Keywords: Heart Failure, Coronary CT Angiography, Cost-Effectiveness, Randomized Controlled Trial

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Abbreviations
HF: Heart Failure
ICA: Invasive Coronary Angiography
CCTA: Coronary Computed Tomography Angiography
CAD: Coronary Artery Disease
LVEF: Left Ventricular Ejection Fraction
NYHA: New York Heart Association
MACE: Major Adverse Cardiovascular Events
CCE: Composite Cardiac Events
ACS: Acute Coronary Syndrome
QoL: Quality of Life
ICER: Incremental Cost-Effectiveness Ratio

Background

The rising global prevalence and burden of heart failure (HF) has resulted in the increase in testing and costs. [1,2] Since patients with ischemic cardiomyopathy potentially benefit from coronary revascularization, invasive coronary angiography (ICA) is often used. [3] Unfortunately, ICA is costly, a limited resource, and has inherent risks; therefore alternative, safe, cost-effective, non-invasive strategies are desirable.

Coronary computed tomography angiography (CCTA) is a non-invasive diagnostic test [4-6] with prognostic value, [7,8] and in HF patients, has a reported sensitivity and specificity of 73-98% and 99-100%, respectively (ref Andreini 18 and Ghostine 19). The 2016 European Society of Cardiology guidelines recommend (class IIb) the use of CCTA in HF patients with low–intermediate pre-test probability for coronary artery disease (CAD). The use of CCTA in HF patients with systolic dysfunction is deemed as 'appropriate'.[9] Whether or not CCTA can reduce costs in HF patients for diagnosis and management is unknown.

The objective of this randomized controlled trial was to determine the financial impact, at 12 months, of an initial diagnostic strategy of CCTA in patients with HF of unknown etiology.

Methods

The design of this multicentre, international randomized controlled trial has been previously described and was part of the IMAGE-HF (Imaging Modalities to Assist with Guiding therapy and the Evaluation of patients with Heart Failure) study. [10] Patients with HF of unknown etiology were screened. Eligible patients had a documented history of left ventricular dysfunction (LVEF <50%), or New York Heart Association (NYHA) class II-IV symptoms, or an HF admission to a hospital or emergency department within the past 12 months. Patients with a history of myocardial infarction could be enrolled if the treating

physician believed that the etiology of HF was uncertain. Exclusions were: age <18 years, lacked informed consent, glomerular filtration rate <45 ml/min, allergy to intravenous contrast agents, contraindications to radiation exposure, inability to perform 20 second breath-hold, history of coronary revascularization, or CCTA or ICA within the preceding 12 months. Enrolled patients were randomized to either the CCTA or ICA strategy and were stratified according to recruitment site. Enrolling centres were from academic institutions in Canada (3 sites) and Finland (3 sites) and are listed in the appendix

Computed Tomography and Invasive Coronary Angiography

Prior to CCTA, non-contrast prospective ECG-triggered CT was acquired to measure coronary artery calcification. [11,12] CCTA was performed using ≥64-slice CT scanners and radiation reduction techniques were encouraged. Patients with uncontrolled heart rates, atrial fibrillation or ectopy were excluded depending on the capability of each institution's scanner and clinical practice. ICA was performed according to standard clinical protocols, with selective coronary injection and imaging from multiple views [13]. CCTA and ICA were evaluated and reported as per local clinical practice. For data capture, a 17-segment model and a 4-point grading score [normal, mild (<50%), moderate (50-69%), severe (≥70%)] was used. [5,7]

Patients with obstructive CAD (defined as coronary diameter stenosis ≥50%) were further categorized as having high-risk or non-high-risk CAD. High-risk CAD was defined as: left main stenosis ≥50%, 3 vessel disease (≥70%), or 2-vessel disease involving the proximal left anterior descending artery (≥70%). [7]

The etiology of HF (ischemic versus non-ischemic) was determined using a modified Felker classification based on history of myocardial infarction or coronary anatomy (≥70% stenosis of the left main, proximal LAD, or ≥2 epicardial arteries). [14]

