NON-INVASIVE CARDIAC DIAGNOSTIC TESTS IN ONTARIO: TEMPORAL TRENDS IN UTILIZATION AND ASSOCIATION WITH OBSTRUCTIVE CORONARY ARTERY DISEASE

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science (Clinical Epidemiology) Institute of Health Policy, Management and Evaluation University of Toronto

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Abstract

Contemporary temporal trends in utilization of graded exercise stress test (GXT), myocardial perfusion scanning (MPI), stress echocardiography (stress echo), and cardiac computed tomography angiography (CCTA) are unknown. The optimal initial testing strategy to evaluate stable coronary artery disease (CAD) is also unknown. We conducted a repeated cross sectional study of the adult population of Ontario in order to assess the temporal trends in utilization of these modalities and a retrospective inception cohort study in order to compare the relationship between differing initial testing strategies and the presence of obstructive CAD on downstream angiography. Our results indicate stable utilization patterns for GXT and MPI. We had insufficient data to make definitive conclusions regarding the temporal trends for CCTA and stress echo. An initial diagnostic strategy consisting of CCTA, MPI or stress echo was not significantly different than an initial strategy with a GXT in detecting obstructive CAD on downstream angiography.
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Chapter 1: Background

1.1 Coronary artery disease – incidence, prevalence and mortality

The incidence of coronary artery disease (CAD) has decreased over the past 3-4 decades in developed countries. The National Health and Nutrition Examination Survey Epidemiological Follow Up Study reported that the incidence of CAD dropped from 133 to 114 cases per 10,000 persons per year of follow up in a period between 1982-1992 when compared to the period between 1971 to 1982. A Mayo clinic report from Olmstead County, Minnesota reported a reduction in the age-adjusted incidence of CAD from 57 to 50 cases per 10,000 persons. The prevalence of CAD has remained stable in Canada over the past several years. Unpublished data from the Canadian Cardiovascular Health Survey suggests that self-reported prevalence of CAD has remained relatively stable from 5.30% in 2003 to 5.22% in 2011. In addition to a stabilization or drop in disease specific prevalence and incidence, there has also been a reduction in disease specific mortality. In fact, mortality rates for CAD have declined by approximately 40-50% since 1975. Despite the temporal trends in disease prevalence, incidence and mortality, CAD remains a major public health problem. The 2010 American Heart Association Heart Disease and Stroke Statistics Update reported that there are approximately 17.6 million people in the United States who have been diagnosed with CAD. CAD remains the cause of approximately 30% of all deaths worldwide in people aged 35 and above and approximately 17% of total deaths. Overall, the World Health Organization estimates that 17.4 million people worldwide died of CAD in 2012. In Canada alone, cardiovascular disease is estimated to cost the Canadian economy $20.9 billion every year in physician services, hospital costs, lost wages and decreased productivity. Given the societal costs of CAD there has been widespread interest
in developing safe and effective diagnostic modalities in order to diagnose the disease at a stage where it more easily treatable with the hopes of reducing downstream disease related complications.

1.2 Non-invasive cardiac diagnostic tests

The current gold standard for diagnosis of CAD is invasive coronary angiography. However, invasive angiography has an overall risk of major complications of approximately 1.7%, including an approximate 1/1,000 risk of death \(^9\text{-}^{12}\). Moreover, recent American registry data reported that between 2004 and 2008, only 38% of those who underwent elective angiography had obstructive CAD \(^{13}\). Thus, patients may be exposed to risk unnecessarily. In order to reduce this risk, there has been longstanding interest in developing safe and effective non-invasive cardiac diagnostic tests for CAD. The first such test was the graded exercise stress test (GXT). The standard modern GXT protocol was first described in 1949 by Robert Arthur Bruce \(^{14}\). The basic idea of the test is that patients with obstructive CAD often do not have coronary flow limitations at rest. During stress, as myocardial oxygen demand increases, the diseased and stenotic coronary arteries are unable to supply the necessary oxygen to the myocardial tissue, resulting in the ischemia and leading to classic anginal symptoms and also diagnostic changes on electrocardiography (ECG). The GXT involves use of motorized treadmills and real-time cardiac electrocardiography monitoring via information transmitted from electrodes attached to the body \(^{15}\). The patient undergoes graded exercise on the treadmill with gradually increasing workload. Stress induced diagnostic ST segment changes on the ECG combined with anginal symptoms are then primarily used to indicate the presence of ischemia and underlying obstructive coronary artery disease. The GXT cannot be used in patients with significant baseline ECG abnormalities or in patients who cannot exercise. Over the last several decades, other modalities have been developed in order to attempt to improve upon the GXT. One approach involves adding an
imaging component to the standard stress test. This approach led to the development of myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) and stress echocardiography (stress echo). Myocardial perfusion imaging with SPECT involves analyzing myocardial perfusion during rest and stress in addition to analyzing ECG changes. Stress induced reduction in ejection fraction, left ventricular dilatation or perfusion deficits are all imaging parameters that can indicate underlying ischemia and obstructive coronary artery disease. In addition to its purported advantages in patients able to exercise, the use of MPI with the vasodilating agents adenosine or dipyridamole allows for the assessment of significant coronary stenosis in those unable to exercise. Stress echocardiography involves taking ultrasound images of the left ventricle at rest and then during peak stress. In addition to ECG changes of ischemia, stress induced reductions in ejection fraction and regional wall motion abnormalities may also indicate the presence of potential ischemia. In addition to providing an alternate mechanism to assess ischemia, both stress induced hypoperfusion (assessed with MPI) and wall motion abnormalities (assessed with stress echo) precede the development of ECG abnormalities and symptoms in the ischemic cascade thus potentially allowing clinicians to diagnose ischemia at an earlier stage of exertion 14.

Another approach involves a non-invasive anatomic assessment of the coronary arteries, most accurately performed with cardiac computed tomography angiography (CCTA). Computed tomography technology was introduced to the medical community in the early 1970s. Initially, the technology involved a simple x-ray source that would emit ionizing radiation across a patient’s body that would ultimately strike a detector. This signal was then used to generate images. Initially, the resolution was not sufficient to accurately detect coronary artery stenoses. The subsequent development of electron-beam computed tomography (CT) in the 1980s allowed for improvements in temporal resolution as well as rapid image acquisitions. However, it was not
until the mid 1990s when multidetector CT was developed, allowing for images to be acquired in three planes (z as well as the x and y), that CCTA use for the assessment of coronary stenosis became feasible for routine clinical use. Over the years, the number of CT detector rows increased from 4 in 2001, to 64 in 2005 to 256 in 2008. Today’s CCTA technology allows for direct anatomical visualization of the epicardial coronary arteries as opposed to the assessment of functional consequences thereof (such as stress induced wall motion abnormalities, perfusion deficits, ECG changes and chest pain).

Disadvantages to using MPI or CCTA when compared to stress echo or GXT include the ionizing radiation that is emitted and absorbed by the patients’ bodies in the case of the former two. The contemporary prospectively gated CCTAs emit between 2.4-4.2 millisieverts (mSv) of radiation. For MPI with technetium-99 the radiation emission is between 9.2-14.8 mSv while for an MPI scan with thallium-201 the emission is between 15.7-18.9 mSv. The clinical significance of this amount of radiation is unclear. Of note, annual background radiation is approximately 3 mSv (approximately the same as a well performed prospectively gated CCTA). Estimates of cancer risk from radiation exposure are based primarily on statistical modeling and extrapolation based on data from the known radiation related health effects on atomic bomb survivors in Japan. Retrospectively gated CCTAs have been linked to accelerated rates of thoracic malignancies based on these modeling studies. For example, the lifetime attributable risk of breast cancer after a retrospectively gated CCTA study was estimated to be approximately 0.70% in 20-year-old women compared with 0.075% in 80-year-old women.
1.3 Temporal trends in the utilization of non-invasive cardiac diagnostic tests

Please see Appendix 1 for our search strategy for this section. Literature search strategies have been provided for this section and for section 1.5 as these two topics formed the bulk of the body of the thesis.

**Ontario**

Available Ontario data regarding the temporal trends of non-invasive cardiac diagnostic tests for CAD suggest an increase in utilization over time for GXT and MPI. Alter et al. (2006) reported an increase in utilization rates of GXT and MPI in Ontario between the years 1992-2001 with an annual relative rate of increase of 2% in GXTs and 7% in perfusion scans performed during that time frame. Age- and sex-standardized rates of GXTs and MPIs climbed from 15.9 to 21.9/1,000 and from 5.1 to 11.1/1,000 respectively during that time frame. In 2008, the Ontario Health Technology Assessment Committee reported an approximately 50% increase in the volumes of MPI in Ontario between the years 2004-2008. Standardized rates were not reported. There were no studies examining trends in utilization patterns from 2009 and onwards. Further, there is no published data available from Ontario regarding the temporal trend utilization patterns of CCTA or stress echocardiography since the introduction of their respective billing codes in 2011. However, a recent study examining outpatient resting transthoracic echocardiograms reported that age- and sex-standardized rates of echocardiography grew from 39.1 per 1,000 persons in 2001 to 59.9 per 1,000 persons in 2009, for an annual relative rate of increase of 5.5%.

**International**

The majority of published temporal trend studies in utilization have evaluated myocardial perfusion imaging. These studies indicate a trend of increasing utilization patterns from the
1990s until the mid to latter 2000s, after which there appears to be a stabilization or reduction in utilization. Lucas et al., examined American Medicare recipients aged ≥ 65 years from 1993-2001. They reported a nearly 3-fold increase in the use of MPI (from 29 to 82 per 1,000 beneficiaries) with a mean annual increase of 6.1 tests per 1,000 beneficiaries per year. Another study of American Medicare recipients between the years 1999-2008 reported a 3.2 fold increase in the utilization of MPI (from 68.1 to 218.5/1,000) in studies billed by cardiologists. A Taiwanese study, using data from Taiwan’s National Health Insurance research database, reported a 45% increase in MPI utilization between the years 2005-2009 from 3,008/million (3.0/1,000) people to 4,371 (4.37/1,000) people. Taiwan has a population of approximately 23 million people and has a universal single payer healthcare system that is similar to Canada. In contrast to older data, more recent data indicate a reduction in MPI utilization. A recent Medicare study reported a drop in MPI utilization rates to 76.9/1,000 in 2010 when compared to a peak of 88/1,000 in 2006, representing a 13% reduction. Another recent American study examining clinical data from Kaiser Permanente Northern California health care insurance patients (approximately 2.3 million adults), reported that MPI utilization declined by 51% between the years of 2006-2011.

There is much less international data available on the utilization rates of GXT, stress echo and CCTA especially after 2008. A Medicare study examining cardiologist billings between 1999-2008 reported a 1.5-fold increase in GXT (from 86.1 to 103.9/1,000) and a 10% increase in stress echo (from 10.8 to 12.1/1,000) utilization during that time frame. Further, a recent paper examined the temporal trends in CCTA utilization amongst Medicare patients. They found an increase of 64% from 58,124 to 95,269 tests performed over approximately two years from 2006-2008. Standardized rates were not reported in this study. In summary, international trends indicate increased utilization over time for all four modalities with the exception of MPI.
utilization in recent years.

1.4 Clinical efficacy and effectiveness of MPI, CCTA, and stress echo

A recent workshop sponsored by the National Heart Lung and Blood Institute at the National Institutes of Health reporting on outcomes research in cardiovascular imaging highlighted the importance of the difference between assessing the clinical efficacy and effectiveness of cardiac imaging modalities. Efficacy was defined as the “performance characteristics of a test under ideal conditions performed and interpreted by experts”. In contrast, effectiveness “refers to test performance under “real-life” situations” 30-33. Much of the available literature on cardiac non-invasive diagnostic testing focuses on the assessment of clinical efficacy. The clinical efficacy studies for cardiac non-invasive modalities typically used the presence of obstructive CAD on angiography as the gold standard test. Sensitivities for GXT have been reported in the range of 45-68% with specificities reported in the 77-85% range 14, 34-36. The 2003 ACC/AHA/ASNC Radionuclide Imaging Guidelines pooled the sensitivities and specificities of 4480 subjects derived from 33 different studies for MPI. They reported a pooled sensitivity to detect CAD was 87% (range 71-97%), and a pooled specificity of 73 percent (range 36%-100%) for MPI with sestamibi or thallium tracers 37, 38. For stress echo, sensitivities of 56-85% and specificities of 61-88% have been reported 14, 39, 40. For 64-slice CT scanners, the reported sensitivities and specificities were in a much narrower range. The sensitivity of CCTA ranged from 86-99% and specificity ranged from 95-98% 41-47. The position statement discussed above advocated for more future studies assessing clinical effectiveness of cardiovascular imaging modalities and was subsequently endorsed by major imaging societies and jointly published in the major mainstream cardiovascular imaging journals of JACC Cardiovascular Imaging, Circulation Cardiovascular
1.5 **Real world results on angiography; yield of obstructive CAD**

Please see Appendix 2 for our literature search strategy for this section. The optimal endpoint to assess clinical effectiveness in studies of cardiac non-invasive imaging modalities is controversial. While the assessment of ‘hard’ cardiovascular endpoints such as mortality or myocardial infarction is important, their link to a diagnostic test is often complicated by multiple other patient factors and clinical decisions that are not related to the diagnostic test performance itself. In recent years the concept of using the results of the angiogram (normal, non-obstructive CAD and obstructive CAD) as the outcome measure designed to assess the clinical effectiveness of preceding cardiac diagnostic tests has emerged. Multiple studies have linked obstructive CAD to mortality. There is a dearth of real-world studies comparing the yield of obstructive CAD amongst different modalities. Further, the work that is available clusters tests into groups such as “anatomic” vs. “functional” rather than assessing each modality separately. For example, the PROMISE trial reported that although more patients underwent downstream invasive catheterization, there were significantly less diagnostic angiograms showing non-obstructive CAD in the anatomical (CCTA) vs. the functional (combination of stress echo and MPI) groups. Another recent study concluded that the cardiac imaging strategy (involving a combination of CCTA, MPI and stress echo) resulted in fewer invasive angiograms and a higher yield of obstructive CAD when compared to a strategy of GXT testing alone.

1.6 **Preferred initial cardiac non-invasive diagnostic test for evaluation of stable CAD**

The optimal initial strategy to evaluate patients with suspected stable coronary artery disease is
currently unclear. The 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease recommend GXT as the first line test in patients who are able to exercise in the absence of significant ST-T wave abnormalities. In contrast, the 2013 and 2014 European Society for Cardiology guidelines on stable coronary artery disease and revascularization consider CCTA, GXT, MPI and stress echocardiography all as class 1 indications for the evaluation of patients with stable ischemic heart disease. It is important to note that these recommendations are based on low quality evidence. The reason behind the difference in the European and American approaches may be a consequence of the low quality of evidence that is currently available regarding the optimal initial testing strategy. We speculate that another potential factor that may be contributing to the different recommendations may be the greater clinical availability of stress imaging and CCTA in many western European countries when compared to many jurisdictions in North America.

