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Importance of Nonobstructive Coronary Artery Disease in the Prognosis of Patients With Heart Failure

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ABSTRACT

OBJECTIVES This study sought to examine the prognostic significance of nonobstructive coronary artery disease (CAD) in patients with heart failure (HF), as a distinct category apart from those with normal coronary arteries.

BACKGROUND Individuals with HF are often dichotomized into ischemic versus nonischemic categories according to the underlying etiology. This binary classification creates a heterogeneous group, combining individuals with nonobstructive CAD with those with normal coronary arteries under the nonischemic label.

METHODS A cohort of individuals with HF and reduced ejection fraction undergoing invasive coronary angiography was examined and linked to administrative databases for outcomes evaluation. Patients were divided into those with normal coronary arteries, nonobstructive disease, and obstructive disease. The primary outcome was the composite of cardiovascular death, nonfatal acute myocardial infarction, nonfatal stroke, or HF hospitalization.

RESULTS Of 12,814 individuals, 2,656 (20.7%) had normal coronary arteries, 2,254 (17.6%) had nonobstructive CAD, and 7,904 (61.7%) had obstructive CAD. The risk of the primary outcome was increased in the nonobstructive group (hazard ratio [HR]: 1.17; 95% confidence interval [CI]: 1.04 to 1.32; $p = 0.01$) relative to those with normal coronary arteries. Nonobstructive CAD was associated with an increased hazard of cardiovascular death (HR: 1.82; 95% CI: 1.27 to 2.62; $p = 0.001$) and death of any cause (HR: 1.18; 95% CI: 1.05 to 1.33; $p = 0.005$). There were no significant differences in the rate of acute myocardial infarction, stroke, or HF hospitalization.

CONCLUSIONS Among HF patients with reduced ejection fraction, the presence of nonobstructive CAD was independently associated with an increased hazard of the primary composite outcome and death of any cause. (J Am Coll Cardiol HF 2019;7:493-501) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CAD = coronary artery disease

CI = confidence interval

CV = cardiovascular

Cx = circumflex artery

EF = ejection fraction

HF = heart failure

HR = hazard ratio

ICA = invasive coronary angiogram/angiography

ICD-10-CA = International Classification of Diseases-10th Revision with Canadian Enhancements

LAD = left anterior descending artery

LM = left main artery

RCA = right coronary artery

Coronary artery disease (CAD) is the most common cause of heart failure (HF) (1). In daily practice, health professionals endeavor to identify those patients for whom the underlying etiology of HF is CAD, as opposed to nonischemic causes. The rationale is that individuals with ischemic HF are at high risk for adverse cardiac events and death (1,2) and could potentially be candidates for intervention and secondary preventive measures (3).

While the binary classification (i.e., ischemic vs. nonischemic) is widely employed, this terminology has not been without controversy. Indeed, since the description in the 1970s of an entity of cardiomyopathy caused by atherosclerosis (4), a major point of contention has been the extent of CAD that should be present to be considered prognostically important as opposed to the mere presence of CAD that is not severe enough to impact on prognosis or be considered etiologically responsible for the diagnosis of HF.

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Classically, ischemic HF has been defined as depressed myocardial contractility in the presence of a previous acute myocardial infarction (AMI), a revascularization procedure, or significant CAD defined as a stenosis of 75% or greater in at least 2 epicardial vessels (5). Alternatively, patients with no apparent CAD, or CAD in any number of epicardial vessels below the aforementioned significance threshold (i.e., nonobstructive), or obstructive disease in a single vessel, with no history of AMI or coronary revascularization, have been classified aggregately as nonischemic (5). Consequently, nonischemic HF patients represent a heterogeneous group that combines nonobstructive CAD together with those who demonstrate apparently normal coronary arteries under the assumption that the extent of disease is not clinically important or relevant.

However, recent findings have suggested that in those without HF, the risk of adverse clinical events from nonobstructive lesions is intermediate between those with apparently normal coronary arteries and significant CAD (6–8). As HF patients exhibit a high baseline rate of mortality and morbidity, it is unknown if the presence of nonobstructive CAD is of sufficient prognostic importance to manifest on clinical outcomes. Therefore, our primary objective was to examine the prognostic significance of nonobstructive CAD in patients with HF with reduced EF. As a secondary objective, we aimed to assess the association between the overall CAD burden and prognosis in HF with reduced EF.

