classification of Diseases 10th revision (ICD-10-CA) codes I21 and I22 as the most responsible diagnosis. Hospitalizations for HF included ICD-10-CA codes I50, I25.5, I40-I43, I11 plus I50, and I13 plus I50, and hospitalizations for ischemic stroke were identified using ICD-10-CA codes G45 (excluding G45.5), I63 (excluding I63.6), and I64.

6.3.6 Covariates

We adjusted for variables that were potentially associated with the risk of experiencing study outcomes, including age, sex, urban or rural residence, New York Heart Association (NYHA) HF functional classification, Canadian Cardiovascular Society (CCS) grading of angina pectoris, left ventricular ejection fraction (i.e., 20-34% or <20%), previous HF hospitalization, previous AMI, atrial fibrillation, serum creatinine concentration, diabetes mellitus, hypertension, dialysis, smoking status, hyperlipidemia, previous ischemic stroke or transient ischemic attack (TIA), peripheral vascular disease, chronic obstructive pulmonary disease (COPD), cancer, liver cirrhosis, dementia, depression, and year of catheterization.[206]

6.3.7 Statistical Analysis

A descriptive analysis was performed comparing baseline characteristics across the exposure groups. Continuous variables were expressed as medians (25th, 75th percentiles) and compared with the Kruskal-Wallis test. Categorical variables were compared using the χ^2 statistic. The cumulative incidence function was used to evaluate the incidence of CV death treating non-CV death as a competing event. A cause-specific hazards model was used to estimate the association of non-obstructive CAD with the rate of the occurrence of outcome events, adjusting simultaneously for potential confounding variables.[207] Robust standard errors were used to account for clustering of patients within the same cardiac site.[117] Directly-adjusted cumulative incidence curves under proportional subdistribution hazards models were constructed for the primary outcome and the components of the primary outcome to account for non-CV death as a competing risk[208,209] Survival curves were adjusted using all the previously described covariates.

For the survival analysis, the index date was the date of catheterization. Individuals were censored if they reached the end of follow-up on December 31, 2015, they moved out of the province, or at the date of a major cardiac or non-cardiac surgical procedure (codes used to identify surgical procedures are listed on **Appendix 6.2**). We made this decision (i.e., to censor patients at the time of surgery) because we wanted to examine the prognostic significance of CAD and we assumed that any major surgical procedure in this population with HF would have an elevated risk for perioperative complications including death and CV events, modifying the occurrence of outcome events that could be attributed solely to CAD. However, censoring participants at the time of surgery reduced the observation period and the detected event rate as compared to studies that have enrolled HF patients with the same profile. Multiple imputation was used to impute missing values for serum creatinine and symptoms of HF and angina. We carried out five imputations, and combined the results using Rubin's rules.[210] Adjusted hazard ratios (HR) were calculated with associated 95% Wald confidence limits for non-obstructive

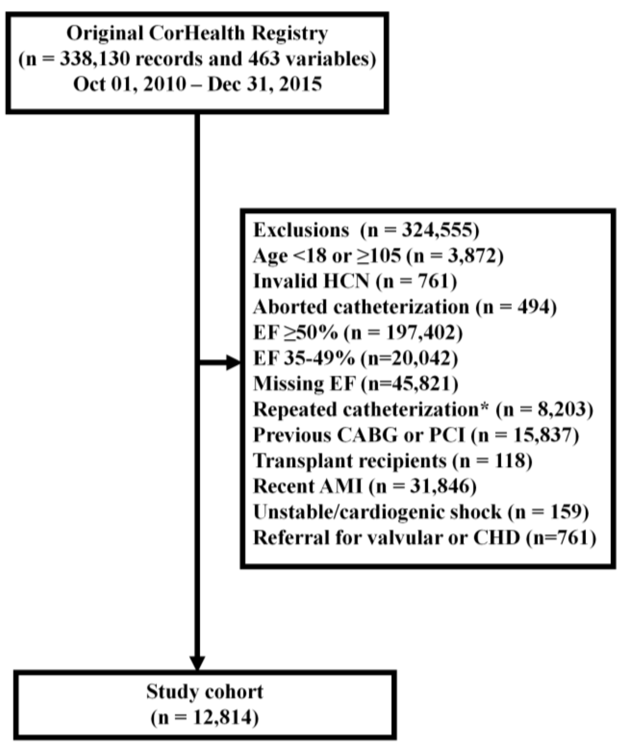
CAD and significant CAD using no apparent CAD as the reference category. For the secondary analysis, adjusted HR were calculated for those with significant CAD identified as having 1-, 2-, 3-vessel, or LM disease using no apparent CAD as the reference category. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) statistical software.

6.4 Results

6.4.1 Study Cohort

We identified 338,130 records in the CorHealth Registry of patients undergoing ICA at 23 cardiac centers. The application of all inclusion and exclusion criteria resulted in a cohort of 12,814 unique individuals with reduced EF (**Figure 6.1**). Reduced EF was detected in 10,098 (78.8%) individuals with non-invasive testing before ICA and in 2716 (21.2%) with left ventriculography at the time of catheterization. In total, 2840 primary outcomes events were observed until December 31, 2015 by examining 24,320 person-years of follow-up.

Figure 6.1. Patient flow diagram.



6.4.2 Baseline Clinical Characteristics

Of 12,814 individuals with reduced EF, 2656 (20.7%) had no apparent CAD, 2254 (17.6%) had non-obstructive CAD, and 7904 (61.7%) had obstructive CAD. The non-obstructive group had demographic and clinical characteristics that were mostly intermediate between those with no apparent CAD and those with significant CAD. Patients with significant CAD tended to be slightly older, were more likely to be male, more likely to have CCS angina class III or IV, and were more likely to have higher creatinine, chronic kidney disease, diabetes, dialysis, hyperlipidemia, hypertension, prior AMI, peripheral vascular disease, and stroke compared to those with non-obstructive CAD or no apparent CAD. Meanwhile, patients with no apparent CAD were less likely to have angina, although remarkably 49% of individuals in that group had some degree of angina. Those same individuals with no apparent CAD were more likely to have advanced NYHA symptoms of HF, atrial fibrillation, and more severe left ventricular dysfunction in contrast to the other two groups (**Table 6.1**).

Table 6.1. Baseline characteristics according to the extent of coronary artery disease.

Variable	No apparent CAD (N=2656)	Non-obstructive (N=2254)	Obstructive (N=7904)	P-value
Age, yrs, median (25^{th}-75^{th})	59 (50-68)	65 (57-74)	67 (59-75)	<.001
Female sex, n (%)	1019 (38.4)	724 (32.1)	1815 (23.0)	<.001
Rural residence, n (%)	348 (13.1)	303 (13.4)	1162 (14.7)	0.07
Current CCS angina class[a], n (%)				
Missing	56 (2.1)	43 (1.9)	218 (2.8)	
0	1274 (48.0)	984 (43.7)	2478 (31.4)	
I	263 (9.9)	238 (10.6)	838 (10.6)	<.001
II	299 (11.3)	253 (11.2)	1095 (13.9)	
III	104 (3.9)	107 (4.7)	614 (7.8)	
IV	660 (24.8)	629 (27.9)	2661 (33.7)	
Current NYHA class[b], n (%)				
Missing	379 (14.3)	344 (15.3)	1908 (24.1)	
I	625 (23.5)	532 (23.6)	2128 (26.9)	
II	644 (24.2)	564 (25.0)	1555 (19.7)	<.001
III	657 (24.7)	571 (25.3)	1565 (19.8)	
IV	351 (13.2)	243 (10.8)	748 (9.5)	
Creatinine[c], mg/dL, median (25^{th}-75^{th})	0.96 (0.81-1.15)	0.98 (0.83-1.19)	1.02 (0.85-1.23)	<.001
LVEF, n (%)				
20 to 34%	1726 (65.0)	1627 (72.2)	5870 (74.3)	

