

Clinical Characteristics, Sex Differences, and Outcomes in Patients With Normal or Near-Normal Coronary Arteries, Non-Obstructive or Obstructive Coronary Artery Disease

Michelle L. Ouellette, MD; Adrián I. Löffler, MD; George A. Beller, MD; Virginia K. Workman, MD; Eric Holland, MD; Jamieson M. Bourque, MD, MHS

Background—Normal or near-normal coronary arteries (NNCAs) or nonobstructive coronary artery disease (CAD) are found on invasive coronary angiography in $\approx 55\%$ of patients. Some attribute this to frequent referral of low-risk patients. We sought to identify the referral indications, pretest risk, key clinical characteristics, sex, and outcomes in patients with NNCAs and nonobstructive CAD versus obstructive CAD on nonemergent invasive coronary angiography.

Methods and Results—Over 24 months, 925 consecutive patients were classified as having NNCAs ($\leq 20\%$ stenosis), nonobstructive CAD (21–49% stenosis), or obstructive CAD ($\geq 50\%$ stenosis). Outcomes included cardiac death, nonfatal myocardial infarction, and late revascularization. NNCAs were found in 285 patients (31.0%), nonobstructive CAD in 125 (13.5%), and obstructive CAD in 513 (55.5%). NNCAs or nonobstructive CAD was found in 40.5% with stress ischemia, 27.9% after a non-ST-elevation myocardial infarction, and in 55.5% with stable or unstable angina. More women than men (53.5% versus 37.2%; $P < 0.001$) had NNCAs or nonobstructive CAD across all referral indications. Pretest risk was high and ICA appropriate in 75.5% and 99.2% of patients, respectively. Annual rates of cardiac death or nonfatal myocardial infarction were 1.0%, 1.1%, and 6.7%, respectively, for patients with NNCAs, nonobstructive CAD, and obstructive CAD ($P < 0.001$). No sex differences in outcomes were observed with either NNCAs, nonobstructive CAD, or obstructive CAD ($P = 0.84$).

Conclusions—Many (44.5%) patients undergoing nonemergent invasive coronary angiography have NNCAs or nonobstructive CAD despite high pretest risk, including ischemia and troponin elevation. Although women had more NNCAs or nonobstructive CAD, there were no differences in event rates by sex. Patients with NNCAs and nonobstructive CAD had very low event rates. (*J Am Heart Assoc.* 2018;7:e007965. DOI: 10.1161/JAHA.117.007965.)

Key Words: coronary angiography • coronary artery disease • outcomes research • sex

Several recent studies have highlighted the high prevalence of angiographically normal or near-normal coronary arteries (NNCAs) or nonobstructive coronary artery disease (CAD) in patients referred for diagnostic invasive coronary angiography (ICA) for suspected CAD.¹ Whereas some normal studies can be expected, the finding of more than 50% of diagnostic studies showing no obstructive CAD in many US

cardiac catheterization laboratories has generated both interest and controversy.^{1–3}

Lack of awareness of, and adherence to, guideline-based appropriateness criteria are commonly proposed reasons for the variable diagnostic yield of ICA.² Past studies using administrative databases do not include accurate data on the reasons for referral of individual patients to ICA and coronary angiographic findings related to sex for each category of ICA indication.⁴ Similarly, cardiac event rates in consecutive patients with NNCA and nonobstructive CAD versus obstructive CAD are not reported in these database studies. Moreover, the frequency and associated clinical, imaging, and biomarker correlates of the findings of NNCAs, nonobstructive CAD, and obstructive CAD at ICA have not been well studied.

In this present study, we determined the prevalence of NNCAs, nonobstructive CAD, and obstructive CAD and outcomes in a large number of consecutive symptomatic patients, including those with a non-ST-elevation myocardial infarction (NSTEMI), referred for nonemergent ICA. Indications

From the Cardiovascular Division and the Cardiovascular Imaging Center, Department of Medicine, University of Virginia Health System, Charlottesville, VA.

Correspondence to: Jamieson M. Bourque, MD, MHS, Cardiovascular Division, Department of Medicine, University of Virginia Health System, Box 800158, 1215 Lee St, Charlottesville, VA 22908. E-mail: jbourque@virginia.edu

Received October 31, 2017; accepted March 20, 2018.

© 2018 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Clinical Perspective

What Is New?

- A high rate of near-normal coronaries or nonobstructive coronary artery disease is consistently found in symptomatic patients referred for invasive coronary angiography irrespective of referral indication and despite high pretest risk and appropriate use.
- Women had a greater prevalence of near-normal coronary arteries or nonobstructive coronary artery disease across referral indications, but had similar low cardiac event rates.

What Are the Clinical Implications?

- These data suggest a potential for increased use of advanced noninvasive imaging evaluation to better characterize coronary anatomy and physiology before invasive angiography.
- Ongoing research is needed to better understand the pathophysiology of ischemia in symptomatic patients without obstructive coronary artery disease.

for ICA, pretest risk, key clinical characteristics, sex differences, and appropriateness of ICA were also examined in detail.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. We reviewed the medical records of 1579 consecutive patients aged ≥ 18 years who underwent an initial ICA at the University of Virginia (Charlottesville, VA) for suspected CAD between January 1, 2012 and December 31, 2013. Patients with known CAD or a history of myocardial infarction (MI; $n=419$) and those with emergent indications for ICA ($n=68$), such as an ST-elevation myocardial infarction, cardiogenic shock, or post-cardiac arrest were excluded. Patients undergoing preoperative evaluation before transplant ($n=76$) or cardiothoracic surgery ($n=91$) were also excluded. No patients who underwent ICA for nonischemic cardiomyopathy or congenital heart disease alone were included. The final study cohort comprised 925 patients. The University of Virginia Institutional Review Board gave approval for the study protocol and rendered waiver of informed consent.

Clinical Characteristics and Definitions of Terms

Key patient demographics, comorbidities, home medications, pertinent laboratory data, and stress test and imaging findings were prospectively entered into the electronic medical record for subsequent review. All data, including classification of

symptoms, were collected from the medical record rather than through analysis of diagnostic codes or other administrative data to maximize accuracy. Atherosclerotic cardiovascular disease (ASCVD) risk score was calculated as the 10-year risk estimates from the pooled cohort equations.⁵ An ASCVD risk score of $\geq 7.5\%$ reflected elevated risk.⁶ A diagnosis of a non-ST-elevation myocardial infarction (NSTEMI) was confirmed by an elevated peak troponin I (Abbot ARCHITECT; Abbott Diagnostics, Abbott Park, IL) within 30 days preceding ICA.

Stress Electrocardiography and Stress Imaging

Patients referred because of an abnormal stress test had undergone stress ECG alone, or in conjunction with echocardiography or perfusion imaging by quantitative gated single-photon emission computed tomography (SPECT),⁷ positron emission tomography (PET), or cardiac magnetic resonance imaging. Exercise and pharmacological stress and imaging protocols were standardized according to recommended guidelines with experienced readers rendering interpretations for the medical record. ECG evidence of ischemia was defined as horizontal or downsloping ST-segment depression of ≥ 1.0 mm measured 80 ms after the J-point for 3 consecutive beats.⁸

Ischemia on imaging was defined as inducible wall motion abnormalities on stress echocardiography or reversible defects on myocardial perfusion imaging.^{9–11} SPECT images were processed using a standard 17-segment model. Percentage of left ventricular (LV) ischemia was calculated as previously described.¹² High-risk ischemia was defined as $\geq 10\%$ LV ischemia.¹³

Invasive Coronary Angiography

ICA was performed using standard clinical protocols with all angiograms interpreted by experienced invasive cardiologists. Our angiography laboratory participates in the National Cardiovascular Data Registry and adheres to its data-quality standards. An angiogram with NNCA was defined as having $\leq 20\%$ stenosis in all coronary vessels. The cutpoint of $\leq 20\%$ was chosen in accord with some past studies in this area.^{1,2,14} It is often difficult by ICA alone to distinguish patients with totally normal coronary arteries from those with minimal atherosclerotic plaques without either intravascular ultrasound or optical coherence tomography. For this reason, the label “near normal” is used because some of these patients may have minimal atherosclerosis. Nonobstructive and obstructive CAD were defined by at least 1 coronary artery with a 21% to 49% or $\geq 50\%$ stenosis, respectively.^{1,2,15} Because of the recognized interobserver variability of evaluating intermediate stenoses, quantitative coronary analysis

was retrospectively performed by an experienced angiographer, blinded to all clinical data, on patient studies in which stenosis of 21% to 69% was recorded on the clinical report.