Outcome Measures

Patient follow-up was performed at 3, 12 months, and annually thereafter until the end of the study, death or study exit. The primary outcome was the direct medical costs (average per-patient healthcare cost) of the CCTA and ICA strategies up to 12 months post randomization. Secondary outcome measures included: all-cause death, cardiac death, myocardial infarction (MI), acute coronary syndrome (ACS), resuscitated cardiac arrest, cardiac re-hospitalization for worsening heart failure or arrhythmia, procedural complications (death, MI, stroke, vascular complications, severe allergic reactions; contrast nephropathy), and rates of normal ICA. Composite outcomes were also collected (major adverse cardiovascular event (MACE): cardiac death and MI; and composite clinical endpoint (CCE): MACE, resuscitated cardiac arrest, ACS, and cardiac hospitalization. An events committee (blinded to patient allocation) reviewed and adjudicated each clinical event.

The study was approved by each institutional research ethics board and informed consent was obtained from each patient. This study was conducted in accordance to the Declaration of Helsinki, Good Clinical Practice and the TriCouncil Policy.

Statistical Analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and STATA 15.1 (StataCorp LLC, College Station, Texas). Categorical variables are presented as frequencies and continuous variables are presented as means with standard deviations or medians with inter-quartile ranges. Continuous variables were compared using the student's t-test and categorical variables using Fisher's exact test. Statistical significance was defined as $p < 0.05$.

An 'intention-to-treat' analysis was performed using all patients who were randomized to CCTA (121 patients) versus ICA (125 patients), irrespective of whether they received the assigned strategy. Clinical decision making was based on CCTA or ICA results and no downstream testing was mandated. Secondary analyses were performed using an 'as-

tested' analysis based on the modality received (116 CT and 130 ICA patients) (Supplemental).

The financial impact in terms of health care costs was assessed in 2017 Canadian dollars (CDN$). Costs were grouped into five main categories: initial imaging modalities, medications, hospitalizations, cardiac procedures and further cardiac diagnostic testing. Outpatient drug utilization data was collected at the time of baseline and follow-up visits: patients were asked to have medication available for all visits. Medications were reviewed directly with the patient in clinic/ via telephone interview/ or review of clinical notes. Current medication and dose in addition to any medications that may have been started or stopped during the follow up period were captured on the case report form. Inpatient drug utilization was calculated using global hospital cost.

The total costs for each patient up to 12 months were estimated through patient follow-up surveys and through valuation of resource use using Canadian unit costs. To assess the financial impact of the management algorithm using CCTA we compared this to ICA (Appendix A). [15] The costs savings associated with the use of CCTA and the underlying uncertainty around this was derived through non-parametric bootstrapping where the clinical trial sample was simulated through sampling from the clinical trial data set with replication. [16] Given the Bayesian nature of the approach adopted, the analysis provides an estimate of the probability that management through CCTA will be cost saving compared to the use of ICA. The primary analysis was conducted using an "intention to treat" approach and given the low degree of missing data at 12 months was based on patients with complete data. Further analyses were conducted adopting a three-month time horizon and adopting 'as treated' approach.

CCE and MACE were analysed using survival analysis (time-to-major adverse cardiac event) using Kaplan-Meier curves and the log-rank test.

The proportion of various procedural complications was compared using chi-square tests. A per-patient analysis of CCTA accuracy was also performed to determine the operating characteristics of CCTA in the identification of obstructive CAD and high-risk coronary anatomy. [5,17]

Results

Of the 253 patients randomized, 6 patients were excluded prior to imaging (5 withdrew consent, 1 inappropriate enrollment) and 1 patient was excluded immediately after baseline testing due to lost to follow-up (Figure 1); the remaining 246 patients were randomized to CCTA (121) and ICA (125). The mean age was 57.8±11.0 years, 175 (71.1%) were men, and the mean left ventricular ejection fraction (LVEF) was 30.1±10.1% (Table 1). Patients randomized to CCTA had a lower prevalence of diabetes and dyslipidemia, and a higher prevalence of beta-blocker use. Mean follow-up was 19.2±9.9 months.