< 20%	930 (35.0)	627 (27.8)	2034 (25.7)	<.001
Medical history, n (%)				
Atrial fibrillation/flutter	549 (20.7)	499 (22.1)	1171 (14.8)	<.001
Cancer	138 (5.2)	183 (8.1)	490 (6.2)	<.001
Chronic kidney disease	268 (10.1)	288 (12.8)	1024 (13.0)	<.001
COPD	303 (11.4)	380 (16.9)	1164 (14.7)	<.001
Current smoker	557 (21.0)	535 (23.7)	1869 (23.6)	<.001
Dementia	17 (0.6)	34 (1.5)	138 (1.7)	<.001
Depression	129 (4.9)	110 (4.9)	312 (3.9)	0.04
Diabetes	689 (25.9)	774 (34.3)	3423 (43.3)	<.001
Dialysis	32 (1.2)	48 (2.1)	183 (2.3)	0.002
Hyperlipidemia	979 (36.9)	1115 (49.5)	4617 (58.4)	<.001
Hypertension	1527 (57.5)	1563 (69.3)	5606 (70.9)	<.001
Liver cirrhosis	53 (2.0)	42 (1.9)	128 (1.6)	0.313
Previous AMI	224 (8.4)	290 (12.9)	2460 (31.1)	<.001
Previous HF hospitalization	951 (35.8)	761 (33.8)	1757 (22.2)	<.001
Peripheral vascular disease	78 (2.9)	118 (5.2)	826 (10.5)	<.001
Stroke	160 (6.0)	194 (8.6)	813 (10.3)	<.001

a: The Canadian Cardiovascular Society angina classification ranges from class 0, which indicates no symptoms, to class IV, which indicates angina at any level of physical exertion.
b: The New York Heart Association functional classification ranges from class I, which indicates no limitation to physical activity, to class IV, which indicates inability to carry on any physical activity without symptoms.
c: 1280 individuals (10.0%) had missing values.
AMI: acute myocardial infarction; CCS: Canadian Cardiovascular Society; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; N: number; NYHA: New York Heart Association; yrs: years of age.

6.4.3 Primary Outcome

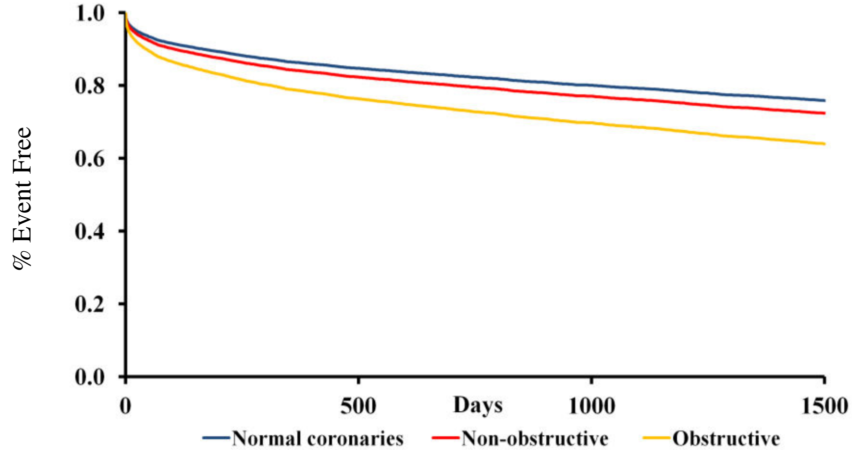
The primary composite outcome occurred in 446 patients (16.8%) in the no apparent CAD group, in 468 (20.8%) in the non-obstructive CAD group, and in 1926 (24.4%) in the obstructive disease group (**Table 6.2**). As compared with no apparent CAD, subjects with non-obstructive CAD had a higher hazard of experiencing the primary composite outcome (adjusted HR 1.17; 95% CI 1.04-1.32; P = 0.013). Significant CAD was associated with an even higher hazard of CV death, AMI, HF hospitalization, or stroke (adjusted HR 1.64; 95% CI 1.33-2.02; P < .001) (**Figure 6.2**).

Table 6.2. Outcomes and number of events according to the extent of coronary artery disease.

	No apparent CAD (N=2656)	**Non-obstructive (N=2254)**	**Obstructive (N=7904)**
Primary outcome			
CV death or hospitalizations by AMI, HF, or stroke	446 (16.8)	468 (20.8)	1926 (24.4)
Secondary outcomes, n (%)			
CV death	48 (1.8)	83 (3.7)	423 (5.4)
Hospitalizations for AMI	17 (0.6)	16 (0.7)	534 (6.8)
Hospitalizations for HF	353 (13.3)	342 (15.2)	851 (10.8)
Hospitalizations for stroke	28 (1.1)	27 (1.2)	118 (1.5)
Death of any cause	282 (10.6)	360 (16.0)	1444 (18.3)

AMI: acute myocardial infarction; CAD: coronary artery disease; HF: heart failure; N: number.

Figure 6.2. Adjusted survival curves for the primary outcome according to the extent of coronary artery disease.



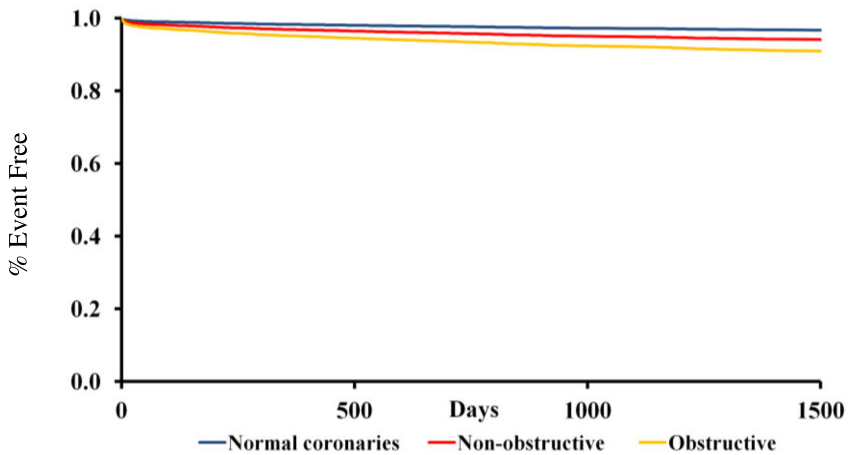
Group	N	Events	HR	95% CI
Normal	2656	446	Ref	Ref
Non-obstructive	2254	468	1.17	1.04-1.32
Obstructive	7904	1926	1.64	1.33-2.02

6.4.4 Secondary Outcomes

The analysis of the secondary outcomes revealed that non-obstructive CAD as compared to no apparent CAD was associated with an increased hazard of CV death (adjusted HR 1.82; 95% CI 1.27-2.62; P = 0.001) and death from any cause (adjusted HR 1.18; 95% CI 1.05-1.33; P = 0.005) (**Figure 6.3**). There were no significant differences between groups in the hazard of experiencing an AMI, a HF hospitalization, or stroke (**Figure 6.4**). Individuals in the obstructive CAD group had greater risks of experiencing all the secondary outcomes in comparison to the no apparent CAD group except for HF hospitalizations.

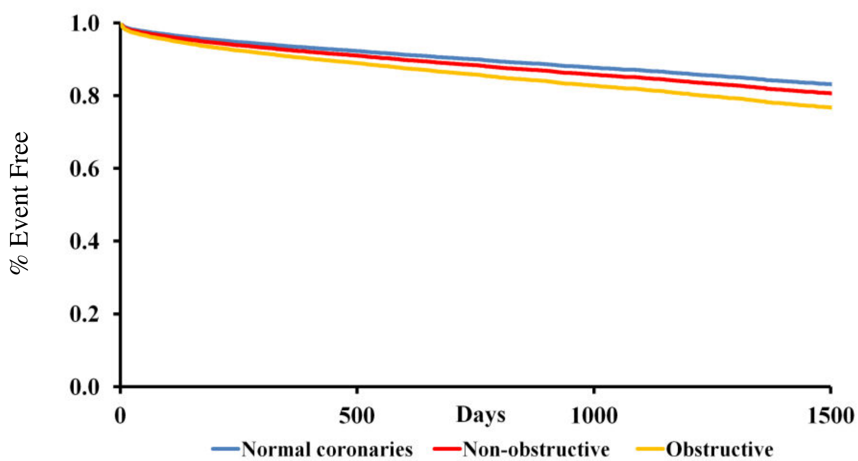
Figure 6.3. Adjusted survival curves for (a) cardiovascular death and (b) death of any cause and adjusted hazard ratios according to the extent of coronary artery disease.