1.7 Gaps in current knowledge

1. There is limited work on the temporal trends in the utilization of cardiac diagnostic non-invasive tests, especially after 2008. In addition, little is known regarding the temporal trends of the physicians who order these tests or the patients who undergo them. Further, to the best of our knowledge, the temporal trends of CCTA, GXT, MPI and stress echo have not been examined head-to-head at the level of the adult population.

2. The vast majority of the studies on cardiovascular imaging/diagnostic testing in the literature have evaluated clinical efficacy. There is a lack of knowledge on clinical effectiveness, especially comparative effectiveness assessing the real-world performance of multiple modalities. There is limited work regarding the relationship between these cardiac non-invasive tests and downstream findings on coronary angiography in the real-world. Specifically, as far as we know, there are no population-based studies that have compared the yield of obstructive CAD
amongst the four initial testing strategies of CCTA, GXT, stress echo and MPI in patients being evaluated for stable angina.

1.8 Importance

Rapid growth in healthcare costs have provided the impetus for understanding utilization patterns of diagnostic tests as well as conducting real-world research to compare their effectiveness. Specifically, the costs of medical imaging have risen sharply in recent years. In the United States for example, Medicare part B costs have increased from 6.89 billion dollars in 2000 to 14.11 billion dollars in 2005. Concern about the potential overuse of diagnostic tests contributing to these costs has led to the development of initiatives such as the Choosing Wisely Canada campaign. This government supported campaign is geared towards both patients and physicians and aims to reduce unnecessary medical tests, treatments and procedures. The campaign has led to recommendations by representatives of numerous medical specialties including cardiology. Further, a recent ACC/AHA statement recommended that consideration be given for inclusion of utilization data in guideline statements as one metric of assessing value. In these contexts, it is important to examine how the utilization of non-invasive cardiac diagnostic tests has changed over time. This is especially important in the context of stable or potentially decreasing CAD prevalence and incidence. One should not expect a sharp increase in utilization of non-invasive cardiac diagnostic tests in this setting. Further, physician self-referral has become an important issue over the past several years. Physician self-referral is a term describing the practice of a physician ordering tests on a patient that are performed by the referring physician him or herself. This potential financial incentive may lead to a physician ordering and performing tests that he or she may not otherwise order or perform. A study from 2007 reported that physicians who self-referred were up to three times more likely to perform imaging tests when compared to those who did not self-refer. A 2004 editorial estimated that
unnecessary tests ordered through self-referral may cost the US healthcare system approximately 16 billion US dollars annually. Therefore, it is also important to examine the proportions of non-invasive cardiac diagnostic tests that are attributable to self-referral and how they change over time. We believe that knowledge regarding trends in utilization and self-referral will help inform future guideline writers and policy makers when making funding allocation decisions by providing insight into areas where particular practice decisions can either be incentivized or discouraged.

Furthermore, in the context of rapidly increasing costs and concern for testing overlap and overuse, the evaluation of comparative clinical effectiveness is important in order to assess the real-world impact of diagnostic tests. The Institute of Medicine in the United States has defined comparative effectiveness research as: "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and/or monitor a clinical condition or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels". There is currently a lack of comparative effectiveness studies examining different initial non-invasive diagnostic strategies in the evaluation of patients for stable CAD. Consequently, the ideal strategy is currently unknown. Obstructive CAD based on invasive angiography is important both prognostically and to help direct future management. However, it would be desirable to reduce the number of unnecessary angiograms, both due to costs and due to potential procedure related risks. An improvement in the yield of obstructive CAD would therefore be desirable. Thus, comparing the real-world yield of obstructive CAD amongst different initial non-invasive diagnostic strategies is important.
1.9 Objectives

1. To describe the temporal trends in the utilization as well as the characteristics of the physicians who perform and the patients who undergo GXT, CCTA, MPI and stress echo in Ontario between the calendar years of 2008-2013. In order to address objective 1, we conducted a population based repeated cross sectional study of the population of Ontario aged 20 and above (please see chapter 2 for details).

2. To describe the relationship between the index non-invasive test (GXT, CCTA, MPI and stress echo) and obstructive CAD on angiography (yield of obstructive CAD) in patients evaluated for stable angina. To address objective two we designed an inception cohort for the 2012 calendar year where individual patients were tracked from their index event (receipt of their first non-invasive diagnostic test) for a maximum of 6 months in order to assess for outcomes (please see chapter 3 for details).

1.10 Hypotheses/Research Questions

1. We hypothesized that the temporal patterns in utilization of all cardiac non-invasive diagnostic tests will be similar to what has been reported in other international jurisdictions during comparable time-frames, when that information was available.

2. We hypothesized that a diagnostic strategy with an initial CCTA, stress echo or MPI would have a higher yield of obstructive CAD when compared to one with an initial GXT. This hypothesis is based on the reported advantages of the former three over GXT in clinical efficacy studies performed under ideal conditions. Moreover, we expected those with an index CCTA to have the highest yield of obstructive CAD based on the superior accuracy demonstrated in efficacy studies when compared to the other modalities.
Chapter 2: Temporal trends of cardiac non-invasive diagnostic tests in Ontario, 2008-2013

2.1 Background

Coronary Artery Disease (CAD) remains a leading cause of death in North America and is currently the number one cause of death worldwide. In fact, according the World Health Organization, an estimated 7.4 million people died from CAD in 2012, representing 17% of all global deaths. Prompt diagnosis is essential to prevent future complications of the disease. Invasive angiography, the current gold standard method to diagnose CAD, is associated with multiple potential complications including a 1/1,000 risk of death. Thus, there has been long-standing interest in developing safe and effective methods to diagnose CAD non-invasively. Recently, the province of Ontario began funding two new non-invasive CAD diagnostic tests; stress echocardiography (stress echo) and coronary computed tomography angiography (CCTA). These join the more established technologies of myocardial perfusion scanning (MPI) and graded exercise stress testing (GXT). The rapid increase in utilization of cardiac diagnostic procedures over the past few decades has received substantial attention from both researchers and policymakers in Canada and the United States. As competition for healthcare resources intensifies and concerns regarding diagnostic test overuse have emerged, initiatives have been developed such as the Choosing Wisely Canada campaign aimed at limiting unnecessary tests, treatments and procedures. It is important to understand how utilization of these tests have changed over time in order to inform policy makers regarding funding allocation decisions. To our knowledge, no studies have assessed the temporal trends in utilization of all clinically available technologies (CCTA, MPI, GXT and Stress Echo) at the adult population level. Thus,
our objective was to examine the temporal trends in utilization as well as the characteristics of patients who undergo and physicians who refer and perform CCTA, MPI, GXT and stress echo in Ontario between the years 2008-2013.

2.2 Methods

2.2.1 Design

We performed a population-based repeated cross sectional study of the population of Ontario aged 20 and above from January 1, 2008 until Dec 31, 2013.

2.2.2 Data sources

The Ontario Health Insurance Plan (OHIP) Physicians Claim Database contains Ontario physician billing claims submitted to OHIP from July 1, 1991. The database contains encrypted physician and patient identifiers, information regarding fee codes for service provided and date of service. Information regarding receipt of non-invasive cardiac testing for our study was obtained through medical claims data from the OHIP claims database between January 1, 2008 until December 31, 2013. Receipt of a cardiac non-invasive diagnostic test was identified with the professional component of physician claims data. For MPI, both exercise and tests involving pharmacological vasodilators were included. Codes for receipt of non-invasive tests are summarized in Table 1. When possible, we used codes that have been previously utilized in other studies. Given that perfusion imaging tests may be conducted over one or more consecutive days, we applied a two-day window on either side of the date of an MPI claim to avoid duplicate counting similar to previous studies by other investigators. Further, physicians performing echocardiograms typically bill both the stress echocardiography and GXT codes. Thus, when
both stress echocardiograms and GXTs were billed on the same day they were considered as stress echocardiograms only. Dobutamine stress echos were excluded from the study.

The Registered Persons Database was used to obtain demographic information including age, sex, and geographic location. Patients’ postal codes of residence were taken from the Registered Persons Database. Postal codes were linked to the Census Area Profile using the Postal Code Conversion File to obtain median neighborhood income and urban density in a manner previously described. Physician specialty was determined by linking the OHIP database with the Institute for Clinical Evaluative Sciences (ICES) physician database (IPDB). The IPDB contains information from the OHIP physician claims database and the OHIP corporate provider database (CPDB). The CPDB contains information regarding physician demographics and specialty. This information is validated against the Ontario Physician Human Resource Data Centre (OPHRDC) database. The OPHRDC conducts periodic telephone interviews with practicing physicians in Ontario. Hospitalizations were determined using the Canadian Institutes for Health Information discharge abstract (CIHI-DAD) database. The CIHI-DAD database is an administrative database containing summary data of discharge abstracts of every inpatient hospital admission. Rural status was defined as a population of <10,000 residents. We used the 2006 population of Canada for standardization purposes. Data for this was obtained from an existing ICES population file with source data provided by Statistics Canada.

### 2.2.3 Statistical analysis

Population-based rates of non-invasive cardiac diagnostic tests were computed by year by dividing the number of procedures by the corresponding adult population of Ontario and estimated per 1,000 individuals. Age and sex standardized rates were obtained through direct standardization with the 2006 Canadian population as previously described. Five-year age
bands were used beginning at age 20. Patients aged 90 and over were grouped together. Test specific patient and physician characteristics were compared over time using the chi square test or Fisher’s exact test as appropriate for categorical variables and analysis of variance (ANOVA) for continuous variables. Further, patient and physician characteristics were compared in a similar manner between the four non-invasive tests for the calendar years 2011-2013. For each cardiac testing modality, a negative binomial regression model was used to compare counts between years during the study period. First, for each cardiac test, the data was manipulated to create a dataset with age group and sex specific strata according to the year that the test was performed. Five year age groups were used and were identical to the age bands used in the standardization procedure and described above. In each strata, the total number of tests for each diagnostic test were tallied. The dependent variable was the stratum specific annual number of tests. Year, sex and age were predictor variables. There was an offset for the stratum specific population. The average annual change in age and sex adjusted rates was calculated by the following equation: 

\[ P = ((f/s) ^ (1/y))-1 \]

Where \( f \) = final value, \( s \) = starting value and \( y \) = number of years \(^{77}\). A two-tailed value of \( p<0.05 \) was considered statistically significant.

Analyses were performed with SAS V 9.3 (SAS Institute Inc., Cary, North Carolina, USA). This study was approved by the research ethics board at Sunnybrook Health Sciences Centre.

### 2.3 Results

#### 2.3.1 Temporal trends of CCTA in Ontario; 2011-2013

Table 2 summarizes the utilization as well as characteristics of patients receiving and physicians performing CCTAs in Ontario. The CCTA billing code was introduced by the government of Ontario on April 1, 2011 \(^{78}\). Our data includes all CCTAs billed on adults in Ontario from April 1, 2011 to December 31, 2013. Since introduction of the code, there were 15,217 studies billed.
The top 3 performing specialties were diagnostic radiology (83.1%), cardiology (12.9%) and nuclear medicine (2.1%). Over the study period, there was a significant reduction in the percent of CCTAs being reported by radiologists with progressively more being reported by cardiologists. In terms of referring specialties, the top 3 specialties were cardiology (76.9%), cardiac surgery (7.3%) and internal medicine (5.0%). While cardiologists still performed the vast majority of the referring (77.6% in 2013), there was a significant trend towards more cardiac surgeons and internists referring for CCTAs over time. Overall, the proportion of tests attributable to self-referral was only 1.4%, however, there was a significant trend towards a higher percentage of self-referral over the study period (0.4% to 2.2%, \( P<0.0001 \)). There was a significant income gradient amongst the patients undergoing CCTAs, with a disproportionate number of scans performed in the highest income quintile (Approximately 24.5% of CCTAs were performed on patients living in the wealthiest 20% of Ontario’s neighborhoods). CCTAs were performed on progressively less acutely ill patients over time, as defined by the reduction of those scans performed on patients who were admitted to hospital within 30 days of the scan (12.8 to 10.7%, \( p=0.004 \)).

### 2.3.2 Temporal trends of GXT in Ontario; 2008-2013

Temporal trends in the utilization as well as characteristics of patients receiving and physicians performing GXT in Ontario are summarized in Table 3. We assessed all GXTs performed on adults in Ontario from January 1, 2008 to December 31, 2013. Over the study period, 1,768,259 GXTs were billed in Ontario. Progressively more females underwent GXT over time (40.2% to 42.1%, \( p<0.0001 \)). There was a significant reduction in the proportion of GXTs being done in rural centres (from 12.1% to 10.3%, \( p<0.0001 \)). In terms of performing specialties, the top 3 were cardiology (67.8%), internal medicine (18.2%) and family medicine (4.8%). Over time,
there was a significant increase in the percentage of cardiologists performing GXT. With respect to referring specialties, the top 3 were family medicine (63.6%), cardiology (19.9%) and internal medicine (7.4%). Over time there was a small but statistically significant increase in the percentage of family physicians and cardiologists referring for GXTs with a small reduction in internist referral. On average, the proportion of tests attributable to self-referral was 23.1%. However, there was a significant downward trend in self-referral over time (23.6% to 22.4%, \( p<0.0001 \)). An income gradient was observed where 21.3% of all GXTs were performed on those living in the wealthiest 20% of Ontario’s neighborhoods. However, there was a trend towards a more equal distribution amongst the different income strata over time. There was a significant trend towards lower 30-day hospitalizations amongst those patients who had GXTs performed (1.9% to 1.7%, \( p<0.0001 \)).

2.3.3 Temporal trends of MPI in Ontario; 2008-2013

Temporal trends in the utilization as well as characteristics of patients receiving and physicians performing MPI in Ontario are summarized in Table 4. We assessed all MPIs performed in Ontario from January 1, 2008 to December 31, 2013. During that time, there were 1,318,681 MPIs performed. Over time, significantly more females were scanned (50.3% vs. 48.6%, \( p<0.0001 \)). The top 3 performing specialties were nuclear medicine (57.7%), cardiology (23.3%) and diagnostic radiology (16.4%). Over time, there was a significant reduction in MPIs read by nuclear medicine and a significant increase in those read by cardiology and diagnostic radiology. In terms of referring specialties, the top 3 were family medicine (36.3%), cardiology (32.3%) and internal medicine (9.1%). The proportion of MPIs that were attributable to self-referral have increased significantly throughout our study period (from 8.9% in 2008 to 10.0% in 2013). There was a fairly even distribution of tests amongst the income quintiles with 19.6% of the tests being
performed in the lowest income quintile and 19.5% in the highest one. Furthermore, over time there was a significant trend towards greater equality of distribution across the income strata. For example, the top income quintile accounted for 20% of all MPIs in 2008 and 19.3% of all MPIs in 2013 (p<0.0001). Approximately 9.5% of MPIs were performed in rural areas. This percentage has significantly increased over the study period (from 8.9% to 10.0%, p<0.0001). Hospital admission rates within 30 days have also increased significantly over time from 4.7% to 5.4% (P<0.0001).