Of the 121 patients randomized to CCTA, 6 crossed over to ICA and 1 patient from the ICA arm crossed over to CCTA (Figure 1). Crossover from CCTA to ICA were due to deteriorating renal function (2), arrhythmia/elevated HR (3) and decompensated HF (1). One ICA patient refused ICA for personal reasons. Of the 116 patients who presented for CCTA, 6 patients had the CCTA cancelled due to severe coronary calcification and 1 CCTA was cancelled for a high HR. The prevalence of obstructive CAD, 1-, 2-, 3- vessel disease, and high-risk CAD were similar in both groups (Table 2). Using the Felker classification, the diagnosis of ischemic cardiomyopathy was made in 45 (18.7%) patients. There were fewer normal ICAs performed in the CCTA than the ICA arm (11 (9.2%) versus 97 (77.6%), p <0.0001). Radiation dose was lower with CCTA (6.0±4.7 mSv) than the ICA strategy (7.9±6.6 mSv, p=0.008).

A total of 93 (76.9%) CCTA patients avoided the need for ICA. Rates of downstream ischemia and viability testing were similar for both arms (Table 3).

When comparing the medical costs of the two interventions; the cost (CDN$ in 2017) savings from the CCTA arm (CDN -$871, 95% confidence interval -$4,116 to $3,028) were not statistically significant (Table 4, Appendix C). The small overall cost reduction was attributed to the lower cost of the CCTA test. The follow-up costs were higher with CCTA and appeared to be driven by hospitalizations. There were a total 44 patients (22 CCTA and 22 ICA) requiring 46 cardiac hospitalizations (24 CCTA and 22 ICA) for a total of 515 days (283 and 232 days for CCTA and ICA, respectively) (Supplemental). The mean hospital stay for CCTA was 2.3±8.1 (CI: 0.86, 3.74) and 1.8±7.1 (CI: 0.56, 2.44). days for ICA. Two patients (cardiac transplantation (58 days), and heart failure/stroke (60 days)) accounted for 44% of CCTA hospital days.

Multiple imputation of missing values for costs did not significantly change the results. The total cost (CDN$ in 2017) of CCTA was CDN$1,267 (95% CI -$2,045 to -$419) lower than ICA.

Using an 'as-tested' analysis, CCTA was associated with a non-significant reduction in healthcare costs (incremental cost saving of CDN -$2,932, 95% CI -$6,248 to $746).

Clinical Outcomes

At follow-up, there was no difference in medication use between arms and CCE was similar between groups (Figure 2, Supplemental). Cardiac death was higher in the CCTA arm (6 (5.0%)) than ICA (1 (0.8%), p=0.0499) but myocardial infarction and acute coronary syndrome trended lower in the CCTA arm than the ICA arm (1 (0.8%) and 4 (4.2%) patients, respectively). Of the 6 cardiac deaths in the CCTA arm, 4 patients had been diagnosed with non-ischemic HF, and 2 of the deaths were attributed to non-ischemic HF. The one death in the ICA arm was attributed to non-ischemic HF.

CCTA Accuracy

In the CCTA patients referred to ICA, the sensitivity, specificity, positive predictive and negative value for detecting obstructive and high-risk CAD were 92%, 13%, 63%, and 50%, respectively and 100%, 54%, 45% and 100%, respectively. Adjusting for verification bias, the adjusted specificity was 86%.

Discussion

The IMAGE-HF (Imaging Modalities to Assist with Guiding therapy and the Evaluation of patients with Heart Failure) consortium begins to examine the utility of non-invasive techniques in the HF population. [10] To our knowledge, this is the first randomized controlled trial examining the clinical utility of CCTA in HF patients. The primary results of our study demonstrate that the financial impact of a CCTA strategy, in patients with HF of unknown etiology, was not statistically different from an ICA strategy. The lower initial diagnostic costs of CCTA were partially offset by higher downstream costs.

It is important to acknowledge that our findings are specific to the HF population since these patients are more likely to require have higher resource utilization which dilute any potential initial cost-savings. Therefore, these results cannot be applied to other populations (e.g. suspected or stable CAD patients).

