

Ischemia and No Obstructive Coronary Artery Disease (INOCA): What Is the Risk?

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An increasing number of stable patients with evidence of ischemia but no obstructive coronary artery disease (CAD) at coronary angiography, now termed INOCA, are seen. Objective myocardial ischemia or limited coronary flow reserve (CFR) consistent with coronary microvascular dysfunction (CMD) are identified in most of these patients. Although these patients were previously thought to be at low risk for major adverse cardiovascular events (MACE) and were provided only reassurance, newer data document that stable INOCA patients are a heterogeneous population with an elevated MACE risk. Primary prevention cardiovascular risk scores for asymptomatic populations may underestimate risk in these patients, while secondary prevention risk scores developed in patients with established cardiovascular disease may overestimate risk. Medical therapies may be underutilized when no obstructive CAD is documented, and patients are commonly discharged from specialty practice. We review the existing knowledge regarding observed and predicted risk using available risk scores in stable INOCA patients to identify knowledge gaps and plan investigation needed to develop evidence-based guidelines for this growing patient population.

INOCA—Prevalence

Patients with chest pain, evidence of ischemia but no obstructive CAD at coronary angiography, now termed ischemia with no obstructive CAD or INOCA,¹ are increasingly recognized. Although there is likely overlap between INOCA

and myocardial infarction (MI) with no obstructive coronary arteries, which appears to be increasingly described, our primary focus is INOCA, the non-MI syndromes. These stable patients typically have symptoms of chest pain suspected to be angina and/or abnormal stress testing, in the setting of no obstructive CAD at coronary angiography.^{1,2} The definition of obstructive CAD varies between different guidelines or studies.^{3–10} In general, “normal”-appearing coronary arteries are defined as 0% luminal stenosis or <20%, and non-obstructive CAD (NOCAD) is defined as luminal stenosis >20% but <50%.^{3,8–10} However, some studies use a threshold of <70% for NOCAD,⁴ while anatomical scores consider a stenosis ≥50% as significant.^{5,6,11} Traditional understanding of obstructive CAD was 70%¹²; however, recent European Society of Cardiology and American College of Cardiology/American Heart Association (ACC/AHA) guidelines shifted to include stenosis of 50% to 70% if there is associated inducible ischemia or fractional flow reserve ≤0.08 when considering the physiological significance of stenosis and revascularization management in patients with stable CAD.^{6,7}

Depending on the study, up to half of patients undergoing coronary angiography have no obstructive CAD,^{13–15} with a relatively higher prevalence in women (65% in women versus 32% in men).¹⁵ Overall estimates in women and men from the Veterans Administration Cardiovascular Assessment Reporting and Tracking System,¹⁶ the National Cardiac Data Registry, and the National Heart, Lung, and Blood Institute-sponsored Women’s Ischemia Syndrome Evaluation (WISE)¹⁰ databases indicate that there are at least 3 to 4 million American women and men with stable INOCA. Incurred healthcare costs are similar to those for obstructive CAD.

Potential explanations for the apparent increasing prevalence of stable INOCA include more sensitive diagnostics, including advanced cardiac imaging and high-sensitive troponins, which likely contribute to earlier detection of ischemic heart disease. Furthermore, improved primary prevention risk factor control (reduced smoking, increased aspirin and statin use) has likely contributed to altered atherosclerosis burden with relatively less large-vessel plaque rupture, potentially leading to less adverse arterial remodeling/obstructive CAD,¹⁷ while increasing rates of obesity¹⁸ and diabetes

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mellitus¹⁹ may contribute to increasing prevalence of CMD or pathology.^{20,21}

The ACC/AHA non-ST-segment-elevation MI guidelines refer to patients with MI and no obstructive CAD as having Cardiac Syndrome X (CSX),²² while the European Society of Cardiology stable CAD guidelines no longer use the term CSX when describing patients with angina and no obstructive CAD¹² because testing now allows the diagnosis of CMD or macrovascular dysfunction¹² in a majority of these patients. Previously, the term CSX was used to refer to patients with no obstructive CAD but did not require proof of ischemia^{23,24} and also included patients with acute coronary syndromes and no obstructive CAD.^{22,23,25} Advanced evaluation can now identify CMD or macrovascular dysfunction by invasive or noninvasive measurements of CFR in a majority of these patients,^{12,26} while coronary atherosclerosis and better characterization of plaques can be assessed by intravascular ultrasound, optical coherence tomography, or computed coronary tomography angiography when not evident or appreciated at invasive coronary angiography.^{27–29} Since CSX also includes clinical entities other than ischemia, such as pericardial pain, inappropriate pain perception, and psychiatric syndromes,³⁰ the term INOCA was established to improve the identification and management of patients with ischemia and no obstructive CAD.¹ In our opinion, the European Society of Cardiology stable CAD guidelines more directly address recent INOCA data and practice implications compared with the ACC/AHA guidelines.