(a)



Group	N	Events	HR	95% CI
Normal	2656	48	Ref	Ref
Non-obstructive	2254	83	1.82	1.27-2.62
Obstructive	7904	423	1.64	1.33-2.02

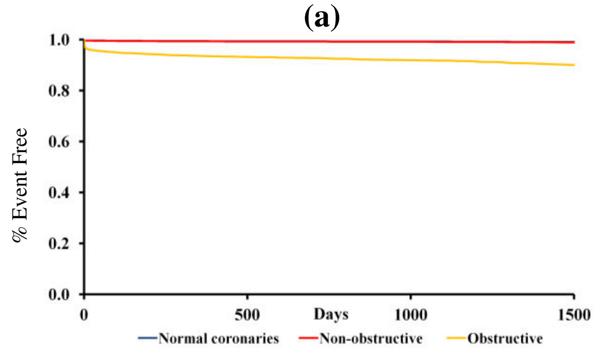
(b)



Group	N	Events	HR	95% CI
Normal	2656	282	Ref	Ref
Non-obstructive	2254	360	1.18	1.05-1.33
Obstructive	7904	1444	1.48	1.28-1.71

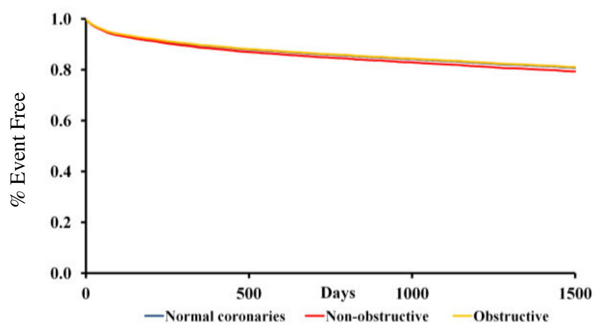
Figure 6.4. Adjusted survival curves for (a) acute myocardial infarction, (b) heart failure hospitalization, (c) and stroke according to the extent of coronary artery disease.

(a)



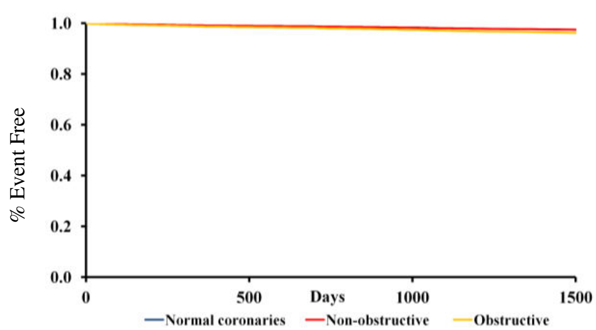
Group	N	Events	HR	95% CI
Normal	2656	17	Ref	Ref
Non-obstructive	2254	16	1.10	0.43-2.82
Obstructive	7904	534	10.7	4.7-24.3

(b)



Group	N	Events	HR	95% CI
Normal	2656	353	Ref	Ref
Non-obstructive	2254	342	1.10	0.95-1.27
Obstructive	7904	851	1.00	0.84-1.18

(c)

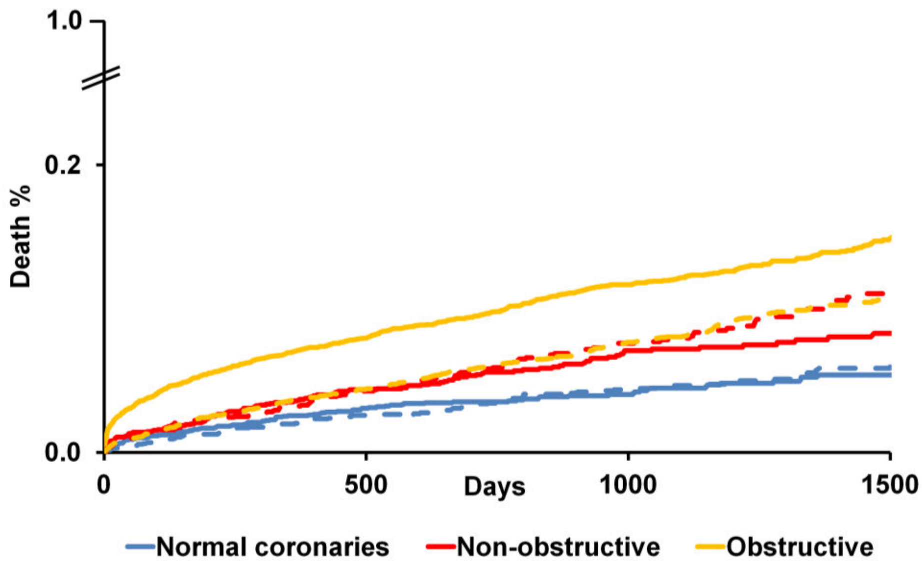


Group	N	Events	HR	95% CI
Normal	2656	28	Ref	Ref
Non-obstructive	2254	27	0.98	0.61-1.59
Obstructive	7904	118	1.47	1.03-2.11

6.4.5 Cumulative Incidence of Cardiovascular and Non-Cardiovascular Death

Among patients with apparently normal coronaries, the 4-year cumulative incidence of CV death and non-CV death was virtually similar (5.4% and 5.8% respectively). For patients with non-obstructive CAD, the 4-year cumulative incidence of non-cardiovascular death was higher (11.0%) than the incidence of CV death (8.0%). Among patients with obstructive CAD, 14.5% died of cardiovascular causes and 10.4% died of non-cardiovascular within 4 years (**Figure 6.5**). Most cardiovascular deaths were caused by CAD while non-cardiovascular deaths were most often caused by malignancy across the three groups of patients.

Figure 6.5. Cumulative incidence functions of cardiovascular death and competing non-cardiovascular death according to the extent of coronary artery disease.



Solid line represents the cumulative incidence function of cardiovascular death and the dashed line represents the cumulative incidence function of non-cardiovascular death.

6.4.6 Secondary Analysis

Of the 7904 individuals with significant CAD, 6376 (79.8%) had documentation of the vessels affected. These individuals were divided according to the number of diseased vessels: 2241 (19.9%) had 1-vessel disease, 1656 (14.7%) had 2-vessel disease, 1639 (14.5%) had 3-vessel disease, and 840 (7.4%) had LM disease. The number of subjects with no apparent CAD and non-obstructive disease remained unchanged for the secondary analysis. Baseline characteristics revealed that as the extent of disease increased from 1-vessel to the presence of LM disease, patients were significantly older, more likely to be male, tended to have more angina and symptoms of HF, were more likely to have had a previous AMI and stroke, diabetes, and peripheral vascular disease (**Table 6.3**). In comparison to the no apparent CAD group, the adjusted HR for the primary outcome was 1.64 (95% CI 1.25-2.14; $P < .001$) for those with 1-vessel disease, 1.81 (95% CI 1.45-2.27; $P < .001$) for 2-vessel disease, 2.12 (95% CI 1.67-2.70; $P < .001$) for 3-vessel disease, and 2.53 (95% CI 2.08-3.07; $P < .001$) for LM disease. Similarly, there were significant associations between 1-, 2-, 3-vessel, and LM disease with the hazard of experiencing CV death and non-fatal AMI (**Tables 6.4**, **6.5, 6.6, and 6.7**).

Table 6.3. Baseline characteristics according to the number of diseased vessels (n=11,286)[a].