METHODS

STUDY DESIGN AND PARTICIPANTS. This was a retrospective cohort study that included patients who had undergone an elective invasive coronary angiogram (ICA) because of suspected or confirmed CAD or HF between October 1, 2010, and March 31, 2015, in Ontario, Canada and had reduced left ventricular ejection fraction (EF) (<35%). The CorHealth Cardiac Registry was used as the primary data source for the study. This registry, previously known as the Cardiac Care Network Registry, has been used extensively in the past (9). Designated trained hospital personnel collected and entered into the database information about demographics, clinical presentation, comorbidities, EF, and coronary anatomy data of all individuals undergoing ICA in the province.

To assemble our study cohort, we excluded patients younger than 18 years or older than 105 years of age, who had invalid health card numbers or were nonresidents of Ontario, who had an aborted ICA, who had an AMI within 30 days before the date of ICA, who had missing EF or EF ≥35%, who had previous heart or lung transplantation, who were being assessed as potential organ donors, who had a previous coronary revascularization procedure, who had been primarily referred for ICA because of valvular disease or congenital heart disease, or who had clinical instability at the time of the catheterization. We excluded patients with a recent AMI to eliminate individuals with an acute coronary syndrome complicated by HF and depressed EF. For patients who underwent more than 1 ICA during the study period, the first procedure was considered the index and the baseline for the analysis.

ADDITIONAL DATA SOURCES. The study cohort created using the CorHealth Registry was linked to other administrative databases: the Ontario Health Insurance Plan database, which contains data on physician billing for both ambulatory and hospital care, the Canadian Institute for Health Information's Discharge Abstract Database for hospital admissions, the Registered Persons Database to determine vital status during follow-up, and the Office of the Registrar General-Death database to determine whether death had a cardiovascular (CV) or non-CV cause. Multiple data sources and validated algorithms combining inpatient and outpatient codes were used to determine the presence of comorbidities

(Online Table 1) (10). All data sources were linked using unique encoded identifiers and analyzed at ICES (Toronto, Canada).

DEFINITIONS. Patients were defined as having no apparent CAD in the absence of any stenoses in the coronary tree (0% stenosis and no luminal irregularities). Nonobstructive disease was defined as the presence of limited atherosclerotic disease demonstrated by a stenosis <50% (1% to 49%) in the left main artery (LM) and <70% (1% to 69%) in the left anterior descending artery (LAD), circumflex artery (Cx), or right coronary artery (RCA). Obstructive CAD was defined as the presence of a stenosis ≥50% in the LM or ≥70% in the LAD, Cx, or RCA. In the registry, information on the specific coronary vessels affected is not provided for patients classified as having nonobstructive disease, while the majority of patients recorded as having obstructive CAD had information about the specific vessels affected (i.e., LM, LAD, Cx, or RCA). The CorHealth Registry records the EF measured before the ICA with noninvasive testing or the EF determined at the time of catheterization with left ventriculography (if performed). The registry allows information about the EF to be entered as a continuous or categorical variable. Most individuals (~75%) in the registry had EF classified into 1 of 4 pre-specified categories: preserved (≥50%), mildly reduced (35% to 49%), moderately reduced (20% to 34%), or severely reduced (<20%) left ventricular EF, while the remaining ~25% had EF recorded as a numerical value. We classified individuals with a numerical EF into 1 of the 4 left ventricular EF categories described previously. To avoid any ambiguity in the definition of depressed EF, we excluded individuals with EF 35% to 49%, restricting the analysis to those with moderately or severely reduced left ventricular EF.

MAIN EXPOSURE. The main exposure was the severity of CAD visualized during catheterization by the operator performing the exam. The accuracy of the coronary anatomy recorded in the CorHealth Registry has been previously validated and demonstrated very good reliability when compared with a random sample of coronary angiography procedures reviewed by cardiologists at a central laboratory (11). For the primary analysis, patients were divided into 3 groups: 1) no apparent CAD; 2) nonobstructive disease; and 3) significant disease. In a secondary analysis, we divided patients with significant CAD, who had information about the specific vessels affected (i.e., LM, LAD, Cx, or RCA), into those with 1-, 2-, or 3-vessel disease, representing the number of major coronary arteries with a significant obstruction. Patients with LM disease were classified as a distinct category irrespective of the number of additional diseased vessels.