2.3.4 Temporal trends of stress echocardiography in Ontario; 2011-2013

Temporal trends in the utilization as well as characteristics of patients receiving and physicians performing stress echocardiography in Ontario are summarized in Table 5. The stress echo billing code was introduced on September 1, 2011 in Ontario. Since that time, there have been 152,791 stress echos performed. Mean age for those undergoing stress echo has come down over time (59.2 ± 13.2 to 58.7 ± 13.5 years, p<0.0001). There was no significant change in sex distribution of the tests over time. The top 3 performing specialties were cardiology (87.1%), internal medicine (5.7%), and family medicine (1.9%). Over time there was an increase in internists and a significant reduction in cardiologists performing stress echos (p<0.0001). The top 3 referring specialties were family medicine (64.1%), cardiology (28.6%) and internal medicine (1.5%). Over time, there has been a significant reduction in cardiologists referring for stress echo and an increase in family physician and internist referrals. The proportion of stress echos attributable to self-referral was approximately 23.1% since implementation of the stress echo billing code. There was an income gradient where 21.7% of the stress echos were performed on patients in the top income quintile while 19.6% were performed on the bottom quintile. There was no significant change in the temporal trends of income distribution of stress echo over time.
Overall, 9% of the stress echos were performed in rural areas. Over time, there was a significant trend towards less stress echos being performed in rural areas (10.3% vs. 8.2%, p<0.0001).

2.3.5 Head-to-head comparison of MPIs, CCTAs, GXTs and stress echos performed in Ontario, 2011-2013

Table 6 summarizes the results of the head-to-head comparison of patient and physician characteristics of MPIs, CCTAs, GXTs and stress echos performed in Ontario for calendar years 2011-2013. We analyzed data for 2011-2013 only as these were the calendar years where all modalities were billable in Ontario. A total of 1,757,009 tests were performed during that time. Patients undergoing MPI had the highest mean age when compared to those undergoing the other tests. Mean age for MPI was approximately 63.2 years and was more than 3 years older, on average, than the next highest modality. MPIs were performed on the highest percentage of females. In the MPI group, 50.2% of tests were performed on females compared to 42.7% of CCTAs, 41.9% of GXTs and 45.7% of stress echos, (p<0.0001). Those undergoing CCTA had the highest number of hospital admissions within 30 days (11.6% vs. 5.2% for MPI, 1.7% for GXT and 1.9% for stress echo (p<0.0001)). A greater proportion of CCTAs were performed on patients in the highest income quintile (24.5%) compared with 19.3% of MPIs, 21.0% of GXTs and 21.7% of stress echos (p<0.0001). In terms of urban/rural distribution of the tests, a greater proportion of GXTs were performed in rural areas (10.8%). In comparison, 10.7% of CCTAs, 9.9% of MPIs and 9.0% of stress echos were performed in rural areas (p<0.0001). Proportions of tests attributable to self-referral varied widely amongst the different tests (from 1.4% for CCTA and 9.8% for MPI to 22.7% and 23.1% for GXT and stress echo respectively). There was wide variation in terms of performing and referring specialties amongst the four tests (see tables 7 and 8). Cardiologists performed the majority of stress echos (87.1%) and GXTs (69%). Radiologists
performed the majority of CCTAs (83.1%). Nuclear medicine physicians performed the majority of MPIs (56.1%). With regards to referring specialties, cardiologists referred the majority of patients for CCTA (76.9%). Family doctors were most likely to refer patients for stress echo (64.1%), GXT (63.8%) and MPI (35.4%).

### 2.3.6 Temporal change in age-and-sex standardized rates of MPI, CCTA, GXT and stress echocardiograms; 2008-2013

Table 9 and Figure 1 display the temporal change in age-and sex-standardized rates of MPI, GXT, CCTA and stress echo per 1,000 adults aged 20 and above in Ontario. MPI rates were the only ones to show a decline, decreasing by an average annual rate of 1.1% (p<0.0001) from 21.1/1,000 in 2008 to 19.8/1,000 in 2013. GXT rates increased slightly by an average of 0.8% annually from 26.7/1,000 in 2008 to 28.0/1,000 in 2013 (p<0.0001). Rates of CCTA and stress echo increased more rapidly, with CCTA increasing on average 26% annually from 0.3 to 0.6/1,000 and stress echo increasing, on average, 60% annually from 1.6 to 6.5 /1,000 between 2011-2013.

### 2.4 Discussion

Age and sex standardized rates of the older technologies, GXT and MPI, were relatively stable between the years of 2008-2013. Both CCTA and stress echo billing codes were introduced in Ontario in 2011. Since their introduction, there has been a larger increase in utilization rates of these newer tests when compared to the more established modalities. However, in terms of absolute numbers, the numbers of CCTAs and stress echos billed were much smaller when compared to the older, more established modalities. When compared head-to-head, there were some clinically meaningful differences in both patients who underwent these tests and physicians who either ordered or interpreted the tests. MPIs were performed on significantly more females.
CCTAs were performed on significantly more patients in the highest income quintile when compared to the other tests. Proportions of tests attributable to self-referral were significantly different, ranging from 1.4% for CCTA to 23.1% for stress echo. For the high self-referring modalities (GXT and stress echo), the proportions of tests that were self-referred stabilized (in the case of stress echo) and significantly declined (in the case of GXT) over the time frame of our study.

2.4.1 Temporal trends in the utilization of cardiac non-invasive diagnostic tests

Ontario

Available Ontario data regarding the temporal trends of non-invasive cardiac diagnostic tests for CAD suggest an increase in utilization over time. Data from 1992-2008 showed increasing utilization rates of MPI and GXT \(^{21, 22}\). There were no studies examining trends in utilization patterns from 2009 and onwards.

International

International studies from the United States, Europe and Asia report increases in the utilization of all four modalities from the 1990s until the mid 2000s \(^{24-26}\). Beginning in the mid 2000s and up until the present time, a stabilization and/or reduction in MPI utilization has been reported \(^{27, 28}\). There is a lack of data with respect to the other modalities during this period.

2.4.2 Self-referral

The recent growth in the utilization of imaging technology in North America has been attributed, in part, to self-referral. Multiple studies have linked self-referral to overutilization of imaging \(^{65, 80-86}\). The concept of self-referral potentially influencing utilization rates of imaging tests is not a
new one. In 1990, Hillman et al., retrospectively analyzed 65,517 episodes of outpatient care by 6,419 American private practice physicians for acute upper respiratory symptoms, pregnancy, low back pain, and/or dysuria. The imaging procedures studied included chest x-ray radiography, obstetrical ultrasound, x-ray radiography of the lumbar spine and urological diagnostic imaging tests. For all four clinical presentations, the self-referring physicians obtained imaging examinations 4.0 to 4.5 times more often\textsuperscript{85}. More recently, Levin et al. reported that the utilization rate increase for MPI was 36.3\% among self–referring physicians compared with only 3.7\% among non-self referring physicians. The growth in utilization rate was therefore approximately 10 times higher amongst self-referring physicians\textsuperscript{80}.

### 2.4.3 Comparison of our results with previous work

To the best of our knowledge, ours is the first study to examine the temporal trends and overall head-to-head characteristics of CCTA, stress echo, GXT and MPI at the adult population level. This is important because it entails analyzing a true cross-section of the population rather than focusing on a subset (for example, those aged 65 and above who would likely be at higher risk of CAD and potentially more likely to receive such testing). Our results indicate that utilization of the most common cardiac non-invasive diagnostic tests, GXT and MPI, remained fairly stable from 2008-2013. These results are similar to results reported by other international jurisdictions for MPI utilization after 2008. In contrast, the newer modalities, stress echo and CCTA, showed a much higher rate of growth in our study. Some of this growth may be spurious and may be related to the natural process of transitioning between billing codes. The stress echo and CCTA billing codes were introduced in Ontario on September 1, 2011 and April 1, 2011 respectively\textsuperscript{79,87,78}. Prior to that, some stress echos and CCTAs were performed in Ontario. However, billing practices for these procedures were highly variable and thus we could not reliable capture their
utilization prior to fee code introduction. When one looks at the 2-3 years of available data for these modalities, there was a large increase between 2011 and 2012 and a much smaller increase between 2012 and 2013. Analysis of trends in the future will be needed in order to determine if utilization rates stabilize further over time. It is difficult to draw comparisons to other jurisdictions because of the lack of international data available on the temporal trends in utilization of GXT, stress echo and CCTA between the years 2009-2013. In addition to assessing trends, it is also interesting to note the difference in absolute numbers of the tests performed. CCTA utilization rates, for example, are approximately 10-fold lower then stress echo rates and approximately 30-40 fold lower then MPI and GXT rates. Further, we note a dramatic difference in the utilization rates between our data from Ontario and available data from the United States with utilization rates for GXT, MPI and stress echo being multiple times lower in Ontario. Interestingly, in terms of MPI, utilization rates in Canada, while lower than American rates, are several fold higher than what were reported in Taiwan and Europe during similar time-frames. The reason for the difference in utilization rates is difficult to identify. However, we speculate that it may be in part related to differences in government policies regarding test availability as well as the type of specialists that are permitted to be reimbursed for these tests.

Another important finding in our study was that CCTAs were more likely to be performed in higher income individuals when compared to the other modalities. This phenomenon is similar to trends observed in the utilization of other high technology diagnostic tests with limited patient access including magnetic resonance imaging. Higher income individuals may be more aware of emerging and new technologies and may be more likely to request that their physicians order a newer modality such as CCTA. Proportions of tests attributable to self-referral were dramatically different amongst the four tests. These ranged from only 1.4% for CCTA to 23.1% of stress echos. This difference may be
partially explained by the difference in types of physicians performing and referring for these tests. It is also important to note that the proportion of tests attributable to self-referral have not increased between 2008-2013 for the high self-referral tests (GXT and stress echo). For stress echo the proportion of tests that were self-referred was stable over time and for GXT the proportion significantly decreased over time (see figure 2). We believe that the stabilization of growth, in terms of both utilization and self-referral, is meaningful from a health policy perspective in light of the current initiatives aiming to reduce unnecessary testing.

2.4.4 Limitations

Limitations of our study should be mentioned. First, we used data related to neighborhood income as a proxy indicator of individual income. This can results in misclassification bias. However, this method of assessing income levels has been shown to be a valid measure and proxy of socio-economic status. Second, there are only approximately 2.5-3 years of data available for the newly approved modalities of stress echo and CCTA. This limits the robustness of the conclusions that we can draw regarding the temporal trends of their utilization. Finally, our data were limited to Ontario. It is possible that utilization patterns may be different in other jurisdictions.

2.5 Conclusions

Age-and sex-standardized GXT and MPI utilization rates have remained relatively stable between 2008-2013 in Ontario. The mean annual rate of increase for these modalities is much lower than previously reported in Ontario. While there was a large difference in the proportion of tests attributable to self-referral amongst the different modalities, there has been a significant trend towards stabilizing (in the case of stress echo) or declining (in the case of GXT) self-
referral percentages for the high self-referral modalities.
Chapter 3: The relationship between an initial diagnostic evaluation with GXT, CCTA, MPI or stress echo and downstream yield of obstructive CAD in the evaluation of patients for stable CAD

3.1 Background

As of September 1, 2011, four cardiac non-invasive diagnostic tests were clinically available and billable in Ontario: GXT, MPI, CCTA and stress echo. There is currently disagreement between the American and European guidelines with respect to which test should be initially used for the evaluation of patients for stable CAD 55-57. Further, although many studies have assessed the clinical efficacy of these tests in select populations, none have assessed the comparative clinical effectiveness of these modalities in a head-to-head fashion in a population-based study. With healthcare budgets rising sharply in many developed countries and with cardiac diagnostic testing and medical imaging contributing heavily to these costs, the assessment of comparative clinical effectiveness is important in order to assess the real-world impact of these modalities 30-33. The ideal outcome measure to assess the clinical effectiveness of cardiac non-invasive diagnostic tests is not currently established. The yield of obstructive CAD has recently been used as an outcome measure in studies designed to assess the clinical effectiveness of non-invasive cardiac diagnostic tests 48, 50, 95. Recent registry data suggest that only approximately 38% of those referred for invasive angiography for the diagnosis of stable CAD had obstructive CAD on invasive angiography 13, 96. Thus, understanding the relationship between the initial non-invasive cardiac diagnostic tests and subsequent downstream yield of obstructive CAD may provide insight as to which non-invasive test to use, thereby reducing unnecessary invasive angiograms, and, consequently, resultant complications thereof.
3.1.1 Objectives

1. To determine the proportion of patients who underwent invasive angiography and a subsequent cardiac non-invasive test within 6 months of their initial cardiac non-invasive test and to compare proportions amongst the different initial test types (CCTA, GXT, MPI and stress echo). To determine if patients undergoing an initial CCTA, MPI or stress echo had a greater or lesser odds of progression to invasive angiography when compared to those receiving an initial GXT, after adjusting for relevant available co-variates.

2. In those patients who had invasive angiograms for the assessment of stable angina, to determine which patients had obstructive CAD. To determine if receipt of an initial MPI, stress echo or CCTA were independently predictive of a higher yield of obstructive CAD when compared to GXT, after adjusting for clinically relevant co-variates.

3.1.2 Hypothesis

In patients being assessed for stable angina and undergoing invasive angiography, we hypothesized that a strategy with an initial MPI, stress echo or CCTA will all lead to a higher yield of obstructive CAD when compared to a strategy with an initial GXT.

3.2 Methods

3.2.1 Design

We conducted a retrospective cohort study for the calendar year 2012.

3.2.2 Derivation of the cohort

Patients began entering the cohort on Jan 1, 2012 (see figure 3). Inclusion criteria were
age ≥ 20 years and receipt of one of GXT, stress echo, CCTA or MPI. The first cardiac non-invasive diagnostic test for each patient was deemed the index event. Index events were collected between January 1, 2012 and December 31, 2012. We employed a lookback window of 20 years (back to January 1, 1992) to exclude patients with prior cardiovascular disease from our cohort. Previous cardiovascular disease was defined by hospitalization for acute myocardial infarction, stroke, congestive heart failure, percutaneous coronary intervention and coronary artery bypass grafting via previously validated algorithms (see table 10) 67,97-102. We also employed a one-year wash-out period where patients who had one of the four non-invasive diagnostic tests during calendar year 2011 were excluded. After the index event, patients were followed for a maximum of 6 months for ascertainment of outcomes. Thus, the observation window extended from January 1, 2012-June 30, 2013 in order to provide a full 6 months of follow up for the last potential person entering the cohort on December 31, 2012.