The financial burden of HF is partially driven by the aging population, growing prevalence of HF, improved survival of HF patients, and increasing access to newer technologies. [1,2] There is a growing need for cost containment, thus, identifying strategies that are accurate, safe and cost-effective is important.

Operating Characteristics and Accuracy of CCTA

Two studies have examined the accuracy of CCTA in HF patients and reported sensitivities, specificities, positive and negative predictive values of 73-98%, 99-100%, 92-

99% and 97-100%, respectively. [18,19] Our accuracy results were subject to referral and verification bias, however support the notion that CCTA is a sensitive test reduced the need for ICA in 75% of CCTA patients.

CT strategies in HF patients have been studied. Abunassar et al. showed that an Agatston score =0 effectively ruled out high risk CAD and ischemic etiology for left ventricular dysfunction. [11] Premaratne et al. performed a systematic literature review and confirmed that an Agatston score =0 was 98.4% specific for non-ischemic cardiomyopathy. [20] The ability of cardiac CT to function as a gatekeeper for HF patients was studied in 93 patients. [21] A strategy using CCTA only for those with an Agatston Score >0 had a sensitivity of 100%, specificity of 95%, positive predictive value of 67% and negative predictive value of 100% for detecting ischemic HF. The cost implications of such strategies have not been studied.

In newly diagnosed HF patients, CAD should be considered [22] and ICA should be considered for patients at intermediate to high pre-test probability for CAD, if ischemia is a contributing factor or in the presence of refractory angina. [3,23] The American College of Cardiology considers the use of CCTA 'appropriate' for newly diagnosed systolic HF and may be appropriate in those with diagnosed diastolic HF. [9] The European Society of Cardiology gives a class IIb recommendation for the use of CCTA in HF patients with low-intermediate pre-test probability of CAD. The lower frequency of normal ICA in the CTCA group suggests that CTCA can function as a gatekeeper and potentially improves the diagnostic yield of ICA.

Clinical Outcomes

The small sample size limits our ability to make conclusions about individual clinical outcomes. There were no differences in MACE and CCE between the 2 strategies.

Healthcare costs continues to be a focus of healthcare payers and is increasingly important in medical research. Our analysis focuses on the financial impact of CCTA compared to ICA – a full economic evaluation would also include a comparison of the health care outcomes of the two management strategies facilitating an assessment of the cost effectiveness of adopting the CCTA algorithm. It is especially relevant when multiple diagnostic tests are available for the same indication. Although the 'intention-to-treat' CCTA strategy was not more costly than ICA, a secondary 'as-treated' analysis found greater cost savings with CCTA. Some would advocate that the 'as-treated' analysis better reflects clinical practice and that these results be considered. Others argue that the 'as-treated' analysis breaks the randomisation within the clinical trial thereby introducing bias. In a sense, the 'as-treated' analysis takes a randomized controlled study and turns it into an uncontrolled observational study. In our study, it is likely that specific patient clinical characteristics led to greater crossovers from the CCTA to the ICA arm. Thus, reliance on the 'as-treated' analysis will lead to bias and false inference and cannot be considered an equally valid analysis to the randomized results.

Several randomized controlled trials have examined the utility of CCTA. Early trials examined CCTA in the emergency department and showed that it was associated with earlier discharges and had potential cost savings. [24] In patients with suspected stable angina, CTCA improved certainty of diagnosis and positively impacted upon downstream investigations and treatment. [25] PROMISE compared to functional testing to CCTA in stable in the patients with stable symptoms suspicious for CAD. [26] CT was not associated with improved patient outcomes but reduced the frequency of normal ICAs. CT-MAN showed that CCTA functioned as a gatekeeper to ICA, and reduced the length of hospital stay without increasing MACE. [27] Our study contributes to the literature by examining CCTA in the HF population.