Variable	No apparent CAD (N=2656)	Non-obstructive (N=2254)	1-V (N=2241)	2-V (N=1656)	3-V (N=1639)	LM (N=840)	P-value
Age, yrs, median (25th-75th)	59 (50-68)	65 (57-74)	67 (58-75)	67 (59-76)	68 (60-76)	71 (62-78)	<.001
Female sex, n (%)	1019 (38.4)	724 (32.1)	557 (24.9)	338 (20.4)	297 (18.1)	151 (18.0)	<.001
Rural residence, n (%)	348 (13.1)	303 (13.4)	343 (15.3)	261 (15.8)	247 (15.1)	141 (16.8)	0.024
CCS angina class[b], n (%)							
Missing	56 (2.1)	43 (1.9)	70 (3.1)	49 (3.0)	32 (2.0)	22 (2.6)	
0	1274 (48.0)	984 (43.7)	626 (27.9)	492 (29.7)	440 (26.8)	207 (24.6)	
I	263 (9.9)	238 (10.6)	234 (10.4)	174 (10.5)	172 (10.5)	85 (10.1)	
II	299 (11.3)	253 (11.2)	260 (11.6)	253 (15.3)	261 (15.9)	127 (15.1)	<.001
III	104 (3.9)	107 (4.7)	153 (6.8)	145 (8.8)	165 (10.1)	87 (10.4)	
IV	660 (24.8)	629 (27.9)	898 (40.1)	543 (32.8)	569 (34.7)	312 (37.1)	
NYHA class[c], n (%)							
Missing	379 (14.3)	344 (15.3)	620 (27.7)	426 (25.7)	423 (25.8)	209 (24.9)	
I	625 (23.5)	532 (23.6)	614 (27.4)	476 (28.7)	476 (29.0)	235 (28.0)	
II	644 (24.2)	564 (25.0)	419 (18.7)	332 (20.0)	289 (17.6)	154 (18.3)	
III	657 (24.7)	571 (25.3)	405 (18.1)	293 (17.7)	305 (18.6)	145 (17.3)	<.001
IV	351 (13.2)	243 (10.8)	183 (8.2)	129 (7.8)	146 (8.9)	97 (11.5)	
Creatinine[d], mg/dL, median (25th-75th)	0.96 (0.81-1.15)	0.98 (0.83-1.19)	1.01 (0.84-1.21)	1.02 (0.84-1.24)	1.03 (0.87-1.29)	1.07 (0.89-1.35)	<.001
LVEF, n (%)							
20 to < 35%	1726 (65.0)	1627 (72.2)	1718 (76.7)	1268 (76.6)	1250 (76.3)	640 (76.2)	<.001
< 20%	930 (35.0)	627 (27.8)	523 (23.3)	388 (23.4)	389 (23.7)	200 (23.8)	
Medical history, n (%)							
Atrial fibrillation/flutter	549 (20.7)	499 (22.1)	354 (15.8)	201 (12.1)	165 (10.1)	89 (10.6)	<.001
Cancer	138 (5.2)	183 (8.1)	140 (6.2)	104 (6.3)	93 (5.7)	46 (5.5)	0.001
Chronic kidney disease	268 (10.1)	288 (12.8)	236 (10.5)	211 (12.7)	248 (15.1)	118 (14.0)	<.001
COPD	303 (11.4)	380 (16.9)	324 (14.5)	262 (15.8)	204 (12.4)	133 (15.8)	<.001
Current smoker	557 (21.0)	535 (23.7)	544 (24.3)	439 (26.5)	376 (22.9)	221 (26.3)	<.001

Dementia	17 (0.6)	34 (1.5)	40 (1.8)	30 (1.8)	26 (1.6)	14 (1.7)	0.006
Depression	129 (4.9)	110 (4.9)	90 (4.0)	59 (3.6)	46 (2.8)	20 (2.4)	<.001
Diabetes	689 (25.9)	774 (34.3)	814 (36.3)	765 (46.2)	870 (53.1)	406 (48.3)	<.001
Dialysis	32 (1.2)	48 (2.1)	40 (1.8)	41 (2.5)	55 (3.4)	18 (2.1)	<.001
Hyperlipidemia	979 (36.9)	1115 (49.5)	1184 (52.8)	1038 (62.7)	1091 (66.6)	540 (64.3)	<.001
Hypertension	1527 (57.5)	1563 (69.3)	1514 (67.6)	1192 (72.0)	1228 (74.9)	619 (73.7)	<.001
Liver cirrhosis	53 (2.0)	42 (1.9)	29 (1.3)	26 (1.6)	24 (1.5)	16 (1.9)	0.480
Previous AMI	224 (8.4)	290 (12.9)	569 (25.4)	614 (37.1)	714 (43.6)	341 (40.6)	<.001
Previous HF hospitalization	951 (35.8)	761 (33.8)	450 (20.1)	289 (17.5)	324 (19.8)	160 (19.0)	<.001
Peripheral vascular disease	78 (2.9)	118 (5.2)	181 (8.1)	178 (10.7)	225 (13.7)	158 (18.8)	<.001
Stroke	160 (6.0)	194 (8.6)	193 (8.6)	184 (11.1)	178 (10.9)	125 (14.9)	<.001

a: 1,528 individuals with significant disease had no information on the specific coronary vessels affected. Therefore, they could not be classified according to the number of diseased vessels and were excluded from the secondary analysis. The number of individuals with no apparent CAD and those with non-obstructive CAD is unchanged in comparison to the primary analysis.
b: The Canadian Cardiovascular Society angina classification ranges from class 0, which indicates no symptoms, to class IV, which indicates angina at any level of physical exertion.
c: The New York Heart Association functional classification ranges from class I, which indicates no limitation to of physical activity, to class IV, which indicates inability to carry on any physical activity without symptoms.
d: 1180 individuals (10.5%) had missing values.
1-V: one-vessel disease; 2-V: two-vessel disease; 3-V: three-vessel disease; AMI: acute myocardial infarction; CCS: Canadian Cardiovascular Society; COPD: chronic obstructive pulmonary disease; LM: left main; LV: left ventricular; N: number; NYHA: New York Heart Association.

Table 6.4. Study outcomes and number of events experienced by the study cohort according to the extent of CAD and number of diseased vessels for the group with obstructive disease.

	No CAD (N=2656)	Non-obstructive (N=2254)	Obstructive (N=6632)			
			1-V (N=2241)	**2-V (N=1656)**	**3-V (N=1639)**	**LM (N=840)**
Primary outcome						
CV death or hospitalizations for AMI, HF, or stroke	446 (16.8)	468 (20.8)	589 (26.3)	429 (25.9)	375 (22.9)	191 (22.7)
Secondary outcomes, n (%)						
CV death	48 (1.8)	83 (3.7)	106 (4.7)	84 (5.1)	103 (6.3)	70 (8.3)
Hospitalizations for AMI	17 (0.6)	16 (0.7)	207 (9.2)	143 (8.6)	121 (7.4)	43 (5.1)
Hospitalizations for HF	353 (13.3)	342 (15.2)	239 (10.7)	173 (10.5)	130 (7.9)	66 (7.9)
Hospitalizations for stroke	28 (1.1)	27 (1.2)	37 (1.7)	29 (1.8)	21 (1.3)	12 (1.4)
Death of any cause	282 (10.6)	360 (16.0)	392 (17.5)	320 (19.3)	318 (19.4)	181 (21.6)

1-v: one-vessel disease; 2-v: two-vessel disease; 3-v: three-vessel disease; AMI: acute myocardial infarction; HF: heart failure; LM: left main disease; N: number.

Table 6.5. Adjusted Cox model results for the hazard of experiencing the primary and secondary outcomes for non-obstructive CAD and 1-V disease compared to no apparent CAD reference category.

	No apparent CAD	Non-obstructive	1-V
		HR (95% CI) P-value	
Primary outcome			
CV death or hospitalizations by AMI, HF, or stroke	Referent	1.19 (1.05-1.35) 0.006	1.64 (1.25-2.14) <.001
Secondary outcomes, n (%)			
CV death	Referent	1.87 (1.29-2.71) 0.016	2.49 (1.72-3.60) <.001
Hospitalizations for AMI	Referent	1.17 (0.48-2.87) 0.710	14.5 (6.6-32.1) <.001
Hospitalizations for HF	Referent	1.08 (0.93-1.25) 0.341	0.86 (0.71-1.05) 0.170
Hospitalizations for stroke	Referent	1.01 (0.62-1.64) 0.907	1.45 (0.86-2.44) 0.230
Death of any cause	Referent	1.21 (1.08-1.36) 0.001	1.30 (1.15-1.48) <.001

Regression models adjusted for age, sex, place of residence, HF symptoms, angina pectoris, EF, previous HF hospitalization, previous AMI, atrial fibrillation, serum creatinine concentration, diabetes mellitus, hypertension, dialysis, smoking status, hyperlipidemia, previous ischemic stroke or TIA, peripheral vascular disease, COPD, cancer, liver cirrhosis, dementia, depression, and year of catheterization.

1-v: 1-vessel disease; 2-v: 2-vessel disease; 3-v: 3-vessel disease; AMI: acute myocardial infarction; CAD: coronary artery disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EF: ejection fraction; HF: heart failure; HR: hazard ratio; LM: left main; N: number of individuals in each group; ref: reference group; TIA: transient ischemic attack.

Table 6.6. Adjusted Cox model results for the hazard of experiencing the primary and secondary outcomes for 2-V and 3-V disease compared to no apparent CAD reference category.

	No apparent CAD	2-V	3-V
		HR (95% CI) P-value	
Primary outcome			
CV death or hospitalizations by AMI, HF, or stroke	Referent	1.81 (1.45-2.27) <.001	2.12 (1.67-2.70) <.001
Secondary outcomes, n (%)			
CV death	Referent	2.97 (1.94-4.55) <.001	4.81 (2.82-8.2) <.001
Hospitalizations for AMI	Referent	15.3 (7.5-31.5) <.001	16.0 (8.7-29.1) <.001
Hospitalizations for HF	Referent	0.96 (0.81-1.13) 0.690	0.99 (0.82-1.18) 0.824
Hospitalizations for stroke	Referent	1.68 (0.85-3.30) 0.163	1.88 (1.12-3.15) 0.015
Death of any cause	Referent	1.58 (1.38-1.80) <.001	2.36 (1.92-2.89) <.001

Regression models adjusted for age, sex, place of residence, HF symptoms, angina pectoris, EF, previous HF hospitalization, previous AMI, atrial fibrillation, serum creatinine concentration, diabetes mellitus, hypertension, dialysis, smoking status, hyperlipidemia, previous ischemic stroke or TIA, peripheral vascular disease, COPD, cancer, liver cirrhosis, dementia, depression, and year of catheterization.