3.2.3 Data sources

Information to identify patient receipt of cardiac non-invasive diagnostic CAD tests was obtained through medical claims data from the OHIP physician claims database during the calendar year 2012 (see table 1). The OHIP physician claims database contains all physician reimbursement claims for GXTs, CCTAs, MPIs and stress echos performed in Ontario. Physician specialty was determined by linking the OHIP database with the Institute for Clinical Evaluative Sciences (ICES) physician database (IPDB). The Registered Person’s database (RPDB), a registry of Ontario residents who are registered for Ontario health insurance coverage, was used to obtain demographic information including age and sex. Median neighborhood income was obtained by linking the Census Area Profile with patients’ postal codes of residence from RPDB using the Postal Code Conversion File. Hospitalizations were determined using the Canadian Institutes for
Health Information Discharge Abstract Database (CIHI-DAD). The Ontario Hypertension and Diabetes databases were used to determine hypertension and diabetes status respectively. The Ontario Hypertension Database contains all Ontario hypertension patients identified since 1988. Hypertension is said to be present if an individual has had:

1. One hospital admission for hypertension (determined via CIHI-DAD) or
2. An OHIP claim with a hypertension diagnosis followed within two years by either an OHIP claim or hospital admission with a hypertension diagnosis. A validation study has reported a sensitivity of 73%, specificity of 95%, positive predictive value of 87% and negative predictive value of 88% when compared to physician assigned diagnoses \(^{103}\). The Ontario Diabetes Database assigns a diagnosis of diabetes if there are 2 OHIP diagnostic code claims or 1 OHIP fee code claim or one diabetes related admission (determined by CIHI-DAD) within a 2-year time frame. The algorithm has been validated against physician determined diagnoses and has been shown to have a sensitivity of 86% and a specificity of 97% \(^{104}\). The Canadian Cardiovascular Network (CCN) registry was used to determine receipt of angiography as well as obstructive CAD status on angiography. The CCN registry is an ongoing prospective registry storing clinical information on all invasive cardiac procedures in Ontario and has been used extensively in clinical research \(^{105\text{-}108}\). The registry contains detailed demographic, co-morbidity and procedural details, including coronary anatomy, which have been validated against chart abstraction and core-lab verification \(^{109, 110}\). The CCN database was used to determine which patients had invasive angiograms performed for the evaluation of stable angina (variable C005-035, CCN data dictionary V9.0). In these patients, it was also used to determine patient clinical co-variate status.
3.2.4 Objective 1: Downstream invasive angiography and subsequent non-invasive tests

**Cohort**

The full cohort as described in section 3.2.2 was used in this analysis.

**Exposure**

The exposure was the receipt of one of the four index cardiac non-invasive diagnostic tests: GXT, MPI, CCTA or stress echo.

**Outcomes**

We determined which patients progressed to invasive angiography and which patients had a subsequent cardiac non-invasive diagnostic test within 6 months of their index test. In those who had a subsequent non-invasive test, the type of non-invasive test was also determined. All angiograms were included, regardless of indication.

**Co-variates**

All co-variates included in multivariable models were selected a priori based on clinical importance. Co-variates used in this analysis were limited to those ascertainable by OHIP, RPDB and CIHI-DAD data. Increasing age, male sex, presence of diabetes, hypertension and a lower income status are cardiovascular risk factors and may increase the likelihood of undergoing invasive angiography for diagnostic purposes. Therefore, it was important to include these variables in the multi-variable model.

**Statistical analysis**

Baseline characteristics of the patient population were compared with chi-square or Fisher’s exact test for categorical variables and ANOVA for continuous variables. We followed patients to see who had angiograms within their respective observation window. We determined the proportion of patients who had any subsequent cardiac non-invasive test (as a dichotomous
yes/no variable) and compared proportions across groups of index cardiac non-invasive
diagnostic index tests using chi-square. Further, for those who had a subsequent non-invasive
cardiac diagnostic test, we performed a chi-square analysis of index and subsequent cardiac non-
invasive diagnostic tests in order to determine the type of subsequent non-invasive test received.

Unadjusted analyses

Unadjusted analyses were performed using logistic regression analyses to assess the relationship
of the index non-invasive tests with receipt of downstream angiography, using GXT as the reference test.

Adjusted analyses

We performed multi-variable logistic regression analyses in order to examine the relationships
between the index non-invasive cardiac diagnostic tests (predictors) and downstream
angiography (outcome), controlling for available clinical co-variates. Prior to performing the logistic regression analyses, all predictor variables were assessed for the presence of multicollinearity. We concluded that there was no significant multicollinearity amongst the predictor variables and co-variates used in the models based on the fact that none of the variables had a variance inflation factor >4 or tolerance <0.25. We performed two different adjusted analyses, first adjusting for age and sex and subsequently adjusting for all relevant co-variates discussed above (the fully adjusted model).

3.2.5 Objective 2: Assessment of obstructive CAD in those patients who underwent invasive angiography for the assessment of stable angina

Cohort

The cohort for this analysis was the subset of patients who underwent angiography within 6 months of an index cardiac non-invasive test for the assessment of stable angina. The subset of
stable angina patients was used for this analysis due to the current state of uncertainty regarding the optimal initial non-invasive cardiac diagnostic strategy for this population as described above.

Exposure

The exposure was the receipt of one of the four index non-invasive tests.

Outcomes

In those patients who underwent angiography for the assessment of stable angina, we determined whether or not their angiogram showed obstructive CAD. Obstructive CAD on angiography was defined as stenosis of ≥ 50% of the left main coronary artery or ≥ 70% or more of a major epicardial or branch vessel according to CCN data in a manner previously described and validated 110, 120.

Co-variates

All co-variates included in multivariable models were selected apriori based on clinical importance. Additional co-variates were available for this analysis (compared to the analysis for objective 1) due to the availability of demographic and co-morbidity data in the CCN registry. Increasing age, male sex, diabetes, dyslipidemia, hypertension, a lower income status, serum creatinine, and smoking are all cardiovascular risk factors associated with a higher risk of developing obstructive CAD 91, 121 111-119. Presence of chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD) and the Charlson comorbidity index score are all measures of co-morbidity that may affect a clinician’s decision making process with respect to choosing a suitable initial diagnostic test 122. Resting electrocardiogram (ECG) abnormalities and Canadian Cardiovascular Society (CCS) angina symptoms are other important factors that may sway the decision regarding the optimal initial diagnostic test 56, 122, 123.

Statistical analysis
Amongst the patients who underwent invasive angiography for the assessment of stable angina, we determined the proportion of patients who had obstructive CAD on their angiograms and compared their proportions across groups of index non-invasive tests using the chi-square test.

*Logistic regression analyses*

*Unadjusted analyses*

Unadjusted analyses were performed using logistic regression models to assess the relationship of the index cardiac non-invasive tests with downstream obstructive CAD, in those patients who underwent invasive angiography for the evaluation of stable angina. GXT was the reference test.

*Adjusted analyses*

We performed multi-variable logistic regression analyses in order to examine the relationships between the index non-invasive cardiac diagnostic tests (predictors) and downstream obstructive CAD (outcome) in those patients who were evaluated for stable angina, controlling for relevant clinical co-variates. Prior to performing the logistic regression analyses, all predictor variables were assessed for the presence of multicollinearity. We concluded that there was no significant multicollinearity amongst the predictor variables and co-variates used in the models based on the fact that none of the variables had a variance inflation factor >4 or tolerance <0.25. Angiographic results may provide a better assessment of a subsequent non-invasive test, when performed, vs. the first test in the diagnostic pathway. Consequently, a subgroup analysis was performed following the removal of patients who had a subsequent cardiac non-invasive diagnostic test. We performed two different adjusted analyses, first adjusting for age and sex and subsequently adjusting for all relevant co-variates discussed above (the fully adjusted model).

A two-tailed value of p<0.05 was considered statistically significant. Analyses were performed with SAS V.9.3 (SAS Institute Inc., Cary, North Carolina, USA). This study was approved by the research ethics board at Sunnybrook Health Sciences Centre.
3.3 Results

3.3.1 Objective 1: Downstream invasive angiography and subsequent non-invasive tests

3.3.1.1 Cohort creation

464,647 subjects ≥ 20 years of age had a GXT, MPI, stress echo or CCTA in Ontario in the calendar year 2012 (see figure 4). Out of these, 45,711 were excluded due to having one of the four cardiac non-invasive diagnostic tests in the preceding 12 months. 69,443 patients were further excluded due to having a previous diagnosis of cardiovascular disease over the preceding 20 years. The final cohort consisted of 349,493 patients.

3.3.1.2 Baseline characteristics of the cohort

In our cohort, 1,748 patients had an index CCTA, 175,900 had an index GXT, 128,622 had an index MPI and 43,223 had an index stress echo (see table 11). Patients with an index MPI were, on average, the oldest (61.6 ± 14.1 years vs. 59.2 ± 13.6 years for CCTA, 54.8 ± 13.3 years for GXT, and 57.1 ± 13.6 years for stress echo, p<0.0001). Patients with an index MPI were also the most likely to be females, have diabetes mellitus and have hypertension. Patients with CCTA were the most likely to reside in one of the wealthiest 20% of neighborhoods in Ontario (28.3% vs. 28.0% for MPI, 21.9% for stress echo and 20.5% for GXT, p<0.0001).

3.3.1.3 Angiography within 6 months of the index cardiac non-invasive diagnostic test

A total of 18,819 patients underwent invasive angiography within 6 months of an index non-invasive test. Patients with an index CCTA were significantly more likely to have a diagnostic invasive angiogram within 6 months when compared to the other non-invasive tests (7.8%, vs. 6.5% for MPI, 4.7% for stress echo and GXT, p<0.0001) (see table 12). On unadjusted analysis, they had a 1.72 greater odds of progressing to invasive angiography when compared to GXT.
(95%CI 1.44, 2.05, p<0.0001). After adjusting for age and sex, patients with an index CCTA had a 1.49 fold greater odds of progressing to angiography when compared to GXT (95%CI 1.25, 1.78, p<0.0001). In the fully adjusted model, the relationship remained unchanged (OR 1.49, 95%CI 1.25, 1.78, p<0.0001). Patients with an index MPI were also more likely to progress to angiography when compared to those undergoing an index GXT. On unadjusted analysis, they were 1.40 fold more likely to progress to invasive angiography (95%CI 1.36, 1.45, p < 0.0001). After adjustment for age and sex, they had a 1.19 fold greater odds of progressing to angiography (95%CI 1.16, 1.23, p < 0.0001). In the fully adjusted model the relationship remained largely unchanged (OR 1.16, 95%CI 1.12, 1.20, p < 0.0001). For patients with an initial diagnostic strategy involving a stress echo, there was no significant difference in the odds of progressing to angiography in the unadjusted analysis (OR 0.96, 95%CI 0.95, 1.05, p=0.83). After age and sex adjustment, patients undergoing an index stress echo were significantly less likely to progress to angiography when compared to GXT (OR 0.95, 95%CI 0.90, 0.97, p=0.03). This relationship persisted in the fully adjusted model (OR 0.94, 95%CI 0.89, 0.98, p=0.009) (see table 15 and figure 6).

### 3.3.1.4 Subsequent cardiac non-invasive tests

Patients with an index GXT were most likely to have another cardiac non-invasive diagnostic test in the follow up period (see table 12). Of those patients who had a subsequent cardiac non-invasive diagnostic test, MPI was the most common test performed regardless of the index test (see table 13). This includes those patients who had an index MPI, in whom approximately 78% of the subsequent non-invasive tests was an additional MPI.
3.3.2 Objective 2: Assessment of obstructive CAD in those patients who underwent invasive angiography for stable angina

3.3.2.1 Cohort creation

This cohort consisted of the subset of patients who underwent angiography for the assessment of stable angina. Out of 349,493 patients aged 20 and above who had index non-invasive testing in Ontario in 2012, a total of 18,819 underwent subsequent invasive angiography. 15,467 of these patients underwent invasive angiography for the indication of stable angina (see figure 5).

3.3.2.2 Characteristics of patients undergoing angiography for the evaluation of stable angina

15,467 patients who entered the cohort underwent angiography for the evaluation of stable angina within 6 months of their index test (see table 14). Of these, there were 113 patients with an index CCTA, 6,742 patients with an index GXT, 6,877 patients with an index MPI and 1,735 patients with an index stress echo. Those patients who underwent an index MPI were, on average, the oldest, had the highest mean serum creatinine levels, and were more likely to have diabetes mellitus, dyslipidemia and hypertension. Patients with an index MPI were also the most likely to have other co-morbidities measured in our study including peripheral vascular disease, chronic obstructive pulmonary disease and had a higher mean Charlson co-morbidity index score. Patients with an index CCTA were more likely to both be females and have CCS class 3-4 angina symptoms. Further, those patients with an index CCTA were significantly more likely to reside in the top 20% of the Ontario’s wealthiest neighborhoods.

3.3.2.3 Yield of Obstructive CAD

On unadjusted analysis, of those who underwent angiography for stable angina, there was no significant difference amongst the index non invasive tests with respect to yield of obstructive CAD when compared to the reference standard of GXT (see table 16). In the fully adjusted
model (see figure 7 and table 16), patients undergoing MPI and subsequent angiography were significantly less likely to have an angiogram showing obstructive CAD (OR 0.92, 95%CI 0.85, 0.99). Patients undergoing an index CCTA (OR 1.50, 95%CI 0.90, 2.48) or stress echo (OR 0.95, 95%CI 0.84, 1.08) and subsequent angiography were not significantly more or less likely to have obstructive CAD when compared to those whose index test was a GXT.

3.3.2.4 Yield of obstructive CAD after removing patients who had a subsequent non-invasive cardiac diagnostic test

After removing those patients who had a subsequent cardiac non-invasive test prior to invasive angiography for the assessment of stable angina (5,823, approximately 38%), none of the initial testing strategies were independently associated with a higher or lower yield of obstructive CAD vs. GXT on unadjusted analysis (see table 17). After adjusting for age and sex, those patients who had an index CCTA and went on to invasive angiography had a 1.67 greater odds of having obstructive CAD when compared to GXT (95%CI 1.02, 2.71). In the fully adjusted model, those with an index CCTA who went on to angiography remained significantly more likely to have obstructive CAD. They had a 1.9 fold greater odds of having obstructive CAD when compared to those who had an index GXT (95%CI 1.06-3.40) (see figure 8). In contrast, in the fully adjusted model, patients with an index stress echo or MPI and subsequent angiography were not significantly more or less likely to have obstructive CAD when compared to a strategy with an index GXT.