TABLE 1 Baseline Characteristics According to the Extent of CAD

	No Apparent CAD (n = 2,656)	Nonobstructive (n = 2,254)	Obstructive (n = 7,904)	p Value
Age, yrs	59 (50–68)	65 (57–74)	67 (59–75)	<0.001
Female	1,019 (38.4)	724 (32.1)	1,815 (23.0)	<0.001
Rural residence	348 (13.1)	303 (13.4)	1,162 (14.7)	0.07
Current CCS angina class*				
Missing	56 (2.1)	43 (1.9)	218 (2.8)	
0	1,274 (48.0)	984 (43.7)	2,478 (31.4)	
I	263 (9.9)	238 (10.6)	838 (10.6)	<0.001
II	299 (11.3)	253 (11.2)	1,095 (13.9)	
III	104 (3.9)	107 (4.7)	614 (7.8)	
IV	660 (24.8)	629 (27.9)	2,661 (33.7)	
Current NYHA functional class†				
Missing	379 (14.3)	344 (15.3)	1,908 (24.1)	
I	625 (23.5)	532 (23.6)	2,128 (26.9)	
II	644 (24.2)	564 (25.0)	1,555 (19.7)	<0.001
III	657 (24.7)	571 (25.3)	1,565 (19.8)	
IV	351 (13.2)	243 (10.8)	748 (9.5)	
Creatinine, mg/dl‡	0.96 (0.81–1.15)	0.98 (0.83–1.19)	1.02 (0.85–1.23)	<0.001
LVEF				
20%–34%	1,726 (65.0)	1,627 (72.2)	5,870 (74.3)	
<20%	930 (35.0)	627 (27.8)	2,034 (25.7)	<0.001
Medical history				
Atrial fibrillation/flutter	549 (20.7)	499 (22.1)	1,171 (14.8)	<0.001
Cancer	138 (5.2)	183 (8.1)	490 (6.2)	<0.001
Chronic kidney disease	268 (10.1)	288 (12.8)	1,024 (13.0)	<0.001
COPD	303 (11.4)	380 (16.9)	1,164 (14.7)	<0.001
Current smoker	557 (21.0)	535 (23.7)	1,869 (23.6)	<0.001
Dementia	17 (0.6)	34 (1.5)	138 (1.7)	<.001
Depression	129 (4.9)	110 (4.9)	312 (3.9)	0.04
Diabetes	689 (25.9)	774 (34.3)	3,423 (43.3)	<0.001
Dialysis	32 (1.2)	48 (2.1)	183 (2.3)	0.002
Hyperlipidemia	979 (36.9)	1,115 (49.5)	4,617 (58.4)	<0.001
Hypertension	1,527 (57.5)	1,563 (69.3)	5,606 (70.9)	<0.001
Liver cirrhosis	53 (2.0)	42 (1.9)	128 (1.6)	0.3
Previous AMI	224 (8.4)	290 (12.9)	2,460 (31.1)	<0.001
Previous HF hospitalization	951 (35.8)	761 (33.8)	1,757 (22.2)	<0.001
Peripheral vascular disease	78 (2.9)	118 (5.2)	826 (10.5)	<0.001
Stroke	160 (6.0)	194 (8.6)	813 (10.3)	<0.001

Values are median (interquartile range) or n (%). *The Canadian Cardiovascular Society (CCS) angina classification ranges from class 0, which indicates no symptoms, to class IV, which indicates angina at any level of physical exertion. †The New York Heart Association (NYHA) functional classification ranges from class I, which indicates no limitation to physical activity, to class IV, which indicates inability to carry on any physical activity without symptoms. ‡A total of 1,280 (10.0%) individuals had missing values.

AMI = acute myocardial infarction; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HF = heart failure; LVEF = left ventricular ejection fraction.