1-v: 1-vessel disease; 2-v: 2-vessel disease; 3-v: 3-vessel disease; AMI: acute myocardial infarction; CAD: coronary artery disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EF: ejection fraction; HF: heart failure; HR: hazard ratio; LM: left main; N: number of individuals in each group; ref: reference group; TIA: transient ischemic attack.

Table 6.7. Adjusted Cox model results for the hazard of experiencing the primary and secondary outcomes for LM disease compared to no apparent CAD reference category.

	No apparent CAD	LM
		HR (95% CI) P-value
Primary outcome		
CV death or hospitalizations by AMI, HF, or stroke	Referent	2.53 (2.08-3.07) <.001
Secondary outcomes, n (%)		
CV death	Referent	7.4 (4.9-11.3) <.001
Hospitalizations for AMI	Referent	12.3 (7.95-19.0) <.001
Hospitalizations for HF	Referent	1.26 (0.96-1.65) 0.174
Hospitalizations for stroke	Referent	2.42 (1.04-5.6) 0.038
Death of any cause	Referent	3.14 (2.61-3.78) <.001

Regression models adjusted for age, sex, place of residence, HF symptoms, angina pectoris, EF, previous HF hospitalization, previous AMI, atrial fibrillation, serum creatinine concentration, diabetes mellitus, hypertension, dialysis, smoking status, hyperlipidemia, previous ischemic stroke or TIA, peripheral vascular disease, COPD, cancer, liver cirrhosis, dementia, depression, and year of catheterization.
1-v: 1-vessel disease; 2-v: 2-vessel disease; 3-v: 3-vessel disease; AMI: acute myocardial infarction; CAD: coronary artery disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EF: ejection fraction; HF: heart failure; HR: hazard ratio; LM: left main; N: number of individuals in each group; ref: reference group; TIA: transient ischemic attack.

6.5 Discussion

In this study of 12,814 patients with HF and reduced EF undergoing ICA, we found that non-obstructive CAD, which, historically, has been included in the non-ischemic group, was an independent prognostic factor associated with an increased rate of the primary composite outcome of death from CV causes, non-fatal AMI, non-fatal ischemic stroke, and HF hospitalizations in comparison to the group with normal coronaries. Examination of the secondary outcomes revealed that the difference between the non-obstructive group and the apparently normal coronaries group was driven by a significant increase of 82% in the rate of cardiovascular death while the presence of non-obstructive CAD showed no association with non-fatal ischemic events (i.e., AMI and ischemic stroke). It is possible that patients with HF and non-obstructive CAD receive less evidence-based therapies than patients with obstructive CAD and when experiencing coronary events and stroke events, they have more fatal events in contrast to non-fatal events [211]. In addition, patients with non-obstructive CAD had a rate of all-cause death that was 18% higher compared to those with no apparent CAD. In the group with obstructive disease, we observed a significant increase in the hazard of not only cardiovascular death, but also AMI, and ischemic stroke in comparison to those with apparently normal coronaries. These long-term outcomes were worse in those with higher disease burden, as defined by the number of diseased vessels and the presence of LM disease. Interestingly, the presence of non-obstructive or obstructive CAD were not associated with an increased hazard of HF hospitalization.

Most studies examining the prognostic importance of CAD have focused on obstructive disease, but the risks associated with non-obstructive CAD have been underappreciated. Our findings are consistent with recent studies that have challenged the assumption that non-obstructive CAD is prognostically insignificant. Maddox *et al.* demonstrated in almost 40,000 veterans who underwent elective ICA for suspected CAD, that the detection of non-obstructive disease was associated with a greater risk of AMI and death of any cause at 1 year following catheterization.[200] Studies using coronary computed tomography angiography (CCTA) have also suggested a significant, progressive increase in the risk of death and adverse cardiac events with the presence and growing extent of non-obstructive CAD.[201,202,212,213] The event-free survival rate for those patients with non-obstructive disease was intermediate compared to the no apparent CAD and obstructive CAD groups.[214,215] However, none of those studies have specifically examined individuals with HF. Therefore, our study is among the first to demonstrate the prognostic relevance of non-obstructive CAD in the HF population.

The current approach to the classification of HF is to apply a binary definition identifying patients with either ischemic or non-ischemic etiology. The main issue created by this dichotomous approach is the erroneous notion that only the presence of CAD above a fixed threshold increases the risk of death and other adverse outcomes. We demonstrated that this risk exists even in the presence of CAD that would have been previously defined as 'non-significant' or 'non-obstructive'. Based on our findings, we propose that clinicians should use a more nuanced perspective, which acknowledges that the risk of death increases progressively with the presence and extent of CAD. Our findings of graded increases in risk suggest that there is a continuum of atherosclerotic risk in patients with HF.[216]

Further research should examine if an expansion in the assessment of coronary anatomy has an incremental benefit in the prognostication of individuals with HF. While ICA remains the gold standard for the evaluation of the coronary anatomy, catheterization is usually reserved for a small subgroup of HF patients who might be potential candidates for revascularization. However, other cardiac imaging modalities, which are non-invasive and have better sensitivity to detect CAD, could be used in a broader role to stratify different levels of risk based on the extent of CAD. Simultaneously, additional studies should investigate if medical therapy with aspirin and statins can improve outcomes of patients diagnosed with HF and non-obstructive CAD. Preliminary evidence in non-HF populations originated from observational studies carrying the limitations inherent in this type of study design, has suggested that the use of statins may improve clinical outcomes in patients with non-obstructive CAD.[202,217,218] Although, a previous clinical trial of statin in HF have showed no apparent clinical benefits over the primary outcome of CV death, nonfatal AMI, or nonfatal stroke, there was a significant reduction in the number of hospital admission when used in those with an ischemic etiology suggesting that there are still reasons for further studies examining the role of statins among patients with ischemic HF.[219,220]

We had a unique opportunity to examine a large cohort of HF patients with reduced EF by using a registry that includes all ICA performed across the largest province in Canada. A considerable sample size with detailed clinical information allowed us to create multiple exposure categories and explore the association with outcomes after extensive covariate adjustment. However, our study had some limitations. First, we were unable to stratify the group with non-obstructive disease according to the number of diseased vessels, similar to previous publications.[200-202] Despite this, our study offered robust evidence that the presence of non-obstructive CAD increases the risk of CV death. Second, coronary anatomy data were recorded by the operator performing the ICA and there was no centralized review of the angiographic images. As such, misclassification of angiographic findings in the interpretation of the exams was possible.[221] However, a survey of Ontario cardiologists performing catheterization has shown that 69%of them consider a normal angiogram to be 0% stenosis and absence of luminal irregularities.[222] Therefore, the possibility of classifying individuals with non-obstructive CAD as having apparent normal coronary anatomy was small. In addition, a validation study demonstrated very good reliability between the coronary anatomy recorded in the CorHealth Registry and a blinded interpretation of angiographic findings by an interventional cardiologist.[205] As a consequence, misclassification bias would likely have minimal impact on our findings. Third, most individuals in the registry had EF already categorized (using our classification scheme) as opposed to EF recorded as a continuous variable. Therefore, we were unable to examine different cut-off values (i.e., 40%) to define reduced EF. Fourth, medications such as beta-blockers, statins, aspirin, or ACE inhibitors were not measured and therefore were not used for the adjustment of the regression models.

6.6 Conclusions

Among HF patients with reduced EF, the presence of non-obstructive CAD was associated with an increased hazard of the primary composite outcome of CV death or CV hospitalization, and an increased risk of death from any cause, in comparison to individuals with no apparent CAD. Our study underscores the prognostic importance of non-obstructive CAD, suggesting that a binary classification, which dichotomizes the risk of adverse clinical events by assigning non-obstructive disease under the non-ischemic label, may be an inadequate estimator of prognosis in the HF population.