3.4 Discussion

The majority of patients in our cohort had a GXT as their index non-invasive test. Those patients undergoing an index MPI or CCTA were significantly more likely to have a downstream
invasive angiogram in the subsequent 6 months, after adjustment for other co-variates. Patients who underwent angiography for the evaluation of stable coronary artery disease who had an index MPI were more likely to have most of the major cardiovascular risk factors as well as measures of co-morbidities such as COPD, PVD and a higher mean Charlson co-morbidity index score. Patients who underwent angiography for the evaluation of stable CAD who had an index CCTA were most likely to be female and have CCS class 3-4 symptoms. After adjusting for relevant co-variates, patients with an index MPI who subsequently underwent angiography for the evaluation of stable CAD were significantly less likely to have obstructive CAD when compared to the reference of GXT. Patients with an index CCTA or stress echo who underwent angiography for the evaluation of stable CAD did not have a statistically significant different yield of obstructive CAD when compared to the reference of GXT. After excluding patients who had a subsequent non-invasive test prior to invasive angiography for the assessment of stable CAD, those with an index CCTA had a 1.9 fold greater odds of having obstructive CAD while those with an index stress echo or MPI had no statistically significant difference in the yield of obstructive CAD when compared to GXT.

3.4.1 Non-invasive diagnostic tests to diagnose coronary artery disease

The optimal strategy to evaluate patients with suspected stable coronary artery disease is currently unclear. The recent proliferation of non-invasive cardiac diagnostic testing technology has led to various potential options for the non-invasive diagnosis of CAD. The 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease recommended GXT as the first line test in patients who are able to exercise in the absence of significant ST-T wave abnormalities. In contrast, the 2013 and 2014 European Society for Cardiology guidelines on stable coronary artery disease and
revascularization considered all of CCTA, GXT, MPI and stress echocardiography as class 1 indications in the evaluation of stable coronary artery disease in intermediate risk patients. There have been many studies examining the efficacy of CCTA, GXT, MPI and stress echo in selected populations. However, despite widespread clinical adoption of newer technologies, there has been limited data comparing their relative clinical effectiveness, specifically by comparing their real-world downstream outcomes. The lack of a clear demonstration of an effect on outcomes has led to calls for regulation aimed at controlling spending and improving quality. There is little comparative effectiveness research published on differing initial non-invasive diagnostic strategies that are currently available to clinicians. In April 2015, the Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease (PROMISE) trial was published. This was a randomized control trial of 10,003 patients being evaluated for stable coronary artery disease who were randomized to an initial strategy of anatomical (CCTA) vs. functional (GXT, stress echo or MPI) strategy. Their primary end-point was a composite of major adverse cardiovascular events including death. There was no significant difference in terms of this outcome between the two diagnostic testing strategies with a median follow up of 2 years.

3.4.2 Yield of obstructive CAD

The optimal endpoint to assess clinical effectiveness is currently unknown. While the assessment of ‘hard’ cardiovascular endpoints is important, their link to a diagnostic test is often complicated by multiple other patient factors and clinical decisions that may not be directly related to diagnostic test performance itself. In recent years, the concept of yield of obstructive CAD has emerged as a surrogate endpoint designed to assess the clinical effectiveness of cardiac diagnostic tests. Multiple studies have linked obstructive CAD to an
increase in mortality. Recent registry data from 398,978 patients reported an obstructive CAD rate of only 37.6% on invasive angiograms of patients being evaluated for stable coronary artery disease. Given the potential risks associated with invasive angiography, it is important to assess the yield of obstructive CAD as related to cardiac non-invasive diagnostic tests. In the PROMISE trial detailed above, one of their secondary outcomes was the rate of non-obstructive CAD on downstream diagnostic angiography. They found that although more patients underwent catheterization, there were significantly less diagnostic angiograms showing non-obstructive CAD in the anatomical vs. the functional groups. They did not report individual performance of the various diagnostic tests that were collectively grouped under the functional testing group.

Another recent study retrospectively collected data on 209 patients evaluated at chest pain clinics at two British Hospitals. The first hospital evaluated patients with a strategy of GXT as the first and only cardiac non-invasive diagnostic test. The second used a “cardiac imaging” pathway that involved a combination of coronary artery calcium score, CCTA, MPI, and stress echocardiography. They concluded that the cardiac imaging strategy resulted in fewer invasive angiograms and a higher yield of obstructive CAD (higher numbers of diagnostic angiograms showing obstructive CAD). They did not analyze the yield of obstructive CAD amongst the different testing modalities in the imaging arm.

This study, to our knowledge, is the first population based analysis to directly compare the yield of obstructive CAD based on strategies of initiation of the diagnostic pathway for stable CAD with either a GXT, MPI, stress echo or CCTA. Thus, we were able to assess the potential ‘real-world’ impact of the initial non-invasive testing strategies in the largest province in Canada (approximate adult population 10.1 million). Our results indicate that in patients undergoing angiography for evaluation of stable CAD, none of the index non-invasive diagnostic tests produced a higher yield of obstructive CAD when compared to GXT. Interestingly, our results
indicate a yield of obstructive CAD of 54% for CCTA. In comparison, the PROMISE trial reported a yield of obstructive CAD of 72%. A potential explanation for this discrepancy lies with the inclusion and exclusion criteria of the PROMISE trial. The PROMISE trial enrolled symptomatic patients and predominantly those with an intermediate pre-test probability of CAD. In contrast, our data assessed what occurred in Ontario in 2012 in all patients undergoing CCTA aged 20 and above. We speculate that in the real-world, a higher percentage of patients at low pre-test probability of disease were scanned, ultimately resulting in a lower yield of obstructive CAD. When looking at a direct comparison between the index test and obstructive CAD on angiography (after removing any patient who had a subsequent cardiac non-invasive diagnostic test), a strategy of initial CCTA was independently associated with a 1.9 fold greater odds of obstructive CAD on subsequent angiography after adjusting for relevant co-variates. Stress echo and MPI were not associated with a greater yield of obstructive CAD when compared to the reference of GXT. We speculate that the difference observed between the overall results and the subgroup analysis may be, in part, due to the removal of those patients who had borderline test results. Some patients with equivocal results on non-invasive testing may undergo a subsequent non-invasive test that may also show an equivocal result. In such cases, the physician may then decide to order an invasive angiogram to obtain a definitive diagnosis. We speculate that these patients may be less prone to having obstructive CAD when compared to those who had more clear-cut results on their initial non-invasive test.”

Our results indicate that in patients in whom a clinical decision was made to undergo angiography, there is no evidence for a greater yield of obstructive CAD of one index modality over the other with the possible exception of CCTA in certain circumstances. This was true even after adjusting for factors such as the presence of baseline ST-T wave abnormalities on ECG that often sway a clinical decision to initiate the diagnostic work-up with a non-GXT based approach.
3.4.3 Limitations

Our study must be interpreted in the context of a number of limitations. First, we had limited access to granular clinical data. For example, we were able to detect whether or not a patient had a non-invasive test but we were unable to discern the result of that test. We assumed that those who were not referred for angiography did not have obstructive CAD. We also did not have access to the individual patients’ pre-test probability of CAD. However, in our multivariable analysis we adjusted for multiple factors that are often included in a clinician’s complex clinical determination of pre-test probability including the presence of major cardiovascular risk factors such as increasing age, male sex, diabetes, smoking and hypertension as well as chest pain characteristics and baseline ST segment abnormalities. Second, we had a limited number of available co-variates for our entire cohort (age, sex, income quintile, presence of hypertension and diabetes mellitus). Thus, our multivariable analysis for the outcome of progression to angiography (objective 1) did not adjust for important known confounders such as smoking status, CCS symptom class and baseline ST-T wave abnormalities. Third, only a small percentage of patients in our study had a downstream invasive angiogram. We did not assess what occurred to the majority of patients who did not undergo invasive angiography. Fourth, our results reflect data from Ontario and may not be generalizable to other jurisdictions. Fifth, our analysis was limited to tests that are currently widely utilized in Ontario. We did not assess other emerging technologies such as stress cardiac magnetic resonance imaging and positron emission tomography nuclear imaging due to the absence of an associated physician billing code and/or limited clinical availability. Sixth, the number of patients who underwent angiography after having an index CCTA was small. Consequently, we were likely underpowered to show a statistically significant difference in yield of obstructive CAD vs. GXT. Finally, although we
attempted to adjust for all the known relevant confounders, the observational nature of this study raises the possibility of the presence unknown confounders that may have inadvertently affected our results.

3.5 Conclusions

Amongst patients who underwent invasive angiography for evaluation of stable CAD, an evaluative strategy consisting of an initial CCTA, MPI or stress echo was not statistically different from an initial strategy with an index GXT with respect to downstream yield of obstructive CAD. It is important to note that we were likely underpowered to detect a statistically significant difference in those patients undergoing an initial CCTA. When removing patients who had a subsequent non-invasive test, a strategy consisting of an index CCTA was associated with an approximate 1.9 fold greater odds of the presence of obstructive CAD on downstream angiography after adjusting for relevant co-variates.
Chapter 4: Synthesis

We sought to address the following gaps in knowledge in this thesis:

1. The temporal trends of all the cardiac non-invasive diagnostic tests available in Ontario (CCTA, GXT, MPI and stress echo) have not been examined head-to-head at the level of the adult population. Further, there is a lack of published literature examining temporal trends in the utilization of these modalities, especially after 2008, both in Ontario and internationally. In order to address these knowledge gaps, we performed a population-based repeated cross-sectional study of the population of Ontario aged 20 and above from January 1, 2008 until Dec 31, 2013.

2. There is limited work addressing the real-world relationship between an initial diagnostic strategy with these cardiac non-invasive tests and downstream findings on coronary angiography. Specifically, as far as we know, there are no population-based studies that have compared the yield of obstructive CAD amongst the four initial testing strategies of CCTA, GXT, stress echo and MPI in patients being evaluated for stable angina. In order to address this knowledge gap, we constructed a retrospective inception cohort for the calendar year 2012 and compared the real world yield of obstructive CAD amongst different initial non-invasive testing strategies.

4.1 Summary of key findings

In chapter 2 of this thesis, we found that between 2008 and 2013, age-and sex-standardized GXT and MPI utilization rates have remained relatively stable. The mean annual rate of increase for these modalities is much lower than previously reported in Ontario. For MPI, the reduction in utilization that we observed is consistent with trends observed internationally during a similar time-frame. Growth rates for the newer testing modalities, CCTA and stress echo, were significantly higher than for the more established modalities. However, part of this increase may
be spurious due to the natural process of conversion between billing codes. In fact, after an initial rapid rise in utilization, growth rate in the utilization of these modalities tended to stabilize. A longer period of analysis is required for CCTA and stress echo before definite comments can be made regarding the temporal patterns in their utilization. There were much higher proportions of tests attributable to self-referral amongst those who underwent GXTs and stress echos vs. those who underwent MPIs or CCTAs. However, the proportions of GXTs and stress echos attributable to self-referral have decreased significantly and stabilized over time respectively. In chapter 3 of this thesis we reported that a diagnostic evaluative strategy consisting of an initial CCTA, MPI or stress echo did not produce a significantly different yield of obstructive CAD in those patients who underwent subsequent angiography for the investigation of stable angina when compared to an initial strategy with GXT. When removing patients who had a subsequent non-invasive cardiac diagnostic test, a strategy consisting of an index CCTA was associated with an approximately 1.9 fold greater odds of the presence of obstructive CAD on downstream angiography after adjusting for relevant co-variates.

4.2 Importance

4.2.1 Trends in Utilization

Our work builds upon and adds to previous work examining utilization of non-invasive cardiac diagnostic tests. Similar to other international studies, our work shows a decline in the age-and sex-standardized utilization rates of MPI over the past several years. We could not compare Ontario’s growth rate of GXT utilization to other jurisdictions due to a lack of available published international data from 2008-2013. Growth in the utilization of GXT has stabilized when compared to previously reported growth rates in the province. The rising costs of healthcare have provided the impetus for understanding the utilization patterns of diagnostic
tests. Concern about the rapid growth in utilization and potential overuse of diagnostic tests has led to the development of initiatives such as the *Choosing Wisely Canada* campaign aimed at reducing unnecessary diagnostic testing.\textsuperscript{58-60} In our head-to-head analysis, GXT and MPI accounted for the lion’s share of cardiac non-invasive diagnostic tests in Ontario. In fact, 1,589,001 out of total of 1,757,009 tests performed in Ontario between 2011 and 2103, or approximately 90%, were either GXTs or MPIs. In this context, we feel that the stabilization in the growth of utilization rates for GXT and MPI in Ontario is meaningful from a health policy perspective. Further, a recent ACC/AHA statement recommended that consideration be given for inclusion of resource utilization data in guideline statements as one metric of assessing value.\textsuperscript{61, 62} It is therefore hoped that our data will be utilized by future guideline statements on non-invasive cardiac diagnostic testing.

Moreover, our results indicate that the proportion of tests attributable to self-referral for the high self-referral tests of GXT and stress echo has decreased significantly or stabilized over time respectively. Physician self-referral has emerged as an important issue over the past several years. The potential financial incentives that arise from self-referral have been implicated as a major factor in the performance of unnecessary diagnostic tests. Therefore, we feel that the stabilization and reduction of the proportion of tests attributable to self-referral that we observed in our data is also important from a health policy point of view in the context of government funded initiatives aimed to reduce unnecessary testing such as the aforementioned *Choosing Wisely Canada* campaign.
4.2.2 Relationship of initial non-invasive diagnostic testing with downstream obstructive CAD on invasive angiography in patients being assessed for stable angina

The financial constraints detailed above along with the current state of uncertainty regarding the optimal initial non-invasive cardiac diagnostic testing strategy have led to a recent emphasis on comparative clinical effectiveness studies in order to assess the real-world impact of these tests. The ideal outcome measure to assess the clinical effectiveness of cardiac non-invasive diagnostic tests is not currently established. Based on the aforementioned prognostic importance of obstructive CAD as well as the desirability to reduce unnecessary invasive angiograms, we used the surrogate outcome of the yield of obstructive CAD to compare amongst the various initial non-invasive diagnostic strategies. This outcome has recently been utilized in multiple settings to assess the clinical effectiveness of non-invasive cardiac diagnostic tests. However, to our knowledge, no studies have directly compared an initial strategy with GXT, MPI, CCTA and stress echo utilizing this outcome in a population based real-world study of patients being evaluated for stable angina. We were surprised by our findings. We had expected that an initial diagnostic strategy consisting of MPI, stress echo and CCTA would have a significantly higher yield of obstructive CAD when compared to one with a GXT. Our hypothesis was based on clinical efficacy studies showing superior accuracy of the former three modalities when compared to GXT. Our results failed to support our hypothesis, with the possible exception of CCTA when patients who had subsequent non-invasive tests were removed from the analysis. Thus, within the context of the limitations of our study, our real-world results were incongruent with the results from efficacy studies where the tests were interpreted by experts and were performed under ideal conditions.
4.3 Future work

Utilization studies

We feel that our findings regarding the stabilization in the utilization and self-referral trends detailed above are significant from a health policy perspective. However, we lacked accurate clinical data on the indications for these tests. Therefore, a focus of future research should involve collecting more clinical information on a sample of the overall study population to supplement the administrative data. This will help provide more granular details which will further aid in the determination of the appropriate use of these technologies. Moreover, it is also possible that one test’s utilization was replaced with that of a newer modality. We will need more years of data for CCTA and stress echo utilization prior to being able to accurately assess for this possibility.