Review of Indications for ICA

The predominant indication for ICA for each individual patient was identified by review of the medical record by 1 of 2 experienced reviewers blinded to the ICA results. When the reviewer was unsure of the indication after assessing the clinical record, both reviewers and the senior author examined the case and agreed upon the most likely indication for ICA. Referral indications included undiagnosed chest pain (CP) syndromes (stable and unstable angina), an abnormal stress test, NSTEMI with a documented troponin elevation, and heart failure of uncertain etiology.

Outcomes

Outcomes, including cardiac death, nonfatal MI, and late revascularization, were ascertained from the electronic medical record. In cases in which outcomes were uncertain or in subjects in whom follow-up was unavailable, telephone contact was made. Follow-up was complete in 923 subjects (99%). Events were classified by a reviewer blinded to the catheterization results. Cardiac death was defined as any death with a cardiac cause or without a clear noncardiac cause. Nonfatal MI was recorded for any troponin elevation ≥ 2 times the upper limit of normal, with or without typical ischemic electrocardiographic changes, in the setting of a history consistent with an acute coronary syndrome. Coronary revascularization procedures included percutaneous coronary interventions and coronary artery bypass grafting. Late revascularization was designated as any coronary revascularization performed ≥ 4 weeks after the initial coronary angiography.

Statistical Analysis

Continuous variables were presented as medians (25th, 75th percentiles) and were compared using Wilcoxon rank-sum and Kruskal–Wallis testing, where appropriate. Tukey's Studentized range testing was used to adjust for multiple comparisons, where appropriate. Categorical variables were given as percentages and compared using chi-square analysis and Fisher's exact testing, where appropriate. Bonferroni adjustment was used for multiple comparisons of categorical variables. Alpha level of significance was set at <0.05 . Interactions between key markers of interest, such as between ischemia and important comorbidities including diabetes mellitus and chronic kidney disease, were compared by univariable logistic regression using a dichotomous

variable, presence of obstructive disease $\geq 50\%$. Event rates were calculated through person-years analysis. Values were adjusted for 1 person-year of follow-up to provide annualized event rates. Kaplan–Meier survival analysis was performed to assess the relationship of the extent of coronary stenosis to cardiac events. The relationship of sex to these outcomes was analyzed through Cox proportional hazards analysis. All statistical analyses were performed using SAS (version 9.3; SAS Institute Inc, Cary, NC) and MedCalc (version 14; MedCalc, Mariakerke, Belgium).

Results

Baseline Characteristics and Severity of Stenosis

Of the 925 patients in the study cohort, 287 (31.0%) had NNCAs, 125 (13.5%) had nonobstructive CAD, and 513 (55.5%) had obstructive CAD. Baseline characteristics of the patient population are provided in Table for the total cohort and divided by severity of angiographic stenosis. Although not all comparisons met statistical significance, patients with a lesser severity of coronary stenosis were younger and more likely to be female. They had a lower prevalence of peripheral and cerebrovascular disease and clinical risk factors for CAD. Patients with NNCAs had a significantly higher body mass index than those with nonobstructive or obstructive CAD. A higher rate of aspirin usage was observed in patients with obstructive CAD. Statins were more commonly used in patients with any degree of CAD at the time of ICA referral. There was a lower rate of CP or dyspnea thought to be an anginal equivalent in those without obstructive CAD. However, no difference was observed in severity of CP as gauged by a Canadian Cardiovascular Society Class of \geq III.

Median 10-year ASCVD risk for the entire study cohort was elevated at 17.8%. Table shows that subjects with obstructive CAD had the highest pretest ASCVD risk, although the majority of patients in all 3 stenosis subgroups had an elevated ASCVD risk of $\geq 7.5\%$. Men had a higher median 10-year ASCVD risk than women (19.9% versus 13.8%; $P<0.001$). Significantly more men than women had an elevated 10-year ASCVD risk score (81.1% versus 68.3%; $P<0.001$).

Indications for Referral for ICA

Indication for ICA was determined in all subjects. Figure 1 shows the prevalence of referral indications for ICA; an abnormal stress test (32.4%) was the most prevalent, followed by NSTEMI (27.9%). CP syndromes without a troponin elevation (stable and unstable angina) and heart failure were the primary indications for ICA in 23.8% and 13.0%, respectively. Other indications, such as ventricular tachycardia, made up a small minority of the patient cohort (2.9%).

Table. Study Cohort Baseline Characteristics in Total and Subdivided by Severity of Angiographic Coronary Stenosis

Clinical Characteristic	Total Cohort, n (%)	Severity of Coronary Stenosis			P Value
		≤20%, n (%)	21% to 49%, n (%)	≥50%, n (%)	
Total patients	925	287 (31.0%)	125 (13.5%)	513 (55.5%)	...
Age, y	62.6 (53.9, 70.9)	57.4 (48.8, 66.3)	65.7 (57.4, 72.8)	64.5 (56.0, 72.4)	<0.001* [†]
Female	411 (44.4)	155 (37.7)	65 (15.8)	191 (46.5)	<0.001 ^{‡,†}
White	754 (81.5)	214 (74.6)	102 (81.6)	438 (85.4)	<0.001 [†]
Diabetes mellitus	326 (35.2)	88 (30.7)	39 (31.2)	199 (38.8)	0.041
Hypertension	718 (77.6)	196 (68.3)	89 (71.2)	433 (84.4)	<0.001 ^{‡,†}
Hyperlipidemia	627 (67.8)	160 (55.8)	70 (56.0)	397 (77.4)	<0.001 ^{‡,†}
Current tobacco	298 (32.2)	86 (30.0)	36 (28.8)	176 (34.3)	0.31
BMI ≥30	434 (46.9)	156 (54.5)	55 (44.0)	223 (43.5)	0.010 [†]
Peripheral vascular disease	112 (12.1)	14 (4.9)	8 (6.4)	90 (17.5)	<0.001 ^{‡,†}
Cerebrovascular disease	35 (3.8)	4 (1.4)	2 (1.6)	29 (5.7)	0.004 [†]
Chronic kidney disease grade ≥3	93 (10.1)	16 (5.6)	7 (5.6)	70 (13.6)	<0.001 ^{‡,†}
ASCVD risk (%) [§]	17.8 (7.9–33.0)	10.2 (3.9–24.2)	14.0 (8.0–28.8)	22.0 (11.6–38.2)	<0.001 ^{‡,†}
ASCVD ≥7.5%	599 (75.5)	142 (59.2)	80 (77.7)	377 (83.8)	<0.001* [†]
Chest pain or anginal SOB	731 (79.0)	218 (76.0)	84 (67.2)	429 (83.6)	<0.001 ^{‡,†}
CCS Class ≥III	512 (55.2)	146 (50.9)	71 (56.8)	294 (57.3)	0.20
Aspirin	488 (53.2)	121 (42.3)	60 (48.8)	307 (60.4)	<0.001 [†]
Statin	437 (47.3)	115 (40.1)	64 (51.6)	258 (50.3)	0.012 [†]
ACE-inhibitor or ARB	454 (49.1)	128 (44.6)	63 (50.4)	263 (51.3)	0.19
Beta-blocker	394 (42.6)	120 (41.8)	53 (42.4)	221 (43.1)	0.94

Continuous variables given as median (25th–75th percentiles). ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CCS, Canadian Cardiovascular Society; SOB, shortness of breath.

*Significant difference between ≤20% and 21% to 49%.

[†]Significant difference between ≤20% and ≥50%.