7 CHAPTER 7: SUMMARY AND DISCUSSION

7.1 Research Synopsis

This thesis examined how individuals with a diagnosis of heart failure (HF) are investigated and managed in Ontario, Canada. Based on the linkage of several population-based administrative databases available at ICES, several research projects were conducted. The essential first step was to identify individuals with a diagnosis of HF among the general population, and for this, a case definition consisting of a combination of administrative codes for HF received during a hospital admission or outpatient visit was employed. A major concern when using a diagnostic algorithm is the possibility of case misclassification. However, to abrogate this possibility, a validated case definition was employed, which has been found to have a sensitivity of 84.8% and a specificity of 97% when compared to primary care electronic medical records. While the sensitivity of the definition is imperfect, since even modest compromises in accuracy result in sizeable errors when studying large populations, a major advantage of the definition used is the high specificity. In contrast, an algorithm such as the Framingham criteria, which is based on a combination of symptoms and signs and has been advocated by some as the gold standard method to identify individuals with HF, has a high sensitivity of 97% but a moderate specificity of 79% thus potentially including false positive cases.

In *Chapter 2,* after identifying individuals with HF across the province, the incidence, prevalence, and survival after a new diagnosis of the disease among adults older than 20 years of age was determined. In this chapter, it was reported that every year approximately 40,000 new individuals received a diagnosis of HF and this number remained stable during the study period (38,560 cases in 2002 and 39,754 in 2016; $P = .209$). Meanwhile, the number of individuals living with HF increased by 26%, exceeding 300,000 individuals in 2016 (243,882 in 2002 and 307,023 in 2016; $P < .001$). Analysis of the age- sex- standardized incidence rate demonstrated that the risk of developing HF decreased 32% which was characterized by a dramatic reduction from 380 new cases of HF per 100,000 individuals in 2002 to 256 per 100,000 in 2016 ($P <$ .001). The age- and sex- standardized prevalence rate decreased from 2408 cases per 100,000 individuals in 2002 to 1979 per 100,000 in 2016 ($P < .001$) suggesting that the relevance of HF at the population level is not increasing. Meaningful changes in the epidemiological profile of individuals affected by HF were also observed. Among the group younger than 65 years of age, the annual number of new cases of HF increased from 8,011 in 2002 to 8,751 in 2016 (P <.001), and the total number of cases increased 34% from 50,976 in 2002 to 68,628 in 2016 (P < .001). The age-specific incidence rate of HF remained stable in this age-group ranging between 107 new cases per 100,000 individuals in 2002 and 101 cases per 100,000 in 2016 (P = .282). Meanwhile, the age-specific prevalence increased from 681 cases per 100,000 in 2002 to 792 per 100,000 in 2016 (P < .001).

In *Chapter 3*, the use of non-invasive and invasive cardiac imaging among individuals with HF was examined. It was determined that the investigation of HF is based primarily on the utilization of traditional modalities specifically, rest echocardiography, myocardial perfusion scintigraphy (MPS), and invasive coronary angiography (ICA). Rest echocardiography remained the most used technique exceeding the utilization of any other modality. Alone, echocardiography was responsible for more than 50% of all costs associated with cardiac imaging in HF. Until 2011, a rapid increase in the use of those traditional modalities was observed. After that, there was a decrease in the utilization of echocardiography, ICA, and MPS which coincided temporally with the emergence of advanced techniques which became publicly insured services under the provincial health insurance plan and efforts to improve the appropriateness of the use of cardiac imaging such as an accreditation program for echocardiography. Despite a significant growth in recent years in the utilization of cardiac magnetic resonance imaging (CMRI), coronary computed tomography angiography (CCTA), and cardiac positron emission tomography (CPET), the use of those advanced modalities was responsible for less than 5% of all expenditures with cardiac imaging in HF. Perhaps relatedly, in the last two years of the study period, the overall costs with cardiac imaging in HF stabilized even though the number of prevalent cases of HF has continued to increase.

In *Chapter 4*, the use of ICA, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery among patients with HF was examined. The annual age- sex-standardized utilization rate of ICA increased from 201 procedures per 1,000 HF patients in 2002 to 275 procedures per 1000 in 2009. After 2009, the adjusted utilization of angiography decreased to 252 tests per 1000 remaining stable until experiencing further reduction in the last year of the study period reaching 229 tests per 1000 in 2016. When examining the utilization of coronary revascularization, the age- and sex- standardized rate of PCI climbed from 13 procedures per 1000 new HF cases in 2002 to 33 procedures per 1,000 in 2014 ($P < .001$). This trend was followed by a decline to approximately 26 procedures per 1,000 in 2015 and 2016. Meanwhile, the annual age- sex- standardized use of isolated CABG surgery decreased 35% from 23 procedures per 1000 new HF cases in 2002 to 17 per 1000 in 2016 ($P < .001$). Until 2005, CABG was the preferred coronary revascularization modality for the management of ischemic HF but after 2005, PCI became the most used technique. Despite the impressive increase in the use of PCI, there was no apparent net increase in the utilization rate of revascularization procedures suggesting that PCI is replacing CABG and being used for patients who in the past would have undergone surgical revascularization. There was also a decline in the utilization of both revascularization modalities in the last two years of follow-up. In addition to those trends, we found that the publication of the STICH and the COURAGE trials, which are landmark trials for the management of coronary artery disease (CAD), were not associated to any significant changes in revascularization practice among patients with HF.

In *Chapter 5*, a systematic review of the published literature was conducted to identify classification systems developed to measure the burden of CAD based on the findings of ICA. This review revealed 30 studies proposing 40 different CAD classifications published between 1960 and 2018. Over time, there was progressive incorporation of anatomic details into each new attempt to quantify the extent of CAD in greater detail. According to the anatomic details used, the methods of classification could be divided into four groups: (i) number of diseased vessels, (ii) scores based on segments of coronary vessels affected, (iii) myocardium at risk, and (iv) percutaneous coronary intervention scoring systems. The anatomic features that differed across classifications included the severity of the stenosis used to define a significant obstruction, vessels and branches considered and their importance according to blood flow and area of myocardium supplied, procedure adopted to accommodate left main disease, lesion morphology, and location in the coronary tree. Of the 30 studies included, 12 studies established that left ventricular function was independently associated with survival irrespective of the burden of CAD measured by arteriographic indices. Only four studies that had been conducted to compare the prognostic performance of different CAD classifications making it unclear if additional granularity to measure the burden of CAD offered additional information about the prognosis of individuals with CAD.

Finally, in *Chapter 6*, the prognostic significance of non-obstructive CAD among individuals with HF and reduced ejection fraction was examined using the CorHealth Cardiac Registry as the main data source for the project. The CorHealth registry database records left ventricular function and coronary anatomy for patients undergoing invasive coronary angiography in Ontario. Based on an analysis of more than 12,000 individuals, it was found that the presence of non-obstructive CAD was associated with an increased risk of the primary composite outcome of cardiovascular death, non-fatal acute myocardial infarction, non-fatal stroke, or HF hospitalization (hazard ratio (HR) 1.17, 95% confidence interval (CI) 1.04-1.32, P =0.013) relative to those individuals with normal coronaries. These results were driven primarily by an increased hazard of cardiovascular death (HR 1.82; 95% CI; 1.27-2.62; p = .001) with no significant differences in the rate of AMI, stroke, or HF hospitalization when examined as individual components of the primary outcome. Non-obstructive CAD was also associated with an increased hazard of death from any cause (HR 1.18; 95% CI 1.05-1.33; P = .005). The study underscored the prognostic importance of non-obstructive CAD, suggesting that a binary classification of ischemic and non-ischemic, which dichotomizes the risk of adverse clinical events by assigning non-obstructive disease under the non-ischemic group, is an inadequate estimator of the risk of CAD in the HF population.

7.2 Implications of Present Work

This dissertation has implications for individuals with HF and their families, health care professionals, and administrators. First, in *Chapter 2*, the total number of individuals living with HF is increasing every year surpassing 300,000 in 2016, which may be attributed partly to better prognosis after diagnosis. This rise of individuals living longer with HF will present a challenge to the health care system and strain existing resources since patients will require more cardiac imaging which are key decision-making tools that provide a gatekeeper function to cardiac procedures such as implantable cardiac devices and coronary revascularization, new medications that have been primarily designed for patients with HF with reduced ejection fraction, and the attendant costs of clinical care by healthcare professionals. Another finding of *Chapter 2* was the detection of changes in the epidemiological profile of individuals affected by HF. While the risk of developing HF is decreasing dramatically in the province and the prevalence rate has decreased for most individuals in the province, the group younger than 65 years of age faced the greatest proportional increase in the frequency of HF during the study period with an unaltered incidence rate and a rise in the prevalence rate. These numbers indicate that HF is becoming a larger problem among this age group. Although HF is traditionally described as a disease of the elderly, the observed trends underscore the importance of disease surveillance to plan prevention and care programs for younger individuals affected by this condition.