OUTCOMES. The primary outcome was the composite of CV death and hospitalizations with a primary diagnosis of AMI, HF, or ischemic stroke. Secondary outcomes included the individual components of the composite outcome and death from any cause. Hospitalizations caused by an AMI were identified using the International Classification of Diseases-10th Revision with Canadian Enhancements (ICD-10-CA)

TABLE 2 Study Outcomes and Number of Events According to the Extent of CA

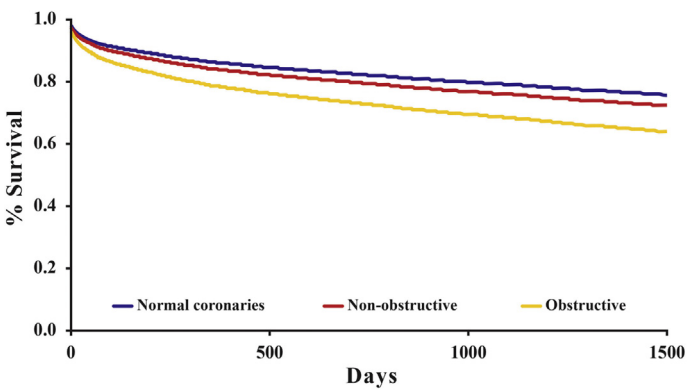
	No Apparent CAD (n = 2,656)	Nonobstructive (n = 2,254)	Obstructive (n = 7,904)
Primary outcome			
CV death or hospitalizations by AMI, HF, or stroke	446 (16.8)	468 (20.8)	1,926 (24.4)
Secondary outcomes			
CV death	48 (1.8)	83 (3.7)	423 (5.4)
Hospitalizations for AMI	17 (0.6)	16 (0.7)	534 (6.8)
Hospitalizations for HF	353 (13.3)	342 (15.2)	851 (10.8)
Hospitalizations for stroke	28 (1.1)	27 (1.2)	118 (1.5)
Death of any cause	282 (10.6)	360 (16.0)	1,444 (18.3)

Values are n (%).
CV = cardiovascular; other abbreviations as in Table 1.

codes I21 and I22 as the most responsible diagnosis. Hospitalizations for HF included ICD-10-CA codes I50, I25.5, I40-I43, I11 plus I50, and I13 plus I50, and hospitalizations for ischemic stroke were identified using ICD-10-CA codes G45 (excluding G45.5), I63 (excluding I63.6), and I64.

COVARIATES. We adjusted for variables that were potentially associated with the risk of experiencing study outcomes, including age, sex, urban or rural residence, New York Heart Association functional class, Canadian Cardiovascular Society grading of angina pectoris, left ventricular EF (i.e., 20% to 34% or <20%), previous HF hospitalization, previous AMI, atrial fibrillation, serum creatinine concentration, diabetes mellitus, hypertension, dialysis, smoking status, hyperlipidemia, previous ischemic stroke or transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, liver cirrhosis, dementia, depression, and year of catheterization (12).

FIGURE 1 Adjusted Survival Curves for the Primary Outcome According to the Extent of Coronary Artery Disease



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

CI = confidence interval; HR = hazard ratio.

STATISTICAL ANALYSIS. A descriptive analysis was performed comparing baseline characteristics across the exposure groups. Continuous variables were expressed as median (interquartile range) and compared with the Kruskal-Wallis test. Categorical variables were compared using the chi-square statistic. The cumulative incidence function was used to evaluate the incidence of CV death treating non-CV death as a competing event. A cause-specific hazards model was used to estimate the association of nonobstructive CAD with the rate of the occurrence of outcome events, adjusting simultaneously for potential confounding variables (13). Robust SEs were used to account for clustering of patients within the same cardiac site (14). Directly adjusted cumulative incidence curves under proportional subdistribution hazards models were constructed for the primary outcome and the components of the primary outcome to account for non-CV death as a competing risk. For death from any cause, we used the corrected group prognosis method (15,16). Survival curves were adjusted using all the previously described covariates.

For the survival analysis, the index date was the date of catheterization. Individuals were censored if they reached the end of follow-up on December 31, 2015; if they moved out of the province; or at the date of a major cardiac or noncardiac surgical procedure (codes used to identify surgical procedures are listed on Online Table 2). We made this decision (i.e., to censor patients at the time of surgery) because we wanted to examine the prognostic significance of CAD and we assumed that any major surgical procedure in this population with HF would have an elevated risk for perioperative complications including death and CV events, modifying the occurrence of outcome events that could be attributed solely to CAD. Multiple imputation was used to impute missing values for serum creatinine and symptoms of HF and angina. We carried out 5 imputations and combined the results using Rubin's rules (17). Adjusted hazard ratios (HRs) were calculated with associated 95% Wald confidence limits for nonobstructive CAD and significant CAD using no apparent CAD as the reference category. For the secondary analysis, adjusted HRs were calculated for those with significant CAD identified as having 1-, 2-,

or 3-vessel disease or LM disease using no apparent CAD as the reference category. All analyses were performed with SAS version 9.4 statistical software (SAS Institute, Cary, North Carolina).