Comparative effectiveness studies

An advantage of our cohort study is that it provides real-world population based data on the relationship between index non–invasive testing and downstream angiography. Given the observational nature of the study, there is potential for unaccounted for unknown confounders that may have inadvertently affected our results. Further, while multi-variable logistic regression analysis is a reasonable and valid way to adjust for known confounders, it is imperfect. The best way to control for confounding (both known and unknown) is via a randomized control trial. However, traditional trials often have rigid inclusion and exclusion criteria that limit their generalizability (external validity). This can be partially overcome by designing a ‘pragmatic’ randomized control trial where all patients being evaluated for stable angina would be randomized to one of the four initial interventions of GXT, stress echo, CCTA or MPI. Outcomes would include yield of obstructive CAD, costs and major adverse cardiac events (for example using a composite endpoint of death, myocardial infarction and unstable angina).
Ideally, there would be little to no patient selection beyond the indication of interest (i.e. workup of stable CAD). Thus, a ‘pragmatic’ RCT may be the ideal design for future comparative effectiveness studies comparing different diagnostic cardiac testing modalities. Second, this study focused on patients in whom a clinical decision was made to pursue angiography. While looking at yield of obstructive CAD is a useful outcome, it would also be important to assess the other side of coin, i.e. those patients in whom the non–invasive test identified insignificant disease and correctly terminated their diagnostic cascade. Specifically, it would be useful to consider other metrics of clinical effectiveness (such as quality of life measures) in this patient population. This information could be relevant to the overall question of how useful the tests are relative to each other. Third, further research is needed to identify possible clinical circumstances where an initial diagnostic strategy with a CCTA, MPI or stress echo may confer a higher yield of obstructive CAD vs. an initial diagnostic strategy with a GXT. For example, for many of these tests, there are no governmental regulations regarding who is allowed to interpret them. For example, any physician in Ontario is allowed to perform and interpret stress echo. There are training programs and certification streams available, however, at this point, they are purely voluntary. Would the performance of these tests relative to GXT improve if they were interpreted by certified physicians? Further, would there be differing results if these studies were read in hospital settings vs. outpatient facilities? In academic vs. community institutions? These are all important questions that require further work and are outside the scope of this thesis. Fourth, emerging technologies such as stress MRI and cardiac PET scanning were not included in this study. Currently, these are niche tests that are either unfunded (in the case of stress MRI) or confined to use primarily by a single centre (as in the case of cardiac PET). If these tests become more prevalent in the future, it would also be important to assess their comparative effectiveness in the context of other non-invasive cardiac diagnostic tests. Finally, future work
comparing the direct and downstream health-care costs of the cardiac non-invasive diagnostic
tests is important in order to help place our data in context given the limited resources available
to our healthcare system.

4.4 Conclusions

Our results indicate that the most prevalent cardiac non-invasive testing modalities (GXT and
MPI) in Ontario had relatively stable utilization patterns from 2008-2013. Further, the
proportions of tests attributable to self-referral have stabilized or declined significantly over time
for the high self-referral tests. An initial diagnostic strategy consisting of CCTA, MPI or stress
echo did not have a significantly higher yield of obstructive CAD when compared to an initial
strategy with a GXT in those patients referred for invasive angiography for the workup of stable
angina in an Ontario real-world setting. Given the small numbers of those with an index CCTA
who underwent invasive angiography and the resultant wide confidence intervals, it is likely that
our study was underpowered to detect a statistically significant difference in downstream
obstructive CAD between those who had index CCTAs and GXTs.
Tables

Table 1: Ontario Health Insurance Plan (OHIP) diagnostic codes used to determine receipt of the non-invasive cardiac diagnostic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>OHIP Diagnostic Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress Echo</td>
<td>G583, G584</td>
</tr>
<tr>
<td>GXT</td>
<td>G319 21</td>
</tr>
<tr>
<td>MPI</td>
<td>J607, J608, J609, J666, J807, J808, J809, J866 21</td>
</tr>
<tr>
<td>CCTA</td>
<td>X235 72</td>
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</tbody>
</table>

Abbreviations

**GXT**: graded exercise stress test, **stress echo**: stress echocardiogram, **MPI**: myocardial perfusion imaging study, **CCTA**: coronary computed tomography angiography
Table 2: Characteristics of patients receiving and physicians performing coronary computed tomography angiography in Ontario, 2011-2013

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>2,777</td>
<td>5,427</td>
<td>7,013</td>
<td>15,217</td>
<td></td>
</tr>
<tr>
<td><strong>Age in years (mean ± standard deviation)</strong></td>
<td>59.5 ± 12.5</td>
<td>59.7 ± 12.9</td>
<td>60.3 ± 12.9</td>
<td>60.0 ± 12.8</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Female sex (%)</strong></td>
<td>1,192 (42.9%)</td>
<td>2,294 (42.3%)</td>
<td>3,007 (42.9%)</td>
<td>6,493 (42.7%)</td>
<td>0.759</td>
</tr>
<tr>
<td><strong>Top 3 performing specialties</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Diagnostic Radiology</em></td>
<td>2,434 (87.6%)</td>
<td>4,634 (85.4%)</td>
<td>5,520 (79.5%)</td>
<td>12,588 (83.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>Cardiology</em></td>
<td>322 (11.6%)</td>
<td>661 (12.2%)</td>
<td>968 (13.9%)</td>
<td>1,951 (12.9%)</td>
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</tr>
<tr>
<td><em>Nuclear Medicine</em></td>
<td>10 (0.4%)</td>
<td>7 (0.1%)</td>
<td>298 (4.3%)</td>
<td>315 (2.1%)</td>
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</tr>
<tr>
<td><strong>Top 3 referring specialties</strong></td>
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<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
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<td><em>Cardiology</em></td>
<td>2,171 (78.4%)</td>
<td>4,069 (75.2%)</td>
<td>5,407 (77.6%)</td>
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<tr>
<td><em>Cardiac Surgery</em></td>
<td>168 (6.1%)</td>
<td>371 (6.9%)</td>
<td>568 (8.1%)</td>
<td>1,107 (7.3%)</td>
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<tr>
<td><em>Internal Medicine</em></td>
<td>105 (3.8%)</td>
<td>295 (5.5%)</td>
<td>351 (5.0%)</td>
<td>751 (5.0%)</td>
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<tr>
<td><strong>Income quintile</strong></td>
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<tr>
<td>1</td>
<td>432 (15.6%)</td>
<td>825 (15.2%)</td>
<td>1,049 (15.0%)</td>
<td>2,306 (15.2%)</td>
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<tr>
<td>2</td>
<td>475 (17.2%)</td>
<td>961 (17.8%)</td>
<td>1,282 (18.3%)</td>
<td>2,718 (17.9%)</td>
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<td>3</td>
<td>555 (20.1%)</td>
<td>1,072 (19.8%)</td>
<td>1,364 (19.5%)</td>
<td>2,991 (19.7%)</td>
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<td>4</td>
<td>634 (22.9%)</td>
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<td>1,603 (22.9%)</td>
<td>3,433 (22.6%)</td>
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</tr>
<tr>
<td>5</td>
<td>672 (24.3%)</td>
<td>1,357 (25.1%)</td>
<td>1,694 (24.2%)</td>
<td>3,723 (24.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Rural (%)</strong></td>
<td>269 (9.7%)</td>
<td>595 (11.0%)</td>
<td>757 (10.8%)</td>
<td>1,621 (10.7%)</td>
<td>0.184</td>
</tr>
<tr>
<td><strong>Same physician referring/performing (%)</strong></td>
<td>12 (0.4%)</td>
<td>42 (0.8%)</td>
<td>156 (2.2%)</td>
<td>210 (1.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hospital admissions within 30 days</strong></td>
<td>355 (12.8%)</td>
<td>657 (12.1%)</td>
<td>749 (10.7%)</td>
<td>1,761 (11.6%)</td>
<td>0.004</td>
</tr>
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</table>
Table 3: Characteristics of patients receiving and physicians performing graded exercise stress tests in Ontario, 2008-2013

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>264,042</td>
<td>287,164</td>
<td>301,009</td>
<td>308,776</td>
<td>301,285</td>
<td>305,983</td>
<td>1,768,259</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± standard deviation)</td>
<td>57.0 ± 13.1</td>
<td>56.8 ± 13.2</td>
<td>57.1 ± 13.2</td>
<td>57.4 ± 13.3</td>
<td>57.4 ± 13.4</td>
<td>57.5 ± 13.4</td>
<td>57.2 ± 13.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>106,128 (40.2%)</td>
<td>119,199 (41.5%)</td>
<td>125,984 (41.9%)</td>
<td>128,382 (42.1%)</td>
<td>126,953 (42.1%)</td>
<td>128,858 (42.1%)</td>
<td>735,504 (41.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Top 3 performing specialties</td>
<td>174,262 (66.0%)</td>
<td>190,139 (66.2%)</td>
<td>202,400 (67.2%)</td>
<td>211,910 (68.6%)</td>
<td>207,924 (69.0%)</td>
<td>211,798 (69.4%)</td>
<td>1,198,433 (67.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiology</td>
<td>48,986 (18.6%)</td>
<td>51,886 (18.1%)</td>
<td>53,018 (17.6%)</td>
<td>55,452 (18.0%)</td>
<td>54,701 (18.2%)</td>
<td>57,063 (18.7%)</td>
<td>321,106 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>15,610 (5.9%)</td>
<td>15,720 (5.5%)</td>
<td>14,970 (5.0%)</td>
<td>14,344 (4.6%)</td>
<td>13,258 (4.4%)</td>
<td>10,850 (3.6%)</td>
<td>84,752 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Family Medicine</td>
<td>128,085 (63.7%)</td>
<td>137,267 (63.8%)</td>
<td>140,612 (62.9%)</td>
<td>146,074 (62.8%)</td>
<td>156,819 (64.6%)</td>
<td>184,839 (63.9%)</td>
<td>893,696 (63.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Top 3 referring specialties</td>
<td>38,240 (19.0%)</td>
<td>42,221 (19.6%)</td>
<td>46,134 (20.6%)</td>
<td>47,420 (20.4%)</td>
<td>46,312 (19.1%)</td>
<td>59,839 (20.7%)</td>
<td>280,166 (19.9%)</td>
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</tr>
<tr>
<td>Family Medicine</td>
<td>16,230 (8.1%)</td>
<td>16,863 (7.8%)</td>
<td>17,076 (7.6%)</td>
<td>17,791 (7.6%)</td>
<td>17,178 (7.1%)</td>
<td>18,767 (6.5%)</td>
<td>103,905 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>Cardiology</td>
<td>50,890 (19.3%)</td>
<td>55,133 (19.3%)</td>
<td>58,079 (19.4%)</td>
<td>59,146 (19.2%)</td>
<td>57,889 (19.3%)</td>
<td>58,948 (19.3%)</td>
<td>340,085 (19.3%)</td>
<td></td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>52,742 (20.0%)</td>
<td>57,378 (20.0%)</td>
<td>59,995 (20.0%)</td>
<td>62,589 (20.3%)</td>
<td>61,098 (20.3%)</td>
<td>61,914 (20.3%)</td>
<td>355,716 (20.2%)</td>
<td></td>
</tr>
<tr>
<td>Income quintile</td>
<td>46,199 (17.5%)</td>
<td>50,624 (17.7%)</td>
<td>52,544 (17.5%)</td>
<td>53,893 (17.5%)</td>
<td>53,425 (17.8%)</td>
<td>54,595 (17.9%)</td>
<td>311,280 (17.7%)</td>
<td>&lt;0.0001</td>
</tr>
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<td>2</td>
<td>50,890 (19.3%)</td>
<td>55,133 (19.3%)</td>
<td>58,079 (19.4%)</td>
<td>59,146 (19.2%)</td>
<td>57,889 (19.3%)</td>
<td>58,948 (19.3%)</td>
<td>340,085 (19.3%)</td>
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</tr>
<tr>
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<td>52,742 (20.0%)</td>
<td>57,378 (20.0%)</td>
<td>59,995 (20.0%)</td>
<td>62,589 (20.3%)</td>
<td>61,098 (20.3%)</td>
<td>61,914 (20.3%)</td>
<td>355,716 (20.2%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>56,255 (21.4%)</td>
<td>60,985 (21.7%)</td>
<td>64,993 (21.7%)</td>
<td>66,720 (21.7%)</td>
<td>64,900 (21.6%)</td>
<td>66,378 (21.8%)</td>
<td>380,231 (21.6%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>57,220 (21.7%)</td>
<td>62,209 (21.7%)</td>
<td>64,504 (21.5%)</td>
<td>65,478 (21.3%)</td>
<td>63,066 (21.0%)</td>
<td>63,199 (20.7%)</td>
<td>375,676 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>Rural (%)</td>
<td>31,940 (12.1%)</td>
<td>33,365 (11.6%)</td>
<td>33,990 (11.3%)</td>
<td>34,445 (11.2%)</td>
<td>32,795 (10.9%)</td>
<td>31,640 (10.3%)</td>
<td>198,175 (11.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Same physician referring/performing (%)</td>
<td>47,561 (23.6%)</td>
<td>50,404 (23.4%)</td>
<td>53,926 (24.1%)</td>
<td>56,070 (24.0%)</td>
<td>52,477 (21.6%)</td>
<td>65,356 (22.4%)</td>
<td>325,794 (23.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital admissions within 30 days</td>
<td>4,937 (1.9%)</td>
<td>4,928 (1.7%)</td>
<td>5,039 (1.7%)</td>
<td>5,143 (1.7%)</td>
<td>5,087 (1.7%)</td>
<td>5,134 (1.7%)</td>
<td>30,268 (1.7%)</td>
<td>&lt;0.0001</td>
</tr>
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</table>
Table 4: Characteristics of patients receiving and physicians performing myocardial perfusion imaging scans in Ontario, 2008-2013