The findings of *Chapter 3* suggest that, at the present time, initiatives to assess appropriateness of cardiac imaging are most appropriately targeted toward traditional cardiac imaging techniques. Although, with greater utilization, there may be concerns about the costs of advanced cardiac imaging modalities in the future, it is in fact techniques such as echocardiography, myocardial perfusion scintigraphy, and ICA that are largely utilized in daily clinical practice and responsible for most expenditures with cardiac imaging in HF. It is clearly recognized that echocardiography has an important role in HF since the differentiation between HFpEF and HFrEF is a critical initial first step in deciding upon appropriate treatment [223,224]. However, echocardiography alone is responsible for more than 50% of all costs related to cardiac imaging in the HF population while in contrast advanced modalities accounts for less than 5% of costs. This may be due, in part, to the fact that in Ontario, scanners for CMRI, CCTA, and CPET are restricted to major centers which act as naturally limiting factors for the utilization of these techniques.

The publication of standards for the provision of echocardiography and the creation of an accreditation program for echocardiography readers and laboratories were a major step towards the rational use of this important resource with immediate reductions in the utilization of echocardiography and later by a stabilization in the use of this modality. Myocardial perfusion imaging is a time-tested non-invasive modality for evaluation of ischemia with a wealth of prognostic data, making it useful in management of patients with HF [225,226]. As we have demonstrated, ICA is also prognostically important in the patient with HF, in addition to its diagnostic usefulness [227]. However, these too may necessitate measures to ensure good stewardship of these resources.

Another finding was that CPET was the modality with the lowest utilization among all cardiac imaging techniques. Different from all other modalities, CPET has a narrow number of indications covered by the provincial health insurance plan and it requires mandatory prior authorization by a panel composed of radiologists and cardiologists. Whether this practice should be adopted and become standard practice for novel imaging modalities in the future could be an important topic in any discussion regarding the rational utilization of cardiac imaging. A major finding from this thesis is that any research project addressing the consequences of policies implemented to restrain the use of a diagnostic test should consider all modalities that could be used in a specific scenario. Policies can modify physicians' ordering patterns of diagnostic tests in unintended ways leading them to order less restricted imaging techniques. Consequently, the net effect may not necessarily be a reduction in the number of tests and costs.

In *Chapter 4*, it was found that since 2005, percutaneous coronary intervention (PCI) is the favored coronary revascularization strategy among patients with HF. Although PCI can be used to improve symptoms and reduce angina, there are no randomized clinical trials examining the role for PCI over hard outcomes in the management of chronic HF. While PCI has the potential to allow for coronary revascularization with fewer complications than surgical revascularization, this assumption comes from observational studies and subgroup analysis of clinical trials. In addition, there were no significant changes in coronary revascularization practices following the publication of landmark clinical trials related to the management of CAD.

In *Chapter 5*, it was observed that there was a paucity of comparative studies examining the prognostic performance of 40 different classification systems for CAD based on invasive coronary angiography, making it unclear if there was any improvement in prognostication and prediction of adverse health outcomes with the progressive incorporation of anatomic information to quantify the burden of CAD. The few studies performed suggest that no classification system demonstrates clear superiority to estimate prognosis with the predictive ability being virtually the same across classifications. The lack of data comparing different taxonomies of the burden of angiographic CAD could suggest that simple classification methods, that do not require complicated calculations or computer software, may provide enough information to estimate prognosis and guide decision-making in clinical practice for most scenarios involving patients with CAD. Despite the advent of other cardiac imaging modalities that can obtain information about a multitude of parameters related to the coronary circulation and the myocardium, the anatomic burden of CAD remains the most important factor for prognostication and decision-making underscoring the need for a classification system that could stratify patients according to disease risk, estimating short- and long-term prognosis, and determining the need for a coronary revascularization procedure.

In *Chapter 6*, it was demonstrated that non-obstructive CAD, which has been historically considered to have the same prognostic significance as normal coronary arteries, was in fact associated with an increased rate of cardiovascular death and all-cause death. Most studies examining the importance of CAD have focused on obstructive disease and consequently the risks associated with non-obstructive CAD have been neglected. Individuals with non-obstructive CAD have been traditionally defined according to the etiology as 'non-ischemic' under the assumption that non-obstructive CAD was prognostically insignificant. This study challenges this supposition, and suggests that a binary division of CAD is not adequate to characterize the risk among patients with HF. The evidence suggests that instead of an abrupt increase in risk with the presence of obstructive CAD, there is a risk continuum associated with the burden of CAD rising progressively from those with normal coronaries in one end of the spectrum to those with very high risk due to presence of obstructive disease in multiple coronary vessels at the opposite end. Those with non-obstructive CAD have a risk that it is intermediate between the two extremes. Invasive coronary angiography has remained the gold standard for the evaluation of the coronary anatomy and determining the underlying cause of HF. But in clinical practice, this test is usually reserved for a small subgroup of HF patients who might be potential candidates for revascularization. It is possible that an expansion in the assessment of coronary anatomy using ICA might have an incremental benefit in the prognostication of individuals with HF even when coronary revascularization is not being considered imminently.

7.3 Future Directions

Several questions emerged from this work, which may provide directions for further research. Clinical practice has long been based on the biological theory that coronary revascularization could benefit patients with ischemic HF who had viable myocardium. In contemporary practice, management decisions are often guided by the results of diverse cardiac imaging techniques to detect myocardial viability.

The finding of temporal trends in cardiac imaging, and the rising costs of imaging, suggest that more in-depth analysis is required to determine the pathways of clinical imaging in HF patients, ideally from the time of initial diagnosis and throughout their lifetime. This might provide further insights on patterns of current imaging utilization for HF. Furthermore, the indications for cardiac imaging are varied, and it is unknown if cardiac imaging tests are done for assessment of cardiac function and structure, detection of ischemia, or evaluation for myocardial viability. The temporal relations of these tests with coronary angiography is also unknown, and it is also unknown if these tests in fact influence clinical decisions or downstream outcomes.

While the studies in this thesis did not specifically explore myocardial viability, it is an area of potential future research emanating from this work. PET imaging, SPECT studies, and dobutamine stress echocardiography are sometimes ordered for assessment of myocardial viability, but using administrative data, the indications for these tests could not be determined with certainty. The presence or absence of myocardial viability may prompt downstream coronary revascularization procedures. How frequently viability studies are utilized, variations in their use, and their impacts on downstream revascularization procedures in real-world practice, and their effectiveness could be evaluated in future work. However, to do this would require more detailed information on indications for the procedure and the results of the imaging studies, that is, the presence and extent of viability vs. non-viable myocardium. A study that examines myocardial viability may also need to account for additional factors that are reflective of patient prognosis and physician decision-making behaviors. These factors might include presence of contraindications, such as severity and interactions of comorbidities, and their influences on referral for revascularization.

Improvements with coronary revascularization are not driven by the presence and extent of myocardial viability only. In any patient with ischemic HF, there will be variable amounts of normal, ischemic, scarred, and viable myocardium. Viability cannot be interpreted without considering the presence of inducible ischemia and scar. It is necessary to determine if the ratio of jeopardized (i.e., ischemic plus viable myocardium) to scarred myocardium is more important to clinical outcomes than any of the individual components alone. While advanced techniques have been advocated as superior to detect myocardial viability, most studies have not examined how magnetic resonance imaging and positron emission tomography compare to standard testing (i.e., stress echocardiography and myocardial perfusion scintigraphy) for the prediction of clinical outcomes.

The management of patients with ischemic HF remains controversial. Recent data about myocardial viability contradicting accumulated evidence and the lack of improvement in survival with revascularization reported in the ISCHEMIA trial have left many important questions unanswered [196]. To move beyond the current situation in which studies cannot offer definitive answers, the gaps in knowledge need to be filled with high quality studies, including both observational studies and randomized controlled trials.

7.4 Conclusions

The burden of heart failure in Ontario reflects the chronic clinical course of patients living longer with the disease determining a progressive increase in the total number of cases. The investigation of heart failure is based on the utilization of traditional techniques. Rest echocardiography remained the most used technique with rapid increase until 2011-2012 when a province-wide quality improvement initiative was successfully implemented. Although surgical coronary revascularization has been the standard therapy for the management of coronary disease, percutaneous coronary intervention is now the favorite treatment strategy for individuals with heart failure. Classification systems for coronary artery disease based on the number of diseased vessels, although simple, provide enough prognostic information to guide decision-making in most scenarios in clinical practice in comparison to more complex classifications. The presence of non-obstructive coronary artery disease increases the risk of adverse health outcomes suggesting that classifying individuals with non-obstructive disease as non-ischemic underestimates their prognosis.