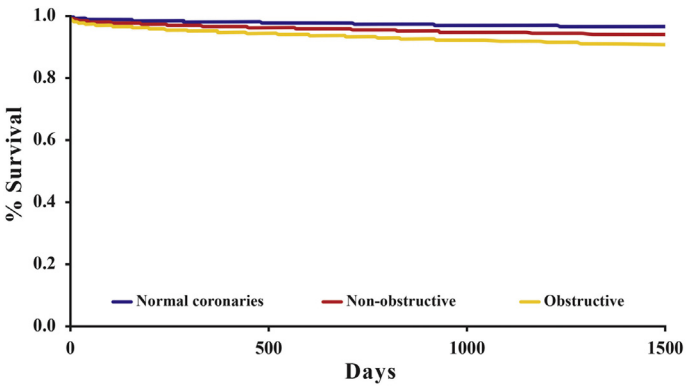
RESULTS

STUDY COHORT. We identified 338,130 records in the CorHealth Registry of patients undergoing ICA at 23 cardiac centers. The application of all inclusion and exclusion criteria resulted in a cohort of 12,814 unique individuals with reduced EF (Online Figure 1). Reduced EF was detected in 10,098 (78.8%) individuals with noninvasive testing before ICA and in 2,716 (21.2%) with left ventriculography at the time of catheterization. In total, 2,840 primary outcomes events were observed until December 31, 2015, by examining 24,320 person-years of follow-up.

BASELINE CLINICAL CHARACTERISTICS. Of 12,814 individuals with reduced EF, 2,656 (20.7%) had no apparent CAD, 2,254 (17.6%) had nonobstructive CAD, and 7,904 (61.7%) had obstructive CAD. The nonobstructive group had demographic and clinical characteristics that were mostly intermediate between those with no apparent CAD and significant CAD (Table 1). Patients with significant CAD tended to be slightly older; more likely to be male; more likely to have Canadian Cardiovascular Society angina class III or IV; and more likely to have higher creatinine, chronic kidney disease, diabetes, dialysis, hyperlipidemia, hypertension, prior AMI, peripheral vascular disease, and stroke compared with those with nonobstructive CAD or no apparent CAD. Meanwhile, patients with no apparent CAD were less likely to have angina, although remarkably 49% of individuals in that group had some degree of angina. Those same individuals with no apparent CAD were more likely to have advanced New York Heart Association symptoms of HF, atrial fibrillation, and more severe left ventricular dysfunction, in contrast to the other 2 groups (Table 1).

PRIMARY OUTCOME. The primary composite outcome occurred in 446 (16.8%) patients in the no apparent CAD group, in 468 (20.8%) in the nonobstructive CAD group, and in 1,926 (24.4%) in the obstructive disease group (Table 2). As compared with no apparent CAD, subjects with nonobstructive CAD had a higher hazard of experiencing the primary composite outcome (HR: 1.17; 95% confidence interval [CI]: 1.04 to 1.32; $p = 0.01$). Significant CAD was associated with an even higher hazard of CV death, AMI, HF hospitalization, or stroke (HR: 1.64; 95% CI: 1.33 to 2.02; $p < 0.001$) (Figure 1).

FIGURE 2 Adjusted Survival Curves for CV Death and Adjusted HRs According to the Extent of Coronary Artery Disease

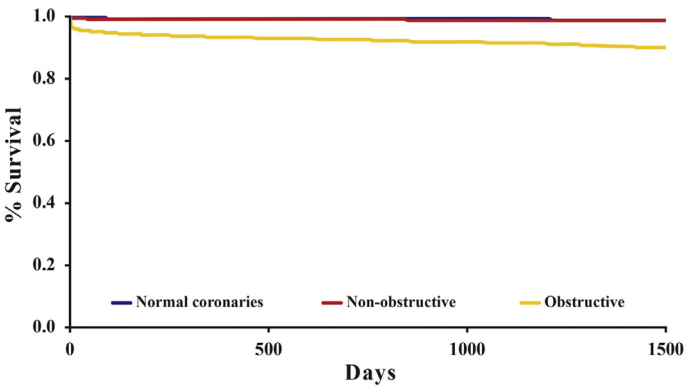


Group	N	Events	HR	95% CI
Normal	2656	48	Ref	Ref
Non-obstructive	2254	83	1.82	1.27-2.62
Obstructive	7904	423	1.64	1.33-2.02

Abbreviations as in Figure 1.