[‡]Significant difference between 21% to 49% and ≥50%.

[§]ASCVD risk was unable to be classified in 134 subjects.

Coronary Angiographic Findings in Men and Women

Figure 2 shows the prevalence of NNCA, nonobstructive CAD, and obstructive CAD in all patients and subdivided by men versus women. Those referred to ICA after an abnormal stress test (with or without imaging) had a 42.1% rate of NNCA or nonobstructive CAD. Those referred for ICA following an NSTEMI had a 27.9% rate of NNCA or nonobstructive CAD, with a 2-fold higher rate of NNCA (18.6%) compared with nonobstructive CAD (9.3%). Stenosis severity varied significantly by sex ($P<0.001$). Women had more NNCA (37.7% versus 25.7%; $P<0.001$) and NNCA+nonobstructive CAD (53.5% versus 37.2%; $P<0.001$). Women had a lower rate of obstructive CAD for each indication (Figure 2).

Abnormal Stress Test Indication

Of the 300 patients referred for ICA after an abnormal stress test, 7 (2.3%) underwent exercise stress ECG testing without imaging. Of the remaining patients, 57 (19.0%) underwent

stress echocardiography, 227 (75.7%) underwent exercise or pharmacological SPECT myocardial perfusion imaging, and 8 (2.7%) had either a PET or cardiac magnetic resonance stress perfusion study. One patient underwent computed tomographic (CT) angiography without stress. This patient was included in this referral group because of abnormal imaging findings warranting ICA. The majority of testing used pharmacological stress (63.3%).

Exercise or pharmacological stress imaging was performed in 292 patients, of whom 247 (84.6%) had ischemia and 20 (6.8%) had only evidence of infarction/scar. Surprisingly, patients exhibiting ischemia or ischemia with infarction/scar by imaging criteria had a 40.5% (100 of 247) rate of either NNCA or nonobstructive CAD. Similarly, this rate was 55.0% (11 of 20) in patients with only imaging evidence of infarction/scar. Figure 3 illustrates the severity of angiographic stenosis according to stress ECG and stress imaging findings in the 217 patients with diagnostic stress ECGs. As shown, those with no ischemia by ECG or imaging criteria had

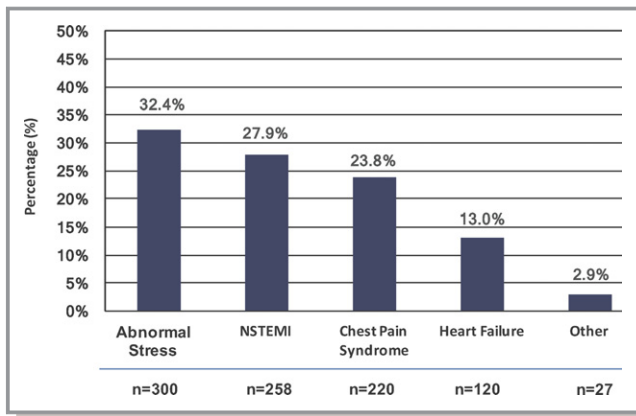


Figure 1. Prevalence of referral indications for invasive coronary angiography. The number of patients in each subgroup is shown below the bars. NSTEMI indicates non-ST-elevation myocardial infarction.

a 72.7% rate of NNCA or nonobstructive CAD. Prevalences of NNCA or nonobstructive CAD were intermediate in patients with ischemia only on the stress ECG (40.0%) or only by imaging criteria (43.6%). However, even patients with ischemia on both the stress ECG and on imaging had a 21.7% prevalence of NNCA or nonobstructive CAD. In the

entire stress imaging cohort, neither sex ($P=0.42$) nor diabetes mellitus ($P=0.91$) affected the relationship of ischemia with the degree of stenosis by logistic regression analysis. In contrast, a significant relationship was observed between a high pretest ASCVD risk of $\geq 7.5\%$ and ischemia ($P<0.001$). A high versus a low or intermediate pretest ASCVD risk substantially increased the likelihood of obstructive CAD in the presence of ischemia (67.6% versus 38.0%; $P<0.001$). With respect to sex differences in subjects referred for an abnormal stress test, the incidence of NNCA or nonobstructive CAD was significantly higher in women (51.1%) compared with men (35.0%; $P=0.005$), despite similar rates of ischemia in women and men in this subgroup (88.0% versus 81.8%; $P=0.14$).

Figure 4 depicts the severity of stenosis in the 152 patients who underwent stress SPECT myocardial perfusion imaging and were found to have either normal perfusion, fixed defects consistent with infarction, $<10\%$ LV ischemia, or $\geq 10\%$ LV ischemia. Rate of NNCA was substantial in both those with mild-to-moderate ischemia encompassing $<10\%$ of the LV (29.5%) and severe ischemia involving $\geq 10\%$ of the LV (20.0%). The 40 patients with severe ischemia had a significantly higher rate of obstructive CAD (75.0%) than the 112 subjects

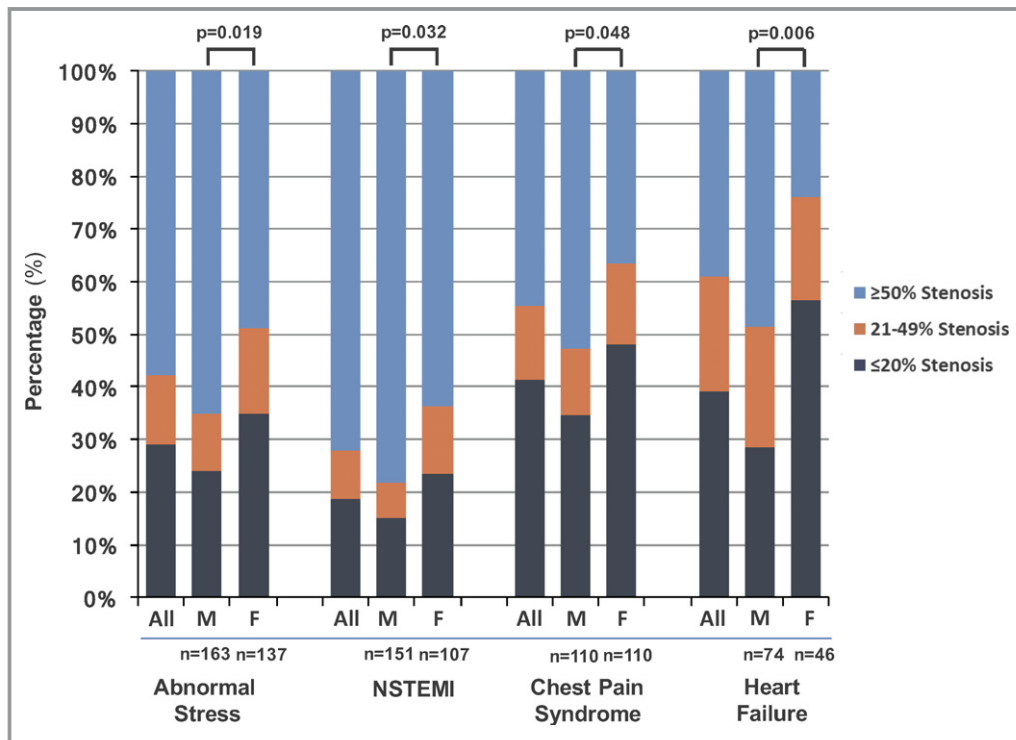


Figure 2. Prevalence of normal or near-normal coronary arteries (NNCA; $\leq 20\%$ stenosis), no-obstructive CAD (21–49% stenosis), and obstructive CAD ($\geq 50\%$ stenosis) in all patients and subdivided into male vs female sex for each invasive coronary angiography referral indication. For each indication, the combined prevalence of NNCA and nonobstructive CAD is significantly higher in female patients compared with male patients. CAD indicates coronary artery disease; F, female; M, male; NSTEMI, non-ST-elevation myocardial infarction.