Limitations

As with many studies, patient preference and physician willingness to enrol patients into trials is a potential source of population bias and impacts on the study population's characteristics. The inherent willingness to enrol those who are less likely to have ischemic cardiomyopathy may overestimate the utility and benefit of the CCTA arm. The lack of blinding may explain the high CCTA crossover rate, is likely a bias of treating physicians and might underestimate the true benefit of CCTA. However, these biases may reflect real-world clinical practice where ICA is reserved for those at higher CAD risk. Similarly, CCTA and ICA interpretation and subsequent patient management were determined by local clinical practice. Although this potentially increases heterogeneity in patient diagnosis and management, it would reflect real-world practice. Our study was not powered to detect differences in clinical outcomes.

Our study is conducted based on cost data from the Canadian setting applied to resource use data primarily from Canadian settings but inclusive of data from Finland. Thus, the generalizability of the findings of the financial impact analysis needs to be considered. Clinical practice in countries may differ but such differences can also exist within the same country. Unfortunately, this is a potential limitation of many multicentre trials including this study. In different clinical contexts there may be greater willingness to change clinical practice based on financial implications and therefore the results should be interpreted specific to the context in which a decision might be made.

Non-invasive downstream testing was similar between groups, however the indications for testing were not collected and thus could not be compared.

The objective of this study was to understand the potential costs directly and immediately associated with the initial diagnostic strategy. Although the authors believe that most cost implications would be captured within 12 months, it is possible that there are potential cost implications beyond this time. All expenditures were calculated as if there were

performed in Canada in 2017. Acknowledging that institutions and payer systems may have different costs, our results should be calculated for each practice.

Conclusion

In patients with HF of unknown etiology, costs and composite clinical outcomes were not statistically different between the CCTA and ICA strategies.

References

1. Johansen H, Strauss B, Arnold JM, Moe G, Liu P. On the rise: The current and projected future burden of congestive heart failure hospitalization in Canada. *CanJ Cardiol.* 2003;19(4):430-435.
2. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol.* 1992;20(2):301-306.
3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-239.
4. Chow BJ, Freeman MR, Bowen JM, et al. Ontario multidetector computed tomographic coronary angiography study: Field evaluation of diagnostic accuracy. *Arch Intern Med.* 2011;171(11):1021-1029.
5. Chow B, Abraham A, Wells G, et al. Diagnostic accuracy and impact of computed tomographic coronary angiography on utilization of invasive coronary angiography. *Circ Cardiovasc Imag.* 2009;2(1):16-23.
6. Meijboom WB, Meijs MFL, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: A prospective, multicenter, multivendor study. *J Am Coll Cardiol.* 2008;52(25):2135-2144.
7. Chow BJW, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography: Severity of coronary artery disease, coronary atherosclerosis and left ventricular ejection fraction. *J Am Coll Cardiol.* 2010;55(10):1017-1028.
8. Ostrom MP, Gopal A, Ahmadi N, et al. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *J Am Coll Cardiol.* 2008;52(16):1335-1343.
9. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2014;63(4):380-406.
10. Chow BJ, Green RE, Coyle D, et al. Computed tomographic coronary angiography for patients with heart failure (CTA-HF): a randomized controlled trial (IMAGE HF Project 1-C). *Trials.* 2013;14:443.
11. Abunassar JG, Yam Y, Chen L, D'Mello N, Chow BJ. Usefulness of the Agatston score = 0 to exclude ischemic cardiomyopathy in patients with heart failure. *Am J Cardiol.* 2011;107(3):428-432.
12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15(4):827-832.
13. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: Executive summary and recommendations : A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (committee on coronary angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation.* 1999;99(17):2345-2357.

14. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. *J Am Coll Cardiol.* 2002;39(2):210-218.
15. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada. 2017; https://www.cadth.ca/about-cadth/how-we-do-it/methods-and-guidelines/guidelines-for-the-economic-evaluation-of-health-technologies-canada.
16. Campbell MK, Torgerson DJ. Bootstrapping: estimating confidence intervals for cost-effectiveness ratios. *QJM.* 1999;92(3):177-182.
17. Diamond GA. Reverend Bayes' silent majority; An alternative factor affecting sensitivity and specificity of exercise electrocardiography. *Am J Cardiol.* 1986;57(13):1175-1180.
18. Andreini D, Pontone G, Bartorelli AL, et al. Sixty-four-slice multidetector computed tomography: an accurate imaging modality for the evaluation of coronary arteries in dilated cardiomyopathy of unknown etiology. *Circ Cardiovasc Imaging.* 2009;2(3):199-205.
19. Ghostine S, Caussin C, Habis M, et al. Non-invasive diagnosis of ischaemic heart failure using 64-slice computed tomography. *Eur Heart J.* 2008;29(17):2133-2140.
20. Premaratne M, Shamsaei M, Chow JD, et al. Using coronary calcification to exclude an ischemic etiology for cardiomyopathy: A validation study and systematic review. *Int J Cardiol.* 2017;230:518-522.
21. ten Kate GJ, Caliskan K, Dedic A, et al. Computed tomography coronary imaging as a gatekeeper for invasive coronary angiography in patients with newly diagnosed heart failure of unknown aetiology. *Eur J Heart Fail.* 2013;15(9):1028-1034.
22. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *Can J Cardiol.* 2017;33(11):1342-1433.
23. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European Heart Journal.* 2013;34(38):2949-3003.
24. Hamilton-Craig C, Fifoot A, Hansen M, et al. Diagnostic performance and cost of CT angiography versus stress ECG--a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). *Int J Cardiol.* 2014;177(3):867-873.
25. Investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet.* 2015;385(9985):2383-2391.
26. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med.* 2015;372(14):1291-1300.
27. Dewey M, Rief M, Martus P, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. *BMJ.* 2016;355:i5441.

Figure Legend

Figure 1. IMAGE HF – 1C Flowchart.

Figure 2. Kaplan Meier Survival Curves (days) of Coronary CT Angiography (blue) and Invasive Coronary Angiography (red) patients for the clinical composite endpoint (cardiac death, MI, cardiac arrest, cardiac hospitalization (HF, ACS, Arrhythmia) and procedural complication).

Table 1. Patient Baseline Characteristics

	CCTA (N=121)	ICA (N=125)	p
Age	58.0 ± 11.1	57.6 ± 10.9	0.69
Men	87 (71.9)	88 (70.4)	0.79
Body Mass Index (kg/m2)	29.6 ± 6.1	29.0 ± 6.1	0.45
Ethnicity			
Caucasian	116 (95.9)	122 (97.6)	0.70
CCS Angina Classification			
0	74 (61.2)	63 (50.4)	0.25
1	35 (29.0)	42 (33.6)	
2	6 (5.0)	13 (10.4)	
3	6 (45.0)	7 (5.6)	
NYHA Classification*			
I	35 (29.0)	27 (21.6)	0.56
II	52 (43.0)	60 (48.0)	
III	30 (24.8)	35 (28.0)	
IV	4 (3.3)	3 (2.4)	
Cardiac Risk Factors			
Hypertension	62 (51.2)	66 (51.5)	0.81
Dyslipidemia	54 (45.0)	74 (58.7)	0.03
Diabetes	15 (12.4)	33 (26.4)	0.01
Smoker/Ex-smoker	68 (56.2)	73 (58.4)	0.73
Family History of CAD	35 (28.9)	44 (35.9)	0.54
History of Cardiovascular Disease			
Documented CAD	4 (3.3)	5 (4.0)	0.89
Cerebrovascular Disease	9 (7.4)	11 (8.8)	0.55
Medications			
Aspirin	46 (38.0)	57 (45.6)	0.23
B-blockers	111 (91.7)	99 (79.2)	0.006
ACE-I	88 (72.7)	91 (73.0)	0.98
ARB	19 (15.7)	20 (16.0)	0.95
Lipid lowering agents	50 (41.7)	67 (53.1)	0.06
Mineralocorticoids	35 (29.2)	28 (22.2)	0.21
Diuretics	72 (59.5)	77 (61.6)	0.74
Nitrates	9 (7.4)	12 (9.6)	0.54
Digoxin	7 (5.8)	9 (7.1)	0.65
Anticoagulants (VKA/NOAC)	25 (20.7)	40 (31.2)	0.06
Creatinine	87.5 ± 20.3	83.5 ± 18.6	0.10
Glomerular Filtration Rate	105.8 ± 41.2	105.4 ± 36.1	0.93
LV Ejection Fraction	31.3 ± 10.3	29.0 ± 9.8	0.15
LV diastolic dimension (mm)	60.6 ± 15.6	62.1 ± 11.4	0.39
Left atrial diameter (mm)	44.2 ± 8.4	45.3 ± 11.2	0.48
Right ventricular systolic pressure (mmHg)	33.3 ± 14.1	31.5 ± 16.2	0.44