SECONDARY OUTCOMES. The analysis of the secondary outcomes revealed that nonobstructive CAD as compared with no apparent CAD was associated with an increased hazard of CV death (HR: 1.82; 95% CI: 1.27 to 2.62; $p = 0.001$) (Figure 2) and death from

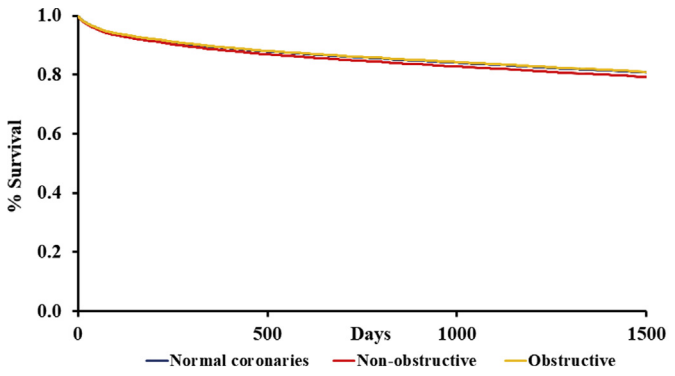
FIGURE 3 Adjusted Survival Curves for Acute Myocardial Infarction and Adjusted HRs According to the Extent of Coronary Artery Disease



Group	N	Events	HR	95% CI
Normal	2656	17	Ref	Ref
Non-obstructive	2254	16	1.10	0.43-2.82
Obstructive	7904	534	10.73	4.73-24.31

Abbreviations as in Figure 1.

FIGURE 4 Adjusted Survival Curves for Heart Failure Hospitalization and Adjusted HRs According to the Extent of Coronary Artery Disease

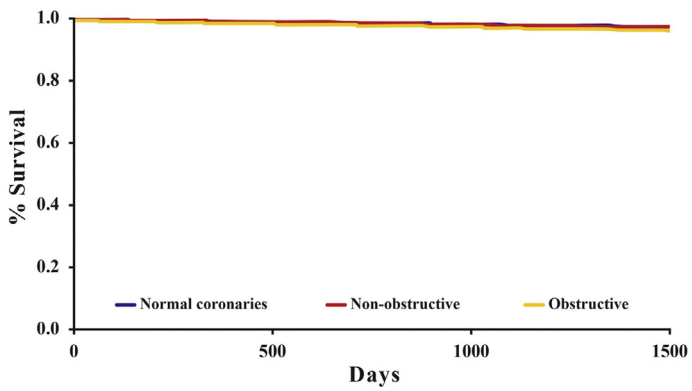


Group	N	Events	HR	95% CI
Normal	2656	353	Ref	Ref
Non-obstructive	2254	342	1.10	0.95-1.27
Obstructive	7904	851	1.00	0.84-1.18

Abbreviations as in Figure 1.

any cause (HR: 1.18; 95% CI: 1.05 to 1.33; p = 0.005) (Figure 3). There were no significant differences between groups in the hazard of experiencing an AMI, a HF hospitalization, or stroke (Figures 4 to 6). Concurrently, individuals in the obstructive CAD group had greater risks of experiencing all the secondary outcomes in comparison with the no apparent CAD group except for HF hospitalizations.

FIGURE 5 Adjusted Survival Curves for Stroke and Adjusted HRs According to the Extent of Coronary Artery Disease



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

Abbreviations as in Figure 1.

CUMULATIVE INCIDENCE OF CV DEATH AND NON-CV DEATH. Among patients with apparently normal coronary arteries, the 4-year cumulative incidence of CV death and non-CV death was virtually similar (5.4% and 5.8%, respectively). For patients with nonobstructive CAD, the 4-year cumulative incidence of non-CV death was higher (11.0%) than the incidence of CV death (8.0%). Among patients with obstructive CAD, 14.5% died of CV causes and 10.4% died of non-CV causes within 4 years (Online Figure 2). The majority of CV deaths were caused by CAD whereas non-CV deaths were most often caused by malignancy across the 3 groups of patients.