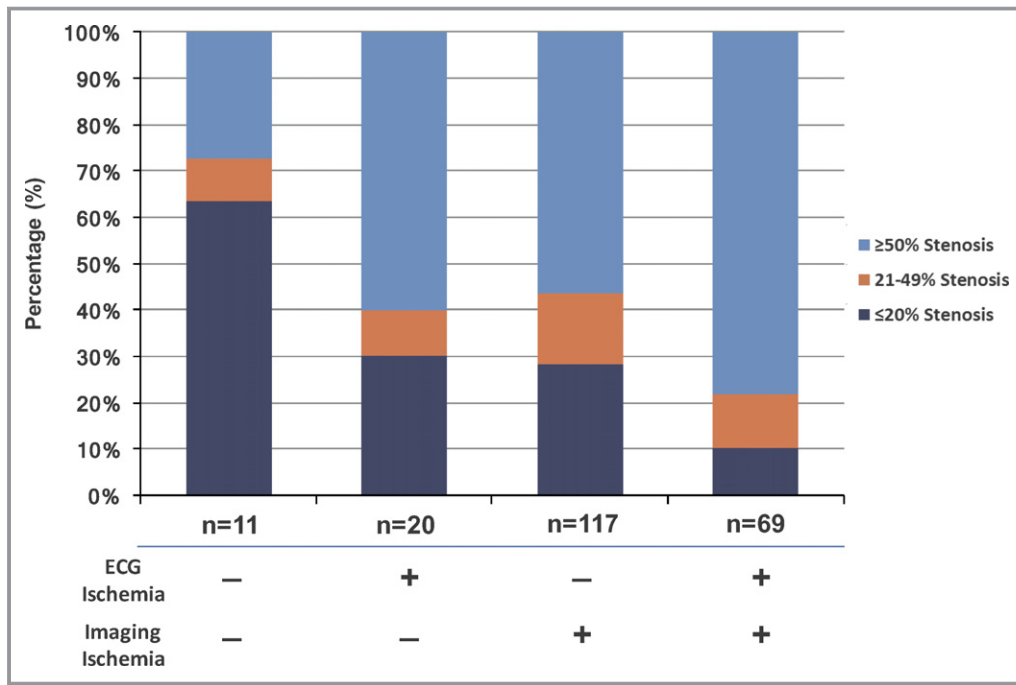


Figure 3. Severity of coronary artery stenosis in the 217 patients who underwent imaging before ICA and had an interpretable stress ECG subdivided according to absence or presence of ischemia by stress ECG and stress imaging criteria. Prevalence of obstructive CAD ($\geq 50\%$ stenosis) was highest in patients exhibiting ischemia on both the stress ECG and imaging ($P < 0.001$) and lowest with both negative ($P = 0.015$). CAD indicates coronary artery disease; ICA, invasive coronary angiography.

without high-risk ischemia (55.4%; $P = 0.029$). Prevalence of obstructive CAD was even higher (91.7%) in the 12 patients with $\geq 20\%$ LV ischemia. Prevalences of NNCA and nonobstructive CAD were similar in patients with normal perfusion and in patients with solely fixed perfusion defects with no ischemia.

NSTEMI Indication

Of the 258 patients referred for NSTEMI, 48 (18.6%) had NNCA, 24 (9.3%) had nonobstructive CAD, and 186 (72.1%) had obstructive CAD. Median troponin level was higher in NSTEMI patients with obstructive CAD (2.6 ng/mL; interquartile range, 0.5–6.7), compared with those with an NSTEMI, but NNCA or nonobstructive CAD (0.7 ng/mL; interquartile range, 0.2–2.2; $P < 0.001$). Nearly 90% of NSTEMI patients with a high troponin level (≥ 5.0 ng/mL) had obstructive CAD (62 of 69 [89.9%]). There was substantial variation in troponin values relative to severity of stenosis in patients with troponin levels of < 5.0 ng/mL. Figure 5 demonstrates the severity of coronary stenosis stratified by clinically relevant troponin cutpoints (borderline elevated, low, intermediate, and high). A step-wise increase in prevalence and likelihood of obstructive CAD was observed with increasing troponin levels. Using a troponin range of < 0.1 as a referent, the odds of obstructive

CAD were 1.64 (0.61–4.43; $P = 0.33$) for a troponin of 0.1 to 0.99, 2.25 (0.81–6.29; $P = 0.12$) for a troponin of 1 to 4.99, and 7.97 (2.42–26.27; $P < 0.001$) for a troponin of ≥ 5 . Patients with a troponin level of < 1.0 ng/mL had 25.9% and 12.5% prevalences of NNCA and nonobstructive CAD, respectively.

Severity of coronary stenosis differed significantly between women and men referred for ICA for an NSTEMI ($P = 0.032$). Women had higher rates of both NNCA (23.4% versus 15.2%) and nonobstructive CAD (13.1% versus 6.6%) compared with men. Women with NSTEMI had a lower rate of obstructive CAD (63.6% versus 78.8%; $P = 0.007$). Female sex decreased the predictive power of the troponin value ($P < 0.001$ for interaction by logistic regression).

CP (Stable and Unstable Angina) Indication

Of the 220 patients referred for CP syndromes without an elevated troponin and without an abnormal stress test preceding ICA, 119 had unstable angina and 101 had stable angina. There was no statistically significant difference in severity of stenosis between those with unstable and stable angina ($P = 0.11$). Of patients referred for ICA for a CP syndrome, 41.4% had NNCA, 14.1% had nonobstructive CAD, and 44.6% had obstructive CAD. Anginal severity did not impact the degree of coronary stenosis, as reflected by a

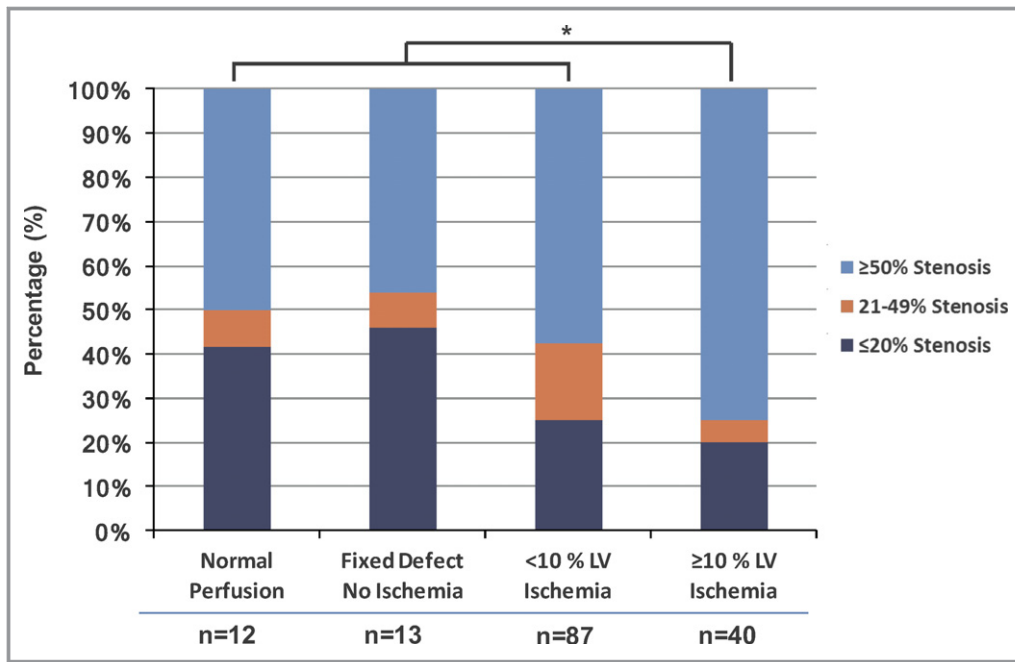


Figure 4. Severity of coronary artery stenosis subdivided by findings on stress single-photon emission computed tomography myocardial perfusion imaging. Although the rate of NNCA or nonobstructive CAD was higher in those without $\geq 10\%$ of the LV ischemic ($P=0.029$), it remained substantial even in this subgroup with severe ischemia (25.0%). CAD indicates coronary artery disease; LV, left ventricle; NNCA, near-normal coronary arteries. $*P<0.05$.