CCTA – Coronary Computed Tomography Angiography, ICA – Invasive Coronary Angiography, CCS – Canadian Cardiovascular Society, NYHA – New York Heart Association, VKA – Vitamin K Antagonist, NOAC – Novel Oral Anticoagulants

*1 patient missing from each of the CCTA and ICA arms

Table 2. Diagnostic Results

	Randomization Modality 'Intention-to-Treat'		
	CCTA (N=121)	**ICA (N=125)**	**p**
Coronary Artery Disease			
Normal or Non-Obstructive CAD	80 (66.1)	98 (78.4)	0.13
Obstructive CAD (≥ 50%)	34 (28.1)	27 (21.6)	
Cancelled CCTA	7 (5.8)		
1 Vessel Disease	12 (10.0)	10 (8.0)	0.85
2 Vessel Disease	11 (9.2)	10 (7.9)	
3 Vessel Disease	11(9.2)	7 (5.6)	
High-Risk CAD	15 (12.5)	9 (7.2)	0.38
Non-High-Risk CAD	20 (16.7)	19 (15.2)	
Coronary Artery Calcium (Agatston Score)	417.1 ± 795.5	-	
Heart Failure Etiology - Ischemic	23 (19.2)	22 (17.6)	0.75
Radiation Exposure			
Dose Length Product (Gy x cm)	408.44 ± 306.3		
Dose Area Product (Gy x cm^2)	48.13 ± 35.74	34.26 ± 28.1	0.25
Effective Dose (mSv)	6.0 ± 4.7	7.9 ± 6.6	0.008

CCTA – Coronary Computed Tomography Angiography, ICA – Invasive Coronary Angiography, CT – Computed Tomography, CAD – Coronary Artery Disease
CT Radiation Dose CT (mSv) = DLP (Gy*cm) x 0.014; ICA Radiation Dose (mSv) = DAP (Gy*cm2) x 0.23

Table 3. Follow-up

	Randomization Modality 'Intention-to-Treat'		
	CCTA N=121	**ICA N=125**	**p**
Downstream Testing			
Invasive Coronary Angiography	28	-	-
Ischemia Testing (SPECT, PET, Stress ECHO, MRI)	16 (13.3)	17 (13.6)	0.95
Viability Testing (PET, MRI, SPECT,)	22 (18.3)	32 (25.6)	0.17

CCTA –Coronary Computed Tomography Angiography, ICA – Invasive Coronary Angiography, SPECT – single photon emission computed tomography, ECHO – echocardiography, MRI - magnetic resonance imaging, PET - positron emission tomography

Table 4. Cost and Quality Adjusted Life Years

	Randomization Modality 'Intention-to-Treat'			
	CCTA N=121	**ICA N=125**	**Probability**	**Comparative p value**
Cost^ (CDN$ in 2017)				
Initial Diagnostic Strategy	$496 (434-597)	$2,562 (2,542-2,581)	1.00	<0.001
Downstream Cost	$7,115 (4,626-10,645)	$5,920 (4,188-8,059)	0.25	0.750
Total Cost	$7,611 (5,096-11,160)	$8,482 (6,735-10,618)	0.69	0.310

CCTA – Coronary Computed Tomography Angiography, ICA – Invasive Coronary Angiography

^ Parenthesis are 95% confidence intervals. The probability value is based on a Bayesian approach and therefore relates to the probability that costs are superior (i.e. lower) with CCTA

* Parenthesis are 95% confidence intervals. The probability value is based on a Bayesian approach and therefore relates to the probability that costs are superior (i.e. lower) with CCTA

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