SECONDARY ANALYSIS. Of the 7,904 individuals with significant CAD, 6,376 (79.8%) had documentation of the vessels affected. These individuals were divided according to the number of diseased vessels: 2,241 (19.9%) had 1-vessel disease, 1,656 (14.7%) had 2-vessel disease, 1,639 (14.5%) had 3-vessel disease, and 840 (7.4%) had LM disease. The number of subjects with no apparent CAD and nonobstructive disease remained unchanged for the secondary analysis. Baseline characteristics revealed that as the extent of disease increased from 1-vessel to the presence of LM disease, patients were significantly older; were more likely to be male; tended to have more angina and symptoms of HF; and were more likely to have had a previous AMI and stroke, diabetes, and peripheral vascular disease (Online Table 3). In comparison with the no apparent CAD group, the adjusted HR for the primary outcome was 1.64 (95% CI: 1.25 to 2.14; p < 0.001) for those with 1-vessel disease, 1.81 (95% CI: 1.45 to 2.27; p < 0.001) for those with 2-vessel disease, 2.12 (95% CI: 1.67 to 2.70; p < 0.001) for those with 3-vessel disease, and 2.53 (95% CI: 2.08 to 3.07; p < .001) for those with LM disease. Similarly, there were significant associations between 1-, 2-, and 3-vessel disease and LM disease with the hazard of experiencing CV death and nonfatal AMI (Online Tables 4 and 5).

DISCUSSION

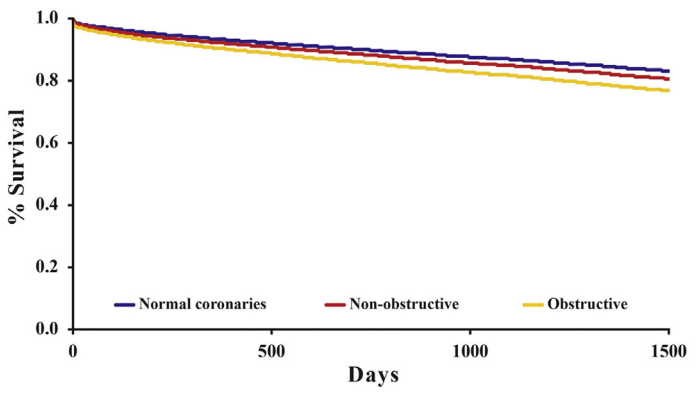
In this study of 12,814 patients with HF with reduced EF undergoing ICA, we found that nonobstructive CAD, which, historically, has been included in the nonischemic group, was an independent prognostic factor associated with an increased rate of the primary composite outcome of death from CV causes, nonfatal AMI, nonfatal ischemic stroke, and HF hospitalizations in comparison with the group of with normal coronary arteries. Observation of the secondary outcomes

revealed that the difference between the nonobstructive group and the apparently normal coronary arteries group was driven by a significant increase of 82% in the rate of CV death whereas the presence of nonobstructive CAD showed no association on nonfatal ischemic events (i.e., AMI and ischemic stroke). In addition, patients with nonobstructive CAD had a rate of all-cause death that was 18% higher compared with those with no apparent CAD. In the group with obstructive disease, we observed a significant increase in the hazard of not only CV death, but also AMI, and ischemic stroke in comparison with those with apparently normal coronary arteries. These long-term outcomes were worse in those with higher disease burden, as defined by the number of diseased vessels and the presence of LM disease. Interestingly, the presence of nonobstructive or obstructive CAD were not associated with an increased hazard of HF hospitalization.

The majority of studies examining the prognostic importance of CAD have focused on obstructive disease, but the risks associated with nonobstructive CAD have been underappreciated. Our findings are consistent with recent studies that have challenged the assumption that nonobstructive CAD is prognostically insignificant. Maddox et al. (6) demonstrated in almost 40,000 veterans who underwent elective ICA for suspected CAD that the detection of nonobstructive disease was associated with a greater risk of AMI and death of any cause at 1 year following catheterization. Studies using coronary computed tomography angiography have also suggested a significant, progressive increase in the risk of death and adverse cardiac events with the presence and growing extent of nonobstructive CAD (7,8,18,19). The event-free survival rate for those patients with nonobstructive disease was intermediate compared with the no apparent CAD and obstructive CAD groups (20). However, none of those studies have specifically examined individuals with HF. Therefore, our study is among the first to demonstrate the prognostic relevance of nonobstructive CAD in the HF population.