60.9% prevalence of NNCA or nonobstructive CAD, in patients with severe angina as defined by a Canadian Cardiovascular Society score of ≥ 3 .

As shown in Figure 6, patients with stable or unstable angina who had an elevated 10-year ASCVD risk of $\geq 7.5\%$ had a higher prevalence of obstructive CAD (48.6%) compared with those

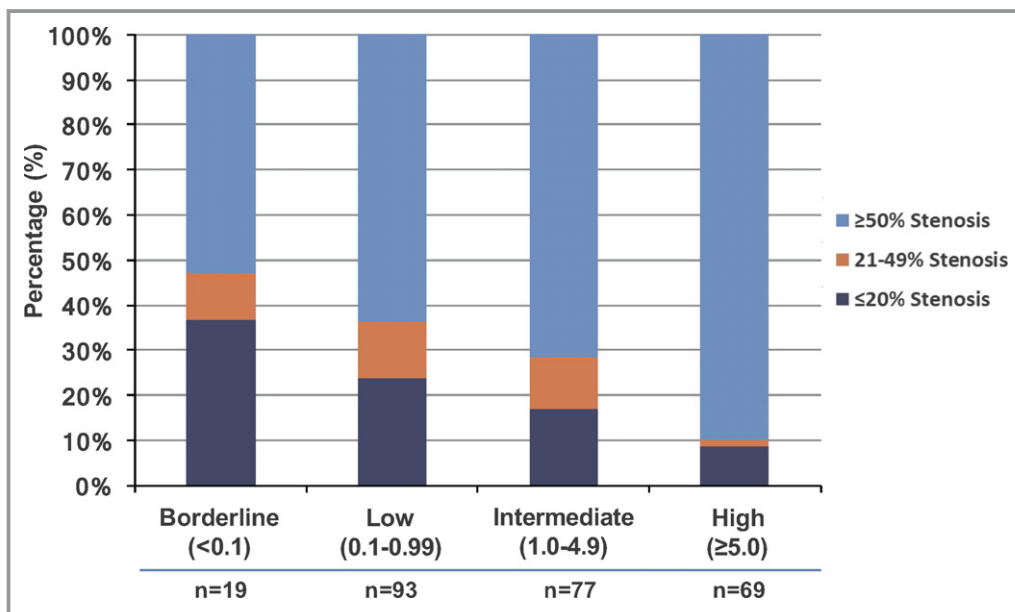


Figure 5. Severity of coronary stenosis subdivided by presence of borderline elevated, low, intermediate, and high troponin I levels. There is a progressive increase in prevalence of obstructive CAD with increasing levels of troponin I ($P<0.001$). CAD indicates coronary artery disease.

with a <7.5% 10-year ASCVD risk (30.4%; $P=0.032$). Compared with men, fewer women referred for a CP syndrome had elevated ASCVD risk (67.7% versus 82.8%; $P=0.017$). However, of those women with elevated risk, 58.7% had NNCA or nonobstructive CAD (compared with 45.5% for men; $P=0.12$).

The rate of normal arteries or NNCA was very high (65.2%) in patients with an ASCVD risk of <7.5%. Female patients with CP syndromes in this group had a lesser degree of angiographic coronary stenosis than men ($P=0.048$). Prevalence of NNCA or nonobstructive CAD in patients with <7.5% ASCVD risk was 63.6% in women and 47.3% in men ($P=0.015$).

Heart Failure Indication

Of the 120 patients referred to ICA with heart failure of uncertain etiology, 47 (39.2%) had NNCA, 26 (21.7%) had nonobstructive CAD, and 47 (39.2%) had obstructive CAD. The majority of patients in this group had systolic heart failure (81.3%). There was no difference in severity of coronary stenosis by type of heart failure ($P=0.33$). In this referral indication subgroup, women had a 76.1% prevalence of NNCA or nonobstructive CAD versus 51.4% for men ($P=0.007$).

Appropriateness of ICA

Appropriateness of ICA in patients without NSTEMI from this cohort was reported previously in a research letter.¹⁶ For this

current expanded patient population, which included 258 NSTEMI patients, ICA was classified as appropriate in 918 patients (99.2%). The 7 patients with inappropriate indications for ICA all had NNCA.

Outcomes

Median follow-up was 2.0 years. In those referred for abnormal stress, NSTEMI, or clinical CP syndromes, Kaplan–Meier survival analysis showed a significant decrease in survival free from cardiac death and nonfatal MI and free of all cardiac events for those with obstructive CAD in both men and women (Figure 7A and 7B) compared with patients with NNCA and nonobstructive CAD. Findings were similar when the analysis was limited to those with a high-risk troponin ≥ 1 ng/mL or ischemia on stress testing (Figure 7C). In the entire cohort, sex was not a significant predictor of cardiac events ($P=0.84$) when assessed by Cox proportional hazards analysis. More specifically, there was no difference in outcomes for men versus women with NNCA, nonobstructive CAD, or obstructive CAD in the entire study cohort. Moreover, logistic regression showed no interaction between sex and severity of coronary stenosis ($P=0.37$). Patients with NNCA and nonobstructive CAD had an excellent prognosis with no difference in event rates between these 2 subgroups. Annual cardiac death and nonfatal MI rates were 1.0% and 1.1%,

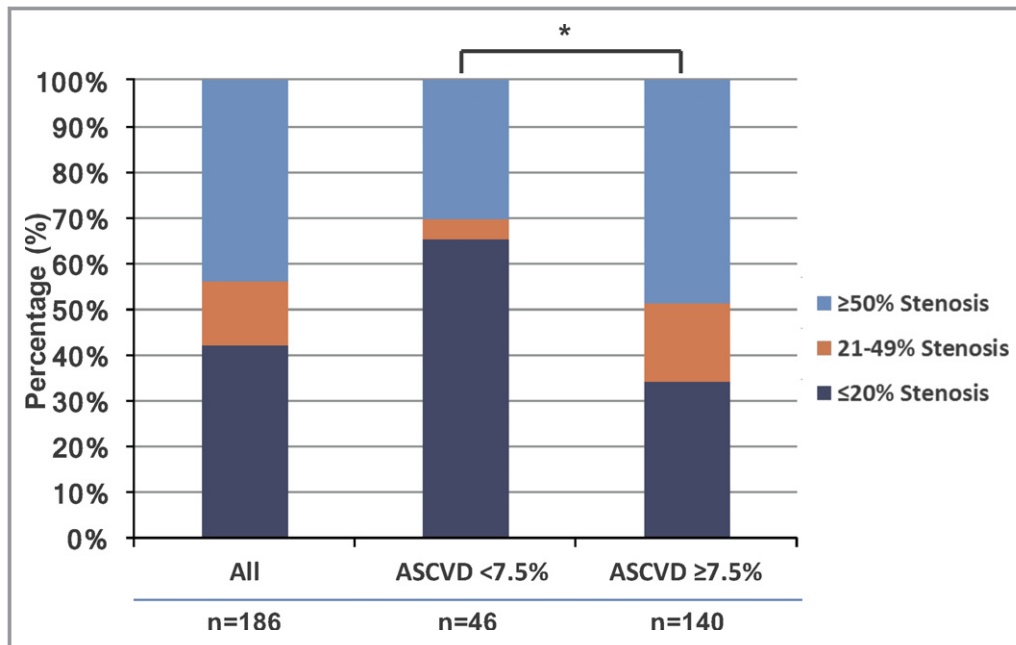


Figure 6. Severity of coronary stenosis in the 186 patients with stable or unstable angina referred for invasive coronary angiography. The group is subdivided by 10-year ASCVD risk of $\geq 7.5\%$ ($n=140$) and $< 7.5\%$ ($n=46$). Although the prevalence of obstructive CAD was greater in the subgroup with elevated pretest 10-year ASCVD risk ($P=0.032$), more than 50% had either normal/near-normal coronary arteries ($\leq 20\%$ stenosis) or nonobstructive CAD (21–49% stenosis). ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease. * $P<0.05$.