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APPENDICES

Appendix 2.1. Codes used to identify a diagnosis of heart failure using administrative databases.

Condition	Codes
Heart failure	ICD-9-CM codes 428, 414.8, 422, 425, 429, 402.9 plus 428, and 404.9 plus 428 and ICD-10CA codes I50, I25.5, I40, I41, I42, I43, I11 plus I50, and I13 plus I50

ICD-9-CM: International Classification of Diseases Ninth Revision Clinical Modification; ICD-10-CA: International Classification of Diseases Tenth Revision Canadian enhanced version.

Appendix 3.1. Codes used to identify a diagnosis of heart failure using administrative databases.

Condition	Codes
Heart failure	ICD-9-CM codes 428, 414.8, 422, 425, 429, 402.9 plus 428, and 404.9 plus 428 and ICD-10CA codes I50, I25.5, I40, I41, I42, I43, I11 plus I50, and I13 plus I50

ICD-9-CM: International Classification of Diseases Ninth Revision Clinical Modification; ICD-10-CA: International Classification of Diseases Tenth Revision Canadian enhanced version.

Appendix 3.2. Recommendations for the use of cardiac imaging modalities among patients with heart failure according to the 2013 American guidelines.

Level	Class	Recommendation
I	C	An echocardiogram should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function.
	C	Repeat measurement of LVEF and measurement of structural remodeling are useful to provide information in patients with HF who have had a significant change in clinical status; who have experienced or recovered from a clinical event; or who have received treatment that might have had a significant effect on cardiac function; or who may be candidates for device therapy.
IIa	B	Viability assessment is reasonable in select situations when planning revascularization in HF patients with CAD.
	B	CMRI is reasonable when assessing myocardial infiltrative processes or scar burden.
	C	Non-invasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with *de novo* HF who have known CAD and no angina unless the patient is not eligible for revascularization of any kind.
	C	Radionuclide ventriculography or CMR can be useful to assess LVEF and volume when echocardiography is inadequate.
	C	When ischemia may be contributing to HF, coronary arteriography is reasonable for patients eligible for revascularization.

CAD: coronary artery disease; CMRI: cardiac resonance imaging; HF: heart failure; LVEF: left ventricular ejection fraction. Source: Yancy *et al.* 2013 ACCF/AHA guideline for the management of heart failure.

Appendix 3.3. Codes used to identify modalities of cardiac imaging using administrative databases.

Modality	Codes
Rest echocardiography	G561, G562, G567, G568, G571, G572, and G575[a]
Myocardial perfusion scintigraphy	J607, J608, J609, J666, J807, J808, J809, and J866[b]
Cardiac magnetic resonance imaging	Combination of code X441 for thorax MRI and code X486 for cardiac gating[c]
Cardiac positron emission tomography	J707, J708
Coronary computed tomography angiography	X235
Stress echocardiography	G583 and G584
Invasive coronary angiography	CCP codes 489.4 to 489.8, 499.6 and 499.7 and CCI code 3.IP.10

CCP: Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CCI: Canadian Classification of Health Interventions

a: Codes for rest echocardiography refer to all cardiac ultrasound imaging techniques, including M-mode, 2- and 3-dimensional imaging, and color Doppler.

b: Myocardial perfusion scintigraphy included exercise or pharmacological myocardial perfusion imaging with or without single photon emission computer tomography using either sestamibi or thallium as its radiotracer). Given that perfusion imaging tests may be conducted over 1 or more consecutive days, we applied a 2-day window on either side of the date of a scintigraphy claim to avoid duplicate counting.

c: This combination has been previously validated to identify receipt of cardiac magnetic resonance imaging. Roifman et al. Validation of billing code combinations to identify cardiac magnetic resonance imaging scans in Ontario, Canada. BMJ Open, In press.

Appendix 5.1. Search strategy.

Ovid MEDLINE(R) 1960 to July Week 4 2018			
#	**Searches**	**Results**	**Search Type**
1	cardiac catheterization/	46,019	Advanced
2	coronary angiography/	60,372	Advanced
3	(score$ or index or criteria or indice$ or grading or extent or scheme).mp.	2,582,490	Advanced
4	1 or 2	101,264	Advanced
5	3 and 4	19,647	Advanced
6	limit 5 to humans	19,305	Advanced
7	limit 6 to yr = “1960-2018”	19,301	Advanced

Appendix 6.1. Algorithms and administrative codes used to identify comorbidities.

Condition	Algorithm	ICD-9-CM	ICD-10-CA
Atrial fibrillation	1 hosp	-	I48
Cancer, lymphoma	1 hosp or 2 claims within 2 ys	200-202, 203	C81-C85, C88, C90.0, C90.2, C96
Cancer, metastatic	1 hosp or 2 claims within 2 ys	196-199	C77-C80
Cancer, non-metastatic[a]	1 hosp or 2 claims within 2 ys	153,154, 162, 163, 174, 180, 185	C18-C21, C33, C34, C38.4, C45.0, C46.71, C50, C53, C61, D01.0-D01.3, D02.2, D05, D06, D07.5
CKD	1 hosp or 3 claims within 1 year	583-586, 592	N00-N23
COPD	1 hosp or 2 claims within 2 ys	491, 492, 496	J41-J44
Dementia	1 hosp or 2 claims within 2 ys	290	F00-F03, F05.1, G30, G31.1
Depression	1 hosp or 2 claims within 2 ys	309, 311	F20.4, F31.3-F31.5, F32, F33, F34.1, F41.2, F43.2
Diabetes	ODD was used to identify a diagnosis of diabetes		
Hypertension	HYPER was used to identify a diagnosis of hypertension		
Liver cirrhosis	1 hosp or 1 claim	571	K70.3, K74.3, K74.4, K74.5, K74.6, I85.0, I85.9, I98.2, I98.3, K65.0, K65.8, K65.9, K67.0, K67.1, K67.2, K67.3, K67.8, K76.7, K93.0, R18
AMI	1 hosp	410	I21, I22
PVD	1 hosp or 2 claims within 2 ys	440, 443, 444	I70.2, I73.9, I74.4
Stroke[b]	1 hosp or 1 claim	430, 431, 433-436	G45 (exc G45.4), I63 (exc I63.6), I64

a: Breast, cervical, colorectal, lung, or prostate.
b: Ischemic stroke or transient ischemic attack.
AMI: acute myocardial infarction; CKD: chronic kidney disease; COPD: chronic obstructive lung disease; exc: excluding; hosp: hospitalization; HYPER: Ontario Hypertension Database; ICD-9-CM: International Classification of Diseases 9th revision; ICD-10-CA: International Classification of Diseases 10th revision; ODD: Ontario Diabetes Database; PVD: peripheral vascular disease; ys: years.

Appendix 6.2. Administrative codes used to identify major cardiac and non-cardiac surgical procedures.

Surgical Procedure	CCI code
Cardiac	
Coronary artery bypass graft	1.IJ.76
Non-cardiac	
Abdominal aortic aneurysm repair	1.KA.76†
Carotid endarterectomy	1.JE.76 (excluded if combined with 1.IJ.76)*
Cystectomy	1.PM.891.PM.90, 1.PM.91, 1.PM.92
Gastrectomy/esophagectomy	1.NF.87 1.NF.89, 1.NF.90 1.NF.91, 1.NF.92, 1.NA.87, 1.NA.88, 1.NA.89, 1.NA.90, 1.NA.91 1.NA.92
Large bowel	1.NM.87 (exclude 1.NM.87.BA)‡, 1.NO.89, 1.NO.90, 1.NM.89, 1.NM.91
Liver resection	1.OA.87
Nephrectomy	1.PC.87, 1.PC.89, 1.PC.91
Pancreaticoduodenectomy	1.OK.87, 1.OK.89, 1.OK.91
Peripheral arterial bypass	1.KG.76, 1.JM.76.MI, 1.KT.76, 1.KG.80
Pneumonectomy	1.GT.89
Pulmonary lobectomy	1.GT.87
Total hip replacement	1.VA.53
Total knee replacement	1.VG.53

* Excludes concurrent coronary artery bypass graft; †excludes aortic rupture; ‡excludes per-orifice approach.
CCI: Canadian Classification of Intervention.