The current approach to the classification of HF is to apply a binary definition identifying patients with either ischemic or nonischemic etiology. The main issue created by this dichotomous approach is the erroneous notion that only the presence of CAD above a fixed threshold increases the risk of death and other adverse outcomes. We demonstrated that this risk exists even in the presence of CAD that would have been previously defined as "nonsignificant" or "nonobstructive." Based on our findings, we propose that clinicians should use a more nuanced perspective, which acknowledges that the risk of death increases progressively with the presence and extent of CAD. Our findings of graded increases in risk suggest that there is a continuum of atherosclerotic risk in patients with HF (21).

FIGURE 6 Adjusted Survival Curves for Death of Any Cause and Adjusted HRs According to the Extent of Coronary Artery Disease



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

Abbreviations as in Figure 1.

Further research should examine if an expansion in the assessment of coronary anatomy has an incremental benefit in the prognostication of individuals with HF. Although ICA remains the gold standard for the evaluation of the coronary anatomy, catheterization is usually reserved for a small subgroup of HF patients who might be potential candidates for revascularization. However, other cardiac imaging modalities, which are noninvasive and have better sensitivity to detect CAD, could be used in a broader role to stratify different levels of risk based on the extent of CAD. Simultaneously, additional studies should investigate if medical therapy with aspirin and statins can improve outcomes of patients diagnosed with HF and nonobstructive CAD. Preliminary evidence in non-HF populations originating from observational studies carrying the limitations inherent in this type of study design has suggested that the use of statins may improve clinical outcomes in patients with nonobstructive CAD (8,22,23). However, previous clinical trials of statins and aspirin in HF have showed no apparent clinical benefits when used in those with an ischemic etiology (24,25).

STUDY LIMITATIONS. We had a unique opportunity to examine a large cohort of HF patients with reduced EF

by using a registry that includes all ICA performed across the largest province in Canada. A considerable sample size with detailed clinical information allowed us to create multiple exposure categories and explore the association with outcomes after extensive covariate adjustment. However, our study had some limitations. First, we were unable to stratify the group with nonobstructive disease according to the number of diseased vessels, similar to previous publications (6–8). Despite this, our study offered robust evidence that the presence of nonobstructive CAD increases the risk of CV death. Second, coronary anatomy data were recorded by the operator performing the ICA and there was no centralized review of the angiographic images. As such, misclassification of angiographic findings in the interpretation of the exams was possible (26). However, a survey of Ontario cardiologists performing catheterization has shown that the large majority (69%) consider a normal angiogram to be 0% stenosis and absence of luminal irregularities (27). Therefore, the possibility of classifying individuals with nonobstructive CAD as having apparent normal coronary anatomy was small. In addition, a validation study demonstrated very good reliability between the coronary anatomy recorded in the CorHealth Registry and a blinded interpretation of angiographic findings by an interventional cardiologist (11). Therefore, misclassification bias would likely have minimal impact on our findings. Third, the majority of individuals in the registry had EF already categorized (using our classification scheme) as opposed to EF recorded as a continuous variable. As a consequence, we were unable to examine different cutoff values (i.e., 40%) to define reduced EF. Fourth, medications such as beta-blockers, statins, aspirin, or angiotensin-converting enzyme inhibitors were not measured and therefore were not used for the adjustment of the regression models. Fifth, ICA has limitations to quantify the burden of CAD, revealing only the lumen of coronary vessels. Intracoronary ultrasound or coronary computed tomography angiography could reveal lesions that may have gone unnoticed in our study based on ICA.

CONCLUSIONS

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

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with HF with reduced left ventricular EF undergoing ICA, nonobstructive CAD was independently associated with a higher rate of both CV and non-CV mortality in comparison with those with apparently normal coronary arteries.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the utility of noninvasive cardiac imaging modalities to quantify the burden of CAD and association with clinical outcomes and to examine whether secondary preventive measures can reduce the incidence of death in those with nonobstructive CAD and HF.

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KEY WORDS atherosclerosis, coronary angiography, coronary artery disease, heart failure, mortality, myocardial infarction

APPENDIX For supplemental tables and figures, please see the online version of this paper.