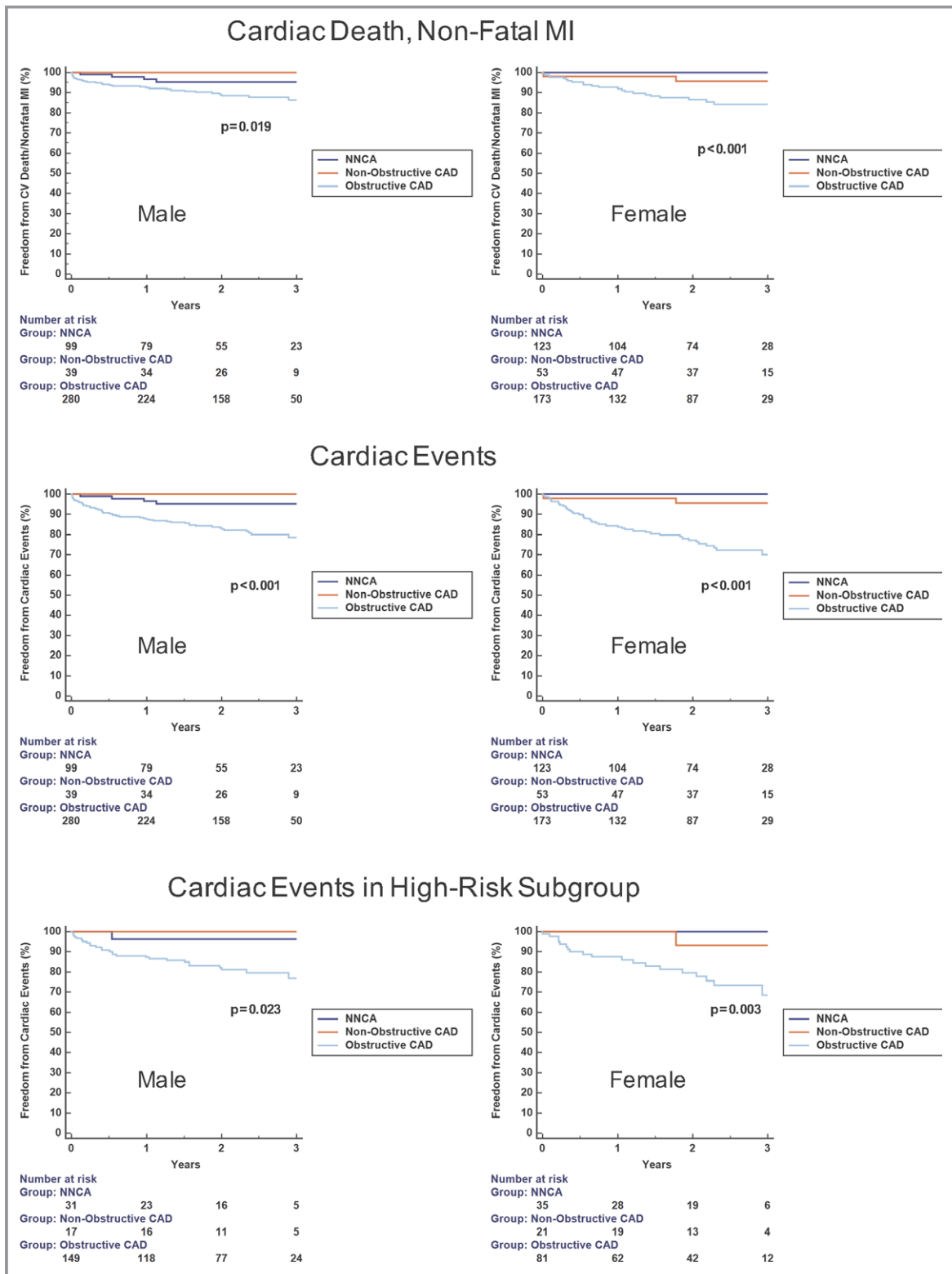


Figure 7. Kaplan–Meier survival curves of freedom from cardiac death and nonfatal myocardial infarction (MI) (A) and freedom from cardiac events (cardiac death, nonfatal MI, and late revascularization) (B) in those referred for abnormal stress, NSTEMI, or CP syndrome with NNCA, nonobstructive CAD, and obstructive CAD stratified by sex. C, Freedom from cardiac events in high-risk patients with ischemia on stress testing or a troponin level ≥ 1 ng/mL. There was a consistently higher risk of events for those with obstructive CAD across all groups. CAD indicates coronary artery disease; CP, chest pain; NNCA, near-normal coronary arteries; NSTEMI, non-ST-elevation myocardial infarction.

respectively, for patients with NNCA and nonobstructive CAD ($P=0.83$). In contrast, the annual cardiac death+nonfatal MI rate was much higher in those with obstructive CAD (6.7%; $P<0.001$ versus NNCA+nonobstructive CAD). The difference in annual event rates was even higher for all cardiac events (11.1% for obstructive CAD versus 1.1% for NNCA+nonobstructive CAD; $P<0.001$).

Discussion

Data derived from large registries have reported an $\approx 40\%$ rate of NNCA in patients referred for elective diagnostic coronary angiography.^{1,2} Douglas et al reported that the hospital variability in the rate of finding obstructive CAD at elective coronary angiography varied from 23% to 100%, with a median rate of 45% for the 691 US hospitals surveyed.² Prevalence of obstructive CAD in our cohort was 55.5%, somewhat higher than this median value. Rates of NNCA and nonobstructive CAD in our cohort were 31% and 13.5%, respectively.

Referral to ICA for an Abnormal Stress Test

An abnormal stress test, predominantly with cardiac imaging, was the most common indication for referral to ICA in our cohort. Only 9% of the patients referred after stress testing had no ischemia or infarction by stress ECG or imaging criteria. These patients all had other abnormal findings at stress testing. Median ASCVD score was high (17.7%) for patients referred after a positive stress test, and nearly 75% were classified as having a high-risk score (≥ 7.5). Despite the high pretest ASCVD risk and few nonischemic stress test results, only 60% of the patients with a positive stress test had obstructive CAD. This value is substantially higher than the 41% prevalence of obstructive CAD in the National Cardiovascular Data Registry database study of patients who underwent stress testing before ICA.¹ This does not necessarily imply that the remaining 40% of patients with NNCA or nonobstructive CAD did not have abnormal coronary flow physiology. In fact, 25% of patients with $\geq 10\%$ LV ischemia had NNCA or nonobstructive CAD. These findings are consistent with the concept that a stenosis of $\geq 50\%$ is not an accurate gold standard for abnormal coronary flow physiology. Microvascular or endothelial dysfunction may play a role in angina symptoms and ischemic changes on stress testing.¹⁷ Consistent with this concept, nearly 50% of women in our study with abnormal stress tests had either NNCA or nonobstructive CAD compared with 33% of men.¹⁸

Referral to ICA for an NSTEMI

Of 258 patients referred for ICA for an NSTEMI, 72 (28%) had NNCA or nonobstructive CAD. Patients with the highest

troponin levels (≥ 5.0 ng/mL) had a high prevalence of obstructive CAD. A substantially larger rate of NNCA or nonobstructive CAD was observed in those with lower troponin levels. Nearly 50% of patients considered to have borderline troponin elevations and 40% of those with low troponin levels had NNCA or nonobstructive CAD. Although some of these patients may have had etiologies other than an acute coronary syndrome as the cause of an elevated troponin level, most had symptoms and/or ECG changes consistent with an NSTEMI. Again, more women than men were observed to have an NSTEMI with NNCA or nonobstructive CAD. Other past studies in the literature have shown variable rates of nonobstructive CAD or NNCA in women with an NSTEMI.¹⁹

Referral to ICA for Stable or Unstable Angina

Unstable and stable CP syndromes comprised the next most common indications for ICA. Despite a high pretest 10-year ASCVD risk for both CP groups, prevalence of NNCA or nonobstructive CAD was substantial in both the stable angina (60%) and unstable angina (50%) groups. As expected, the higher the pretest 10-year ASCVD risk, the higher the rate of obstructive CAD. However, it should be noted that slightly more than 50% of patients with elevated pretest 10-year ASCVD risk scores had NNCA or nonobstructive CAD. Female subjects with stable or unstable angina had a significantly higher prevalence of NNCA or nonobstructive CAD compared with male subjects (see Figure 2). Nearly two thirds of women referred for CP syndromes without a troponin elevation had NNCA or nonobstructive CAD. This is consistent with previous observations of women presenting with angina having less-obstructive CAD than men.²⁰ Interestingly, the percentage of CP patients with severe angina, as assessed by the Canadian Cardiovascular Society Class $\geq III$, was not different between patients with obstructive CAD versus those with either NNCA or nonobstructive CAD.