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<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>210,523</td>
<td>217,095</td>
<td>218,106</td>
<td>225,254</td>
<td>224,244</td>
<td>223,459</td>
<td>1,318,681</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (mean ± standard deviation)</td>
<td>61.7 ± 13.5</td>
<td>62.0 ± 13.5</td>
<td>62.4 ± 13.5</td>
<td>62.8 ± 13.5</td>
<td>63.2 ± 13.5</td>
<td>63.7 ± 13.5</td>
<td>62.7 ± 13.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>102,263 (48.6%)</td>
<td>107,395 (49.5%)</td>
<td>109,360 (50.1%)</td>
<td>112,693 (50.0%)</td>
<td>112,902 (50.3%)</td>
<td>112,343 (50.3%)</td>
<td>656,956 (49.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Top 3 performing specialties</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nuclear Medicine</td>
<td>126,719 (60.2%)</td>
<td>128,622 (59.2%)</td>
<td>128,388 (58.9%)</td>
<td>129,141 (57.3%)</td>
<td>126,145 (56.3%)</td>
<td>121,462 (54.6%)</td>
<td>760,477 (57.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiology</td>
<td>46,328 (22.0%)</td>
<td>48,316 (22.3%)</td>
<td>49,999 (22.9%)</td>
<td>52,791 (23.4%)</td>
<td>53,952 (24.1%)</td>
<td>55,363 (24.9%)</td>
<td>306,749 (23.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diagnostic Radiology</td>
<td>30,489 (14.5%)</td>
<td>33,413 (15.4%)</td>
<td>33,533 (15.4%)</td>
<td>35,800 (15.9%)</td>
<td>39,910 (17.8%)</td>
<td>42,613 (19.1%)</td>
<td>215,758 (16.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Top 3 referring specialties</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family Medicine</td>
<td>79,693 (37.9%)</td>
<td>80,878 (37.3%)</td>
<td>79,913 (36.7%)</td>
<td>81,909 (36.4%)</td>
<td>80,886 (36.1%)</td>
<td>74,958 (33.7%)</td>
<td>478,237 (36.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiology</td>
<td>70,469 (33.5%)</td>
<td>71,403 (32.9%)</td>
<td>70,958 (32.6%)</td>
<td>71,983 (32.0%)</td>
<td>69,981 (31.3%)</td>
<td>70,037 (31.5%)</td>
<td>424,831 (32.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>20,163 (9.6%)</td>
<td>19,310 (8.9%)</td>
<td>19,392 (8.9%)</td>
<td>19,969 (8.9%)</td>
<td>19,992 (8.9%)</td>
<td>20,836 (9.4%)</td>
<td>119,662 (9.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Income quintile</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1</td>
<td>41,342 (19.7%)</td>
<td>42,296 (19.5%)</td>
<td>42,593 (19.6%)</td>
<td>44,003 (19.6%)</td>
<td>43,696 (19.5%)</td>
<td>43,502 (19.5%)</td>
<td>257,432 (19.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>43,266 (20.6%)</td>
<td>44,529 (20.6%)</td>
<td>44,545 (20.5%)</td>
<td>46,010 (20.5%)</td>
<td>45,692 (20.4%)</td>
<td>45,622 (20.5%)</td>
<td>269,664 (20.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>41,647 (19.8%)</td>
<td>43,417 (20.1%)</td>
<td>43,243 (19.9%)</td>
<td>45,040 (20.1%)</td>
<td>45,387 (20.3%)</td>
<td>44,591 (20.0%)</td>
<td>263,325 (20.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>41,702 (19.9%)</td>
<td>43,370 (20.0%)</td>
<td>44,579 (20.5%)</td>
<td>46,120 (20.5%)</td>
<td>45,769 (20.5%)</td>
<td>45,980 (20.6%)</td>
<td>267,520 (20.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5</td>
<td>42,017 (20.0%)</td>
<td>42,852 (19.8%)</td>
<td>42,476 (19.5%)</td>
<td>43,393 (19.3%)</td>
<td>42,994 (19.2%)</td>
<td>43,043 (19.3%)</td>
<td>256,775 (19.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rural (%)</td>
<td>18,825 (8.9%)</td>
<td>19,699 (9.1%)</td>
<td>20,568 (9.4%)</td>
<td>21,839 (9.7%)</td>
<td>22,216 (9.9%)</td>
<td>22,229 (10.0%)</td>
<td>125,376 (9.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Same physician referring/performing (%)</td>
<td>18,825 (8.9%)</td>
<td>19,699 (9.1%)</td>
<td>20,568 (9.4%)</td>
<td>21,839 (9.7%)</td>
<td>22,216 (9.9%)</td>
<td>22,229 (10.0%)</td>
<td>125,376 (9.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital admissions within 30 days</td>
<td>9,861 (4.7%)</td>
<td>10,414 (4.8%)</td>
<td>10,454 (4.8%)</td>
<td>11,262 (5.0%)</td>
<td>11,728 (5.2%)</td>
<td>12,132 (5.4%)</td>
<td>65,851 (5.0%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 5: Characteristics of patients receiving and physicians performing stress echocardiography in Ontario, 2011-2013

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
<th>p-value</th>
</tr>
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<tbody>
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<td><strong>N</strong></td>
<td>16,420</td>
<td>64,332</td>
<td>72,039</td>
<td>152,791</td>
<td></td>
</tr>
<tr>
<td><strong>Age (mean ± standard deviation)</strong></td>
<td>59.2 ± 13.2</td>
<td>58.9 ± 13.3</td>
<td>58.7 ± 13.5</td>
<td>58.8 ± 13.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Female sex (%)</strong></td>
<td>7,425 (45.2%)</td>
<td>29,383 (45.7%)</td>
<td>33,075 (45.9%)</td>
<td>69,883 (45.7%)</td>
<td>0.250</td>
</tr>
<tr>
<td><strong>Top 3 performing specialties</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiology</td>
<td>14,262 (86.9%)</td>
<td>56,427 (87.7%)</td>
<td>62,051 (86.6%)</td>
<td>132,740 (87.1%)</td>
<td></td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>768 (4.7%)</td>
<td>3,101 (4.8%)</td>
<td>4,813 (6.7%)</td>
<td>8,682 (5.7%)</td>
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</tr>
<tr>
<td>Family Medicine</td>
<td>767 (4.7%)</td>
<td>1,400 (2.2%)</td>
<td>792 (1.1%)</td>
<td>2,959 (1.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Top 3 referring specialties</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family Medicine</td>
<td>5,335 (59.9%)</td>
<td>30,307 (67.6%)</td>
<td>42,052 (62.3%)</td>
<td>77,694 (64.1%)</td>
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</tr>
<tr>
<td>Cardiology</td>
<td>2,953 (33.2%)</td>
<td>11,699 (26.1%)</td>
<td>20,081 (29.7%)</td>
<td>34,733 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>122 (1.4%)</td>
<td>605 (1.3%)</td>
<td>1,125 (1.7%)</td>
<td>1,852 (1.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Income quintile</strong></td>
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<td></td>
<td></td>
<td></td>
<td>0.607</td>
</tr>
<tr>
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<td>3,149 (19.2%)</td>
<td>12,542 (19.6%)</td>
<td>14,107 (19.6%)</td>
<td>29,798 (19.6%)</td>
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</tr>
<tr>
<td>2</td>
<td>3,142 (19.2%)</td>
<td>12,158 (19.0%)</td>
<td>13,519 (18.8%)</td>
<td>28,819 (18.9%)</td>
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</tr>
<tr>
<td>3</td>
<td>3,042 (18.6%)</td>
<td>11,907 (18.6%)</td>
<td>13,395 (18.6%)</td>
<td>28,344 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3,536 (21.6%)</td>
<td>13,489 (21.0%)</td>
<td>15,265 (21.3%)</td>
<td>32,290 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3,492 (21.3%)</td>
<td>14,018 (21.9%)</td>
<td>15,542 (21.6%)</td>
<td>33,052 (21.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Rural (%)</strong></td>
<td>1,682 (10.3%)</td>
<td>6,172 (9.6%)</td>
<td>5,936 (8.2%)</td>
<td>13,790 (9.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Same physician referring/performing (%)</strong></td>
<td>2,231 (25.0%)</td>
<td>8,956 (19.9%)</td>
<td>16,956 (25.0%)</td>
<td>28,143 (23.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hospital admissions within 30 days</strong></td>
<td>293 (1.8%)</td>
<td>1,172 (1.8%)</td>
<td>1,383 (1.9%)</td>
<td>2,848 (1.9%)</td>
<td>0.298</td>
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</table>
Table 6: Head-to-head comparison of patients receiving and physicians performing MPIs, CCTAs, GXTs and Stress Echos in Ontario, 2011-2013

<table>
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<tr>
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<th>CCTA</th>
<th>GXT</th>
<th>Stress Echo</th>
<th>Total</th>
<th>p-value</th>
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<tr>
<td>N</td>
<td>672,957</td>
<td>15,217</td>
<td>916,044</td>
<td>152,791</td>
<td>1,757,009</td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Mean ± Standard</td>
<td>63.2 ±</td>
<td>60.0 ±</td>
<td>57.4 ±</td>
<td>58.8 ±</td>
<td>59.8 ±</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>deviation)</td>
<td>13.5</td>
<td>12.8</td>
<td>13.4</td>
<td>13.4</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>337,938 (50.2%)</td>
<td>6,493 (42.7%)</td>
<td>384,193 (41.9%)</td>
<td>69,883 (45.7%)</td>
<td>798,507 (45.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital Admission within 30 days</td>
<td>35,122 (5.2%)</td>
<td>1,761 (11.6%)</td>
<td>15,364 (1.7%)</td>
<td>2,848 (1.9%)</td>
<td>55,095 (3.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Income Quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>131,201 (19.6%)</td>
<td>2,306 (15.2%)</td>
<td>161,913 (17.7%)</td>
<td>29,798 (19.6%)</td>
<td>325,218 (18.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>137,324 (20.5%)</td>
<td>2,718 (17.9%)</td>
<td>175,983 (19.3%)</td>
<td>28,819 (18.9%)</td>
<td>344,844 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>135,018 (20.1%)</td>
<td>2,991 (19.7%)</td>
<td>185,601 (20.3%)</td>
<td>28,344 (18.6%)</td>
<td>351,954 (20.1%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>137,869 (20.6%)</td>
<td>3,433 (22.6%)</td>
<td>197,998 (21.7%)</td>
<td>32,290 (21.2%)</td>
<td>371,590 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>129,430 (19.3%)</td>
<td>3,723 (24.5%)</td>
<td>191,743 (21.0%)</td>
<td>33,052 (21.7%)</td>
<td>357,948 (20.4%)</td>
<td></td>
</tr>
<tr>
<td>Rural (%)</td>
<td>66,284 (9.9%)</td>
<td>1,621 (10.7%)</td>
<td>98,880 (10.8%)</td>
<td>13,790 (9.0%)</td>
<td>180,575 (10.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Same physician referring/performing (%)</td>
<td>66,284 (9.8%)</td>
<td>210 (1.4%)</td>
<td>173,903 (22.7%)</td>
<td>28,143 (23.1%)</td>
<td>248,193 (15.7%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations

GXT: graded exercise stress test, stress echo: stress echocardiogram, MPI: myocardial perfusion imaging study, CCTA: coronary computed tomography angiography
Table 7: Head-to-head comparison of physician specialties performing MPI, CCTA, GXT and stress echo in Ontario, 2011-2013

<table>
<thead>
<tr>
<th>Specialty Performing (%)</th>
<th>MPI</th>
<th>CCTA</th>
<th>GXT</th>
<th>Stress Echo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>24.1</td>
<td>12.9</td>
<td>69.0</td>
<td>87.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diagnostic Radiology</td>
<td>17.6</td>
<td>83.1</td>
<td>&lt;0.01</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Nuclear Medicine</td>
<td>56.1</td>
<td>2.1</td>
<td>0.4</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.2</td>
<td>1.9</td>
<td>30.6</td>
<td>11.7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations

GXT: graded exercise stress test, stress echo: stress echocardiogram, MPI: myocardial perfusion imaging study, CCTA: coronary computed tomography angiography

Table 8: Head-to-head comparison of physician specialties referring for MPI, CCTA, GXT and stress echo in Ontario, 2011-2013

<table>
<thead>
<tr>
<th>Specialty Referring (%)</th>
<th>MPI</th>
<th>CCTA</th>
<th>GXT</th>
<th>Stress Echo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>31.6</td>
<td>76.9</td>
<td>20.1</td>
<td>28.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>9.1</td>
<td>5.0</td>
<td>7.0</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Family Medicine</td>
<td>35.4</td>
<td>6.0</td>
<td>63.8</td>
<td>64.1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>23.9</td>
<td>12.1</td>
<td>9.1</td>
<td>5.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations

GXT: graded exercise stress test, stress echo: stress echocardiogram, MPI: myocardial perfusion imaging study, CCTA: coronary computed tomography angiography
Table 9: Temporal change in the age-and sex-adjusted rates of MPI, GXT, CCTA and stress echo per 1000 adult population of Ontario aged 20 and above, 2008-2013

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Mean Annual Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPI</td>
<td>21.1</td>
<td>21.3</td>
<td>20.8</td>
<td>21.0</td>
<td>20.4</td>
<td>19.8</td>
<td>-1.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GXT</td>
<td>26.7</td>
<td>28.4</td>
<td>29.1</td>
<td>29.3</td>
<td>28.0</td>
<td>28.0</td>
<td>0.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CCTA</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
<td>26%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stress Echo</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.6</td>
<td>5.9</td>
<td>6.5</td>
<td>60%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>52.2</td>
<td>54.8</td>
<td>54.9</td>
<td>1.6%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations

GXT: graded exercise stress test, stress echo: stress echocardiogram, MPI: myocardial perfusion imaging study, CCTA: coronary computed tomography angiography, N/A: Not applicable

Table 10: Definition of cardiovascular disease used in the study

<table>
<thead>
<tr>
<th>Hospitalization with main diagnosis of</th>
<th>ICD-9 code</th>
<th>ICD-10 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myocardial Infarction 99</td>
<td>410</td>
<td>I21, I22</td>
</tr>
<tr>
<td>Stroke 101</td>
<td>430, 431, 434, 436, 362.3</td>
<td>I60, I61, I63 (excluding I63.6), I64, H34.1</td>
</tr>
<tr>
<td>Congestive Heart Failure 102</td>
<td>428</td>
<td>I50</td>
</tr>
<tr>
<td>Percutaneous Coronary Intervention 100</td>
<td>4802, 4803, 4809</td>
<td>Canadian Classification of Health Intervention codes 1IJ50, 1IJ54, 1IJ57GQ</td>
</tr>
<tr>
<td>Coronary Artery Bypass Grafting 100</td>
<td>481</td>
<td>Canadian Classification of Health Intervention code 1IJ76</td>
</tr>
</tbody>
</table>

* ICD-9 codes were used prior to April 1, 2002 after which ICD-10 disease codes were used.
Table 11: Baseline characteristics of the patient population