Pretest Clinical Risk and Appropriateness of ICA Referral

Some observers^{1,2} have proposed that a contributing cause of the high rate of NNCA or nonobstructive CAD observed at ICA is the referral of clinically low-risk patients. For purposes of analysis and comparison with past studies reporting data in patients with elective ICA, we combined the stress test and CP groups to determine the pretest risk for those with obstructive CAD versus those with NNCA or nonobstructive disease. Rates for an elevated pretest risk, defined by an ASCVD score of ≥ 7.5 ,⁵ were 60.1%, 76.3%, and 84.0% for patients with NNCA, nonobstructive CAD, and obstructive

CAD, respectively. Few patients in any of the groups had a pretest risk that was not elevated. Thus, referral of a large number of low-risk patients for ICA was not a major factor that accounted for the overall 31% prevalence of NNCAs in our study. Using the 2012 Appropriate Use Criteria for Diagnostic Catheterization,²¹ all but 7 of the 925 patients in this study had appropriate indications for ICA. This is not surprising given that 76% of patients with NNCAs had CP or dyspnea, with more than 50% having Canadian Class \geq III angina. This high rate of appropriate indications for ICA is also consistent with the high pre-ICA clinical risk of this patient population.

Sex Differences and Outcomes

Women represented a significant percentage (44%) of the patients referred for ICA in this study. For every indication for ICA described, women had a greater percentage of NNCAs or nonobstructive CAD than men. For the entire group of women spanning the various indications for ICA, 38% had NNCAs and 16% had nonobstructive CAD. Women and men had similar prevalence and extent of ischemia and troponin elevations, suggesting that different degrees of objective ischemic findings were not present by sex.

Nearly 50% of women who underwent ICA for stable or unstable angina with no previous stress testing had NNCAs. This finding is not surprising, given that recent studies have shown that women present with more atypical symptoms than men and have less-obstructive CAD at angiography.^{19,20,22} It is likely that microvascular dysfunction was the pathophysiological mechanism for angina in many of the women without obstructive CAD. Microvascular dysfunction can now be identified noninvasively by demonstrating abnormal flow reserve by PET or magnetic resonance imaging perfusion imaging.²³ Women without obstructive CAD and impaired coronary flow reserve by PET have a greater risk of future cardiovascular events than women with preserved flow reserve, and a greater risk than men with either normal or abnormal flow reserve.²⁴

Past studies have conflicting results on whether there is a difference in cardiac outcomes by sex in those with NNCAs, nonobstructive CAD, or obstructive CAD. An analysis of 5632 subjects in the prospective CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) Registry found no significant difference in risk of the composite end point of all-cause mortality and nonfatal MI by sex over 5 years. Likewise, a study of a registry of 11 223 subjects in Eastern Denmark found no Cox model interaction between sex and extent of CAD for major adverse cardiac events, which was defined as cardiovascular death, MI, stroke, heart failure, or all-cause mortality.^{25,26} In contrast to the CONFIRM and Denmark

analyses, Sedlak et al found a 3-fold increased risk of major adverse cardiac events at 1 year for women versus men with nonobstructive CAD in 13 695 subjects in Canada.²⁷ Major adverse cardiac events in this study was defined as all-cause mortality, nonfatal MI or stroke, and heart failure admission. In our study, event-free survival was similar between women and men in those with NNCAs, nonobstructive CAD, and obstructive CAD. It should be pointed out that the rate of cardiac death and nonfatal MI was low in both men and women. A potential explanation for this finding is the use of medications with proven cardiovascular risk reduction, including aspirin and statins, in a substantial proportion of our population.

Future Directions to Reduce Prevalence of NNCAs at ICA

Some approaches might be considered to reduce the prevalence of NNCAs at ICA. Some of the patients with stable angina, who were referred directly for ICA, might indeed have been candidates for noninvasive stress imaging as the initial diagnostic test. Noninvasive CT angiography is emerging as an alternative to stress imaging for detection of epicardial coronary stenosis in low to low-intermediate risk patients, particularly with atypical symptoms.²⁸ This technique has a high negative predictive value for ruling out obstructive CAD.²⁸ It also provides additional prognostic information attributed to the identification of nonobstructive CAD.²⁹ Moreover, given that the entire vessel wall is imaged with CT angiography as opposed to the lumen analysis by ICA, patients with near-normal coronaries can be separated from those with no coronary plaque, a group with a better prognosis. CT angiography might also be used in patients with an equivocal stress test or an unexpected positive test in a patient with a low pretest likelihood of CAD.²⁸ PET or magnetic resonance imaging perfusion imaging can ascertain abnormal flow reserve for identification of patients with microvascular dysfunction, particularly in women with symptoms suggestive of ischemia.³⁰ Hybrid imaging combining SPECT or PET with CT angiography can be utilized for this approach if abnormal flow reserve is detected. If no epicardial disease is observed in the setting of abnormal flow reserve by PET or magnetic resonance imaging, then microvascular or endothelial dysfunction in the absence of obstructive epicardial CAD may be proposed as the cause of symptoms or ischemia. Noninvasive stress imaging to rule out ischemia could be undertaken in patients with a low-to-intermediate risk of an acute coronary syndrome associated with a borderline elevated troponin level.³¹ With greater utilization of noninvasive imaging technology, the rate of NNCAs could be reduced in patients with heart failure referred to ICA to rule out CAD.

Study Limitations

There are several limitations of this study. First, this is a single-center study. Although collection of clinical information, noninvasive test data, and laboratory data was comprehensive and not solely derived from registry or claims data, this study was retrospective in nature and not all data were collected in all patients. Symptom review was, at times, challenging, particularly gauging the severity of angina, which is an inherent limitation to retrospective analysis. However, the higher likelihood of disease in this cohort referred for angiography compared with the entire population undergoing stress testing and the added evaluation by clinicians in the catheterization laboratory may increase the accuracy. Moreover, severity of angina did not impact degree of stenosis identified. Rate of obstructive CAD in patients undergoing elective ICA in this study (55%) was somewhat higher than the median rate (45%) found at ICA in the analysis of US hospitals participating in the National Cardiovascular Data Registry Registry.¹ This may be attributed to fewer low-risk patients undergoing ICA and the inclusion of patients with NSTEMI in our study. Another limitation is that the functional significance of coronary artery stenoses was not routinely assessed by fractional flow reserve measurements at ICA. Plaque burden and diffuse disease could not be quantified because intravascular ultrasound measurements were not routinely made and these patients did not receive optical coherence tomography. Without use of these advanced plaque-imaging techniques, it is not possible to differentiate between those with 1% to 20% plaque and those with no coronary plaque, a group with a better prognosis. This may have led to an overestimation of risk and events in the NNCA group, though the event rates were very low (annual cardiac death and nonfatal MI rate of 1.0%). Given the challenge in predicting the angiographic site of likely future events, it is possible that a small intraluminal plaque of $\leq 20\%$ stenosis could serve as a culprit lesion for a future event. We did retrospectively perform quantitative angiography in patients with intermediate stenosis to enhance the correct classification into those with 21% to 49% stenosis versus those with $\geq 50\%$ stenosis. Also, a longer duration of follow-up might yield greater differences in event rates between patients with NNCA versus those with nonobstructive CAD, especially given the high rates of antiatherosclerotic therapy use (53.2% on aspirin, 47.3% on a statin).

Conclusions

In conclusion, this study of consecutive patients, most with a high pre-ICA risk of CAD and appropriate referral for nonemergent ICA, showed a high prevalence (44.5%) of normal arteries or NNCA or nonobstructive CAD. For each major referral indication (ie, an abnormal stress test, NSTEMI,

stable or unstable CP syndrome, or heart failure), women had a greater prevalence of NNCA or nonobstructive CAD than men. The short-term prognosis of patients with NNCA and nonobstructive CAD was excellent compared with those with obstructive CAD. No sex differences were noted in cardiac event rates related to stenosis severity. Research in many centers is ongoing to better understand the pathophysiological mechanisms for ischemia (eg, coronary microvascular dysfunction) in such symptomatic patients with no obstructive CAD.³² Reduction in the referral of symptomatic patients with NNCA to ICA, and the identification of patients with nonobstructive CAD, may be accomplished by use of coronary CT angiography. Detection of abnormal coronary flow reserve in conjunction with NNCA or nonobstructive CAD can be identified using hybrid imaging with PET-CT.³²

Sources of Funding

This work was supported by NIH 1K23HL119620.

Disclosures

Dr Bourque has received research support from Astellas Pharmaceuticals (nonrelevant). The remaining authors have no disclosures to report.

References

1. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.
2. Douglas PS, Patel MR, Bailey SR, Dai D, Kaltenbach L, Brindis RG, Messenger J, Peterson ED. Hospital variability in the rate of finding obstructive coronary artery disease at elective, diagnostic coronary angiography. *J Am Coll Cardiol*. 2011;58:801–809.
3. Patel MR, Dai D, Hernandez AF, Douglas PS, Messenger J, Garratt KN, Maddox TM, Peterson ED, Roe MT. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am Heart J*. 2014;167:846–852.e2.
4. Patel MR, White RD, Abbara S, Bluemke DA, Herfkens RJ, Picard M, Shaw LJ, Silver M, Stillman AE, Udelson J; American College of Radiology Appropriateness Criteria, American College of Cardiology Foundation Appropriate Use Criteria Task Force. 2013 ACCF/ACR/ASE/ASNC/SCCT/SCMR appropriate utilization of cardiovascular imaging in heart failure: a joint report of the American College of Radiology Appropriateness Criteria Committee and the American College of Cardiology Foundation Appropriate Use Criteria Task Force. *J Am Coll Cardiol*. 2013;61:2207–2231.
5. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2935–2959.
6. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2889–2934.
7. Watson DD, Smith WH II. The role of quantitation in clinical nuclear cardiology: the University of Virginia approach. *J Nucl Cardiol*. 2007;14:466–482.
8. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, Coke LA, Fleg JL, Forman DE, Gerber TC, Gulati M, Madan K, Rhodes J, Thompson PD,

- Williams MA. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128:873–934.
9. Bourque JM, Holland BH, Watson DD, Beller GA. Achieving an exercise workload of ≥ 10 metabolic equivalents predicts a very low risk of inducible ischemia: does myocardial perfusion imaging have a role? *J Am Coll Cardiol*. 2009;54:538–545.
 10. Bourque JM, Patel CA, Ali MM, Perez M, Watson DD, Beller GA. Prevalence and predictors of ischemia and outcomes in outpatients with diabetes mellitus referred for single-photon emission computed tomography myocardial perfusion imaging. *Circ Cardiovasc Imaging*. 2013;6:466–477.
 11. Futamatsu H, Wilke N, Klassen C, Shoemaker S, Angiolillo DJ, Siuciak A, Morikawa-Futamatsu K, Suzuki N, von Ziegler F, Bass TA, Costa MA. Evaluation of cardiac magnetic resonance imaging parameters to detect anatomically and hemodynamically significant coronary artery disease. *Am Heart J*. 2007;154:298–305.
 12. Bourque JM, Beller GA. Stress myocardial perfusion imaging for assessing prognosis: an update. *JACC Cardiovasc Imaging*. 2011;4:1305–1319.
 13. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900–2907.
 14. Bradley SM, Maddox TM, Stanislawski MA, O'Donnell CI, Grunwald GK, Tsai TT, Ho PM, Peterson ED, Rumsfeld JS. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insights from the VA CART program (veterans affairs clinical assessment reporting and tracking). *J Am Coll Cardiol*. 2014;63:417–426.
 15. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA, Antman EM, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP; American College of Cardiology/American Heart Association Task Force on Practice Guidelines Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery; American Society for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *J Am Coll Cardiol*. 2004;44:e213–e310.
 16. Ouellette ML, Beller GA, Löffler AI, Workman VK, Bourque JM. Appropriate referrals of angiography despite high prevalence of normal coronary arteries or nonobstructive CAD. *J Am Coll Cardiol*. 2017;69:2673–2675.
 17. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, Camici PG, Cerqueira MD, Chow BJ, Di Carli MF, Dorbala S, Gewirtz H, Gropler RJ, Kaufmann PA, Knaepen P, Knuuti J, Merhige ME, Rentrop KP, Ruddy TD, Schelbert HR, Schindler TH, Schwaiger M, Sdringola S, Vitarello J, Williams KA Sr, Gordon D, Dilsizian V, Narula J. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol*. 2013;62:1639–1653.
 18. Reis SE, Holubkov R, Lee JS, Sharaf B, Reichel N, Rogers WJ, Walsh EG, Fuisz AR, Kerensky R, Detre KM, Sopko G, Pepine CJ. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol*. 1999;33:1469–1475.
 19. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133:916–947.
 20. Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging microvascular dysfunction and mechanisms for female-male differences in CAD. *JACC Cardiovasc Imaging*. 2016;9:465–482.
 21. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ, Kirtane AJ, Wann LS, Ward RP. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;59:1995–2027.
 22. Kohli P, Gulati M. Exercise stress testing in women: going back to the basics. *Circulation*. 2010;122:2570–2580.
 23. Marinescu MA, Loffler AI, Ouellette M, Smith L, Kramer CM, Bourque JM. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. *JACC Cardiovasc Imaging*. 2015;8:210–220.
 24. Taqueti VR, Shaw LJ, Cook NR, Murthy VL, Shah NR, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577.
 25. Schulman-Marcus J, Hartaigh BO, Gransar H, Lin F, Valenti V, Cho I, Berman D, Callister T, DeLago A, Hadamitzky M, Hausleiter J, Al-Mallah M, Budoff M, Kaufmann P, Achenbach S, Raff G, Chinnaiyan K, Cademartiri F, Maffei E, Villines T, Kim YJ, Leipsic J, Feuchtner G, Rubinshtein R, Pontone G, Andreini D, Marques H, Shaw L, Min JK. Sex-specific associations between coronary artery plaque extent and risk of major adverse cardiovascular events: the CONFIRM Long-Term Registry. *JACC Cardiovasc Imaging*. 2016;9:364–372.
 26. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, Madsen JK, Jorgensen E, Kelbaek H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–744.
 27. Sedlak TL, Lee M, Izadnegahdar M, Merz CN, Gao M, Humphries KH. Sex differences in clinical outcomes in patients with stable angina and no obstructive coronary artery disease. *Am Heart J*. 2013;166:38–44.
 28. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Cardiovasc Comput Tomogr*. 2010;4:407.e1–407.e33.
 29. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, Huang M, Pencina M, Mark DB, Heitner JF, Fordyce CB, Pellikka PA, Tardif JC, Budoff M, Nahhas G, Chow B, Kosinski AS, Lee KL, Douglas PS; PROMISE Investigators. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135:2320–2332.
 30. Loffler AI, Bourque JM. Coronary microvascular dysfunction, microvascular angina, and management. *Curr Cardiol Rep*. 2016;18:1.
 31. Beller GA. Is there a role for myocardial perfusion imaging in patients with an elevated high-sensitivity troponin? *J Nucl Cardiol*. 2013;20:705–706.
 32. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation*. 2017;135:1075–1092.