<table>
<thead>
<tr>
<th></th>
<th>CCTA N= 1,748</th>
<th>GXT N=175,900</th>
<th>MPI N=128,622</th>
<th>Stress Echo N=43,223</th>
<th>Total N=349,493</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Age ± SD</strong></td>
<td>59.2 ± 13.6</td>
<td>54.8 ± 13.3</td>
<td>61.6 ± 14.1</td>
<td>57.1 ± 13.6</td>
<td>57.6 ± 14.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Female Sex (%)</strong></td>
<td>742 (42.4)</td>
<td>81,515 (46.3)</td>
<td>71,734 (55.8)</td>
<td>21,812 (50.5)</td>
<td>175,803 (50.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (%)</strong></td>
<td>328 (18.8)</td>
<td>32,689 (18.6)</td>
<td>34,931 (27.2)</td>
<td>8,782 (20.3)</td>
<td>76,730 (22.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>977 (55.9)</td>
<td>78,331 (44.5)</td>
<td>73,458 (57.1)</td>
<td>21,842 (50.5)</td>
<td>174,608 (50.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Income quintile (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1</td>
<td>235 (13.4)</td>
<td>30,045 (17.1)</td>
<td>24,565 (19.1)</td>
<td>8,371 (19.4)</td>
<td>63,216 (18.1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>317 (18.1)</td>
<td>33,589 (19.1)</td>
<td>25,750 (20.0)</td>
<td>8,029 (18.6)</td>
<td>67,685 (19.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>316 (18.1)</td>
<td>36,162 (20.5)</td>
<td>25,597 (19.9)</td>
<td>7,990 (18.5)</td>
<td>70,065 (20.0)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>360 (20.6)</td>
<td>38,077 (21.6)</td>
<td>25,902 (20.1)</td>
<td>8972 (20.8)</td>
<td>73,311 (21.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>495 (28.3)</td>
<td>36,078 (20.5)</td>
<td>36,078 (28.0)</td>
<td>9453 (21.9)</td>
<td>71,012 (20.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**

GXT: graded exercise stress test, stress echo: stress echocardiogram, MPI: myocardial perfusion imaging study, CCTA: coronary computed tomography angiography
Table 12: Invasive angiography and subsequent non-invasive cardiac diagnostic tests amongst patients with index CCTA, GXT, MPI and stress echo

<table>
<thead>
<tr>
<th></th>
<th>CCTA N= 1,748</th>
<th>GXT N=175,900</th>
<th>MPI N=128,622</th>
<th>Stress Echo N=43,223</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive angiogram within 6 months (%)</td>
<td>137 (7.8)</td>
<td>8,299 (4.7)</td>
<td>8,354 (6.5)</td>
<td>2,029 (4.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Another non-invasive test within 6 months (%)</td>
<td>252 (14.4)</td>
<td>29,127(16.6)</td>
<td>19,008(14.8)</td>
<td>4,541 (10.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Abbreviations**

**GXT:** graded exercise stress test, **stress echo:** stress echocardiogram, **MPI:** myocardial perfusion imaging study, **CCTA:** coronary computed tomography angiography
Table 13: Type of subsequent cardiac non-invasive diagnostic test

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Subsequent CCTA (%)</th>
<th>Subsequent GXT (%)</th>
<th>Subsequent MPI (%)</th>
<th>Subsequent Stress Echo (%)</th>
<th>Total subsequent tests (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index CCTA</td>
<td>28 (11.1)</td>
<td>89 (35.3)</td>
<td>110 (43.7)</td>
<td>25 (9.9)</td>
<td>252 (14.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Index GXT</td>
<td>664 (2.3)</td>
<td>4,308 (14.8)</td>
<td>20,825 (71.5)</td>
<td>3,330 (11.4)</td>
<td>29,127 (16.6)</td>
<td></td>
</tr>
<tr>
<td>Index MPI</td>
<td>647 (3.4)</td>
<td>2816 (14.8)</td>
<td>14,814 (77.9)</td>
<td>731 (3.9)</td>
<td>19,008 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Index Stress echo</td>
<td>344 (7.6)</td>
<td>471 (10.8)</td>
<td>3,043 (67.0)</td>
<td>683 (15.0)</td>
<td>4,541 (10.5)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations

**GXT**: graded exercise stress test, **stress echo**: stress echocardiogram, **MPI**: myocardial perfusion imaging study, **CCTA**: coronary computed tomography angiography
Table 14: Characteristics of patients who underwent angiography for evaluation of stable angina, by index cardiac non-invasive test

<table>
<thead>
<tr>
<th></th>
<th>CCTA N=113</th>
<th>GXT N=6,742</th>
<th>MPI N=6,877</th>
<th>Stress Echo N=1,735</th>
<th>Total N=15,467</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>62.8 ± 9.8</td>
<td>61.4 ± 10.5</td>
<td>64.6 ± 10.9</td>
<td>63.1 ± 10.7</td>
<td>63.0 ± 10.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum Creatinine in umol/l (mean ± SD)</td>
<td>78.06 ± 18.58</td>
<td>83.17 ± 48.70</td>
<td>94.14 ± 102.88</td>
<td>83.74 ± 59.56</td>
<td>88.22 ± 79.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>39 (34.5%)</td>
<td>1,981 (29.4%)</td>
<td>2,672 (38.9%)</td>
<td>513 (29.6%)</td>
<td>5,205 (33.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>77 (68.8%)</td>
<td>4,309 (65.1%)</td>
<td>4,898 (71.7%)</td>
<td>1,136 (67.9%)</td>
<td>10,420 (68.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76 (67.3%)</td>
<td>4,097 (60.8%)</td>
<td>4,838 (70.4%)</td>
<td>1,082 (62.4%)</td>
<td>10,093 (65.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female Sex (%)</td>
<td>49 (43.4%)</td>
<td>2,415 (35.8%)</td>
<td>2,822 (41.0%)</td>
<td>696 (40.1%)</td>
<td>5,982 (38.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (%)</td>
<td>&lt;6</td>
<td>236 (3.7%)</td>
<td>363 (5.4%)</td>
<td>64 (4.0%)</td>
<td>667 (4.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>&lt;6</td>
<td>201 (3.1%)</td>
<td>356 (5.3%)</td>
<td>55 (3.4%)</td>
<td>617 (4.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Charlson score (mean ± SD)</td>
<td>0.19 ± 0.53</td>
<td>0.15 ± 0.60</td>
<td>0.27 ± 0.83</td>
<td>0.17 ± 0.70</td>
<td>0.21 ± 0.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>21 (18.9%)</td>
<td>1,312 (19.6%)</td>
<td>1,272 (18.6%)</td>
<td>349 (20.4%)</td>
<td>2,954 (19.2%)</td>
<td>0.617</td>
</tr>
<tr>
<td>Former</td>
<td>26 (23.4%)</td>
<td>1,763 (26.3%)</td>
<td>1,853 (27.1%)</td>
<td>451 (26.3%)</td>
<td>4,093 (26.6%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>64 (57.7%)</td>
<td>3,536 (52.8%)</td>
<td>3,646 (53.2%)</td>
<td>890 (52.0%)</td>
<td>8,136 (52.9%)</td>
<td></td>
</tr>
<tr>
<td>ST changes at rest on ECG (%)</td>
<td>7 (6.2%)</td>
<td>697 (10.3%)</td>
<td>822 (12.0%)</td>
<td>179 (10.3%)</td>
<td>1,705 (11.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CCS symptom scale (%) (stable angina)</td>
<td>&lt;6</td>
<td>186 (2.8%)</td>
<td>152 (2.2%)</td>
<td>25 (1.4%)</td>
<td>365 (2.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Income quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>15 (13.4%)</td>
<td>1,130 (16.8%)</td>
<td>1,255 (18.3%)</td>
<td>354 (20.4%)</td>
<td>2,754 (17.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (16.1%)</td>
<td>1,359 (20.2%)</td>
<td>1,479 (21.6%)</td>
<td>324 (18.7%)</td>
<td>3,180 (20.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 (21.4%)</td>
<td>1,497 (22.3%)</td>
<td>1,435 (20.9%)</td>
<td>337 (19.5%)</td>
<td>3,293 (21.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 (23.2%)</td>
<td>1,370 (20.4%)</td>
<td>1,386 (20.2%)</td>
<td>354 (20.4%)</td>
<td>3,136 (20.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (25.9%)</td>
<td>1,363 (20.3%)</td>
<td>1,302 (19.0%)</td>
<td>363 (21.0%)</td>
<td>3,057 (19.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations

GXT: graded exercise stress test, stress echo: stress echocardiogram, MPI: myocardial perfusion imaging study, CCTA: coronary computed tomography angiography

(SMALL CELLS <6 HAVE BEEN SUPRESSED)
Table 15: Unadjusted, age-and-sex adjusted and fully adjusted logistic regression models for the outcome of progression to invasive angiography

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCTA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.72 (1.44, 2.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.49 (1.25, 1.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.49 (1.25, 1.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MPI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.40 (1.36, 1.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.19 (1.16, 1.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.16 (1.12, 1.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Stress Echo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.96 (0.95, 1.05)</td>
<td>0.83</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>0.95 (0.90, 0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.94 (0.89, 0.98)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

**Abbreviations**

**GXT**: graded exercise stress test, **stress echo**: stress echocardiogram, **MPI**: myocardial perfusion imaging study, **CCTA**: coronary computed tomography angiography
Table 16: Unadjusted, age- and sex-adjusted and fully adjusted logistic regression models for the outcome of obstructive CAD in patients who underwent angiography for the assessment of stable coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCTA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.31 (0.89, 1.92)</td>
<td>0.17</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.44 (0.96, 2.16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.50 (0.90, 2.48)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>MPI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.97 (0.91, 1.04)</td>
<td>0.42</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>0.90 (0.84, 0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.92 (0.85, 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Stress Echo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.92 (0.82, 1.02)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>0.88 (0.78, 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.95 (0.84, 1.08)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Abbreviations**

**GXT**: graded exercise stress test, **stress echo**: stress echocardiogram, **MPI**: myocardial perfusion imaging study, **CCTA**: coronary computed tomography angiography
Table 17: Unadjusted, age- and sex-adjusted and fully adjusted logistic regression models for the outcome of obstructive CAD in patients who underwent angiography for evaluation of stable angina- after removal of patients who had a subsequent non-invasive cardiac diagnostic test

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCTA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.45 (0.92, 2.29)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.67 (1.02, 2.71)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.90 (1.06, 3.40)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>MPI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.10 (1.00, 1.21)</td>
<td>0.05</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1.01 (0.91, 1.11)</td>
<td>0.91</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.04 (0.93, 1.17)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Stress Echo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.89 (0.77, 1.04)</td>
<td>0.14</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>0.84 (0.71, 0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.87 (0.73, 1.04)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Abbreviations**

GXT: graded exercise stress test, stress echo: stress echocardiogram, MPI: myocardial perfusion imaging study, CCTA: coronary computed tomography angiography
Figures

Figure 1: Temporal change in the age-and sex-adjusted rates of MPI, GXT, CCTA and stress echo per 1000 adult population of Ontario aged 20 and above, 2008-2013
Figure 2: Proportion of MPIs, GXTs, CCTAs and stress echos attributable to self-referral in Ontario, 2008-2013
Figure 3: Schematic representation of the design of the cohort study

Figure 4: Derivation of the study cohort (objective 1)

464,647 patients ≥ 20 years of age had GXT, MPI, Stress echo or CCTA in Ontario in 2012

45,711 excluded due to having non-invasive diagnostic test in past year

418,936 patients

69,443 excluded due to previous CVD diagnosis

349,493 patients in final cohort
Figure 5: Derivation of the study population (objective 2)

349,493 patients in full cohort

18,819 patients underwent subsequent invasive angiography

15,467 patients evaluated for stable angina
Figure 6: Multivariable model displaying the odds ratios and 95% confidence intervals of progression to invasive angiography amongst patients with differing index cardiac non-invasive diagnostic tests (GXT is the reference test)

* adjusted for age, sex, presence of diabetes mellitus, hypertension and income quintile
Figure 7: Multivariable model displaying the odds ratios and 95% confidence intervals of the yield of obstructive CAD amongst the different index cardiac non-invasive diagnostic tests in patients who underwent invasive angiography for the assessment of stable angina (GXT is the reference test)

* adjusted for age, sex, presence of diabetes mellitus, dyslipidemia, hypertension, income quintile, resting ECG abnormalities, Charlson co-morbidity index score, serum creatinine, smoking history, CCS class angina symptom scale, COPD and PVD
Figure 8: Multivariable model displaying the odds ratios and 95% confidence intervals of the yield of obstructive CAD amongst the different index cardiac non-invasive diagnostic tests in patients who underwent invasive angiography for the assessment of stable angina - after removing patients who had a subsequent non-invasive test (GXT is the reference test)

* adjusted for age, sex, presence of diabetes mellitus, dyslipidemia, hypertension, income quintile, resting ECG abnormalities, Charlson co-morbidity index score, serum creatinine, smoking history, CCS class angina symptom scale, COPD and PVD
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Appendices

Appendix 1: Search strategy for identifying published literature examining the temporal trends in the utilization of cardiac non-invasive diagnostic tests

We systematically searched for articles via a MEDLINE search between the years 1966-2015. A combination of the following keywords used were:

1. For CCTA: “coronary computed tomography angiography” OR “coronary CTA” OR “CCTA” OR “CTA” OR “coronary CT” OR “cardiac CT” AND “temporal trends” OR “resource utilization” OR “utilization”.

2. For MPI: “MPI” OR “myocardial perfusion scan” OR “SPECT” AND “temporal trends” OR “resource utilization” OR “utilization”.

3. For GXT: “GXT” OR “graded exercise stress test” OR “exercise stress test” AND “temporal trends” OR “resource utilization” OR “utilization”.

4. For stress echo: “stress echo” OR “stress echocardiogram” AND “temporal trends” OR “resource utilization” OR “utilization”.

These searches produced a total of 370 English language articles. Out of these, 8 papers were found to have pertinent information on the temporal utilization trends of CCTA, stress echo, GXT and/or MPI. Further, the references of all pertinent papers were scanned and we were able to identify another relevant non-MEDLINE listed publication.
Appendix 2: Search strategy for identifying published literature assessing the results on angiography (normal, obstructive, non-obstructive) relative to an upstream cardiac non-invasive diagnostic test

We systematically searched for articles via a MEDLINE search between the years 1966-2015. A combination of the following keywords used were:

1. “Yield of obstructive coronary artery disease” OR “Yield of obstructive CAD”

2. For CCTA: “coronary computed tomography angiography” OR “coronary CTA” OR “CCTA” OR “CTA” OR “coronary CT” OR “cardiac CT” AND “downstream obstructive CAD” OR “downstream obstructive coronary artery disease” OR “downstream normal angiography” OR “downstream normal angioogram” OR “downstream non-obstructive CAD”

3. For stress echo: “stress echo” OR “stress echocardiogram” AND “downstream obstructive CAD” OR “downstream obstructive coronary artery disease” OR “downstream normal angiography” OR “downstream normal angioogram” OR “downstream non-obstructive CAD”

4. For MPI: “MPI” OR “myocardial perfusion scan” OR “SPECT” AND “downstream obstructive CAD” OR “downstream obstructive coronary artery disease” OR “downstream normal angiography” OR “downstream normal angioogram” OR “downstream non-obstructive CAD”

5. For GXT: “GXT” OR “graded exercise stress test” OR “exercise stress test” AND “downstream obstructive CAD” OR “downstream obstructive coronary artery disease” OR “downstream normal angiography” OR “downstream normal angioogram” OR “downstream non-obstructive CAD”
These searches yielded a total of 41 studies, 4 of which discussed downstream normal angiography, obstructive CAD, non-obstructive CAD or yield of obstructive CAD for any of the cardiac non-invasive diagnostic tests.