Among both women and men, up to 60% of stable INOCA patients have documented CMD defined as the presence of microvascular endothelial-dependent and/or nonendothelial-dependent dysfunction.^{31–33} Furthermore, while the CMD was shown to be poorly correlated with traditional risk factors, age was found to be an independent predictor of CMD in both women and men.³³ Female sex had a nearly significant association with CMD, with an odds ratio of 1.21 (95% confidence interval, 0.98–1.40) compared with men.³³ The high prevalence of endothelial and/or nonendothelial-dependent CMD^{26,31,33} and their correlation with outcomes²⁶ underscores the role of comprehensive assessment in patients with INOCA. Such functional alterations can be identified at a stage when atherosclerotic lesions are not evident³⁴ and may be useful in designing early effective interventions to prevent the occurrence of subsequent coronary events.

Evidence of an Adverse Prognosis

Evidence from prospective registries indicate that stable INOCA patients are at more elevated risk for future MACE, including death, nonfatal MI, nonfatal stroke, and hospitalization for heart failure or angina than previously thought.

Documented MACE rates in stable INOCA patients are summarized in Table 1.^{4,10,15,26,35–41} Additionally, many of these patients have an adverse quality of life, functional status, and exercise capacity with relatively frequent visits to healthcare providers for persistent or recurring disabling symptoms.⁴² Elevated MACE rates are observed both early after the index coronary angiogram (eg within the first year) and at longer-term follow-up. In a study of 13 695 subjects, women with nonobstructive CAD demonstrated a 3-fold higher MACE rate compared with men and 2.55-fold increase compared with women with normal coronary arteries in the first year.⁴³ Hospitalization for heart failure was the most frequent event, with an observed 10-fold higher rate during longer-term follow-up compared with asymptomatic community-based women.³⁵ Studies that additionally characterized function or anatomy such as myocardial ischemia, CFR, plaque characterization, or calcium scoring further demonstrate relatively higher MACE rates related to the presence or degree of such abnormalities (Table 1), in both sexes. CMD was shown to be highly prevalent in stable INOCA patients and a CFR <2 was a powerful incremental predictor of MACE in both women and men.²⁶ In symptomatic subjects from the CONFIRM (coronary CT angiography evaluation for clinical outcomes international multicenter) study there was a 2.5-fold increase in risk of MI and all-cause mortality related to a higher CT-Leaman plaque score.⁴⁴ Similarly, an increased coronary calcium score was related to greater risk of both 5-year mortality and MACE in symptomatic subjects without significant luminal narrowing.^{37,45} The degree of global cardiac magnetic resonance myocardial perfusion imaging was related to outcome in women with INOCA.³⁹

Longer-term follow-up data from the WISE project confirmed a worse prognosis than previously thought for stable INOCA women where 10-year all-cause death and cardiac death rates were 17% and 11%, respectively, in women with nonobstructive CAD, and 10% and 6%, respectively, in women with normal coronary arteries.⁴⁰ Furthermore, a recent meta-analysis of 48 studies including patients presenting with stable symptoms undergoing either invasive or noninvasive coronary angiography demonstrated odds ratios of 1.57 to 1.7 for MACE defined as cardiac death, nonfatal MI, hospitalization for unstable angina, or revascularization in patients with NOCAD compared with their counterparts with normal coronary arteries. The odds ratio remained high after excluding revascularization as an outcome event.⁴⁶

A number of studies now include comparison of patients with normal coronary arteries, nonobstructive CAD, and obstructive CAD (Figure 1).^{4,41,47} Specifically, in the Veterans Administration—Clinical Assessment, Reporting and Tracking System, patients with nonobstructive CAD in 3 coronary arteries had a similar annual risk for MI and death as patients with single-vessel obstructive CAD.⁴ Risk was related not only

Table 1. Annual* MACE Rates in INOCA Patients

Author, Publication Year	Study Population	Test Performed	End Point	Results—Annual Events Rate* (%)	
No Obstructive CAD—Anatomical Testing				Normal Coronary Arteries	Nonobstructive CAD
Gulati, 2009 ³⁵	Chest pain or noninvasive positive tests for ischemia	Coronary angiography	All-cause death, nonfatal MI, nonfatal stroke, hospitalization for heart failure	1.5	3.1
Ovrehus, 2011 ³⁶	Stable angina	Coronary computed tomography angiography	Death and MI	0	0.6
			Cardiac death, MI, revascularization	0	1
Jespersen, 2012 ¹⁵	Chest pain	Coronary angiography	Cardiovascular mortality, hospitalization for MI, heart failure, or stroke	1.8	2.8
Petretta, 2012 ³⁷	Anginal symptoms and 15%–85% pretest likelihood of CAD	Coronary computed tomography angiography	Cardiac death, nonfatal MI, unstable angina, revascularization	0	3.4
Maddox, 2014 ⁴	Chest pain or noninvasive positive tests for ischemia	Coronary angiography	All-cause death, MI	1.48	2.41
Nielsen, 2017 ⁴¹	Chest pain	Coronary computed tomography angiography	Revascularization MI, and all-cause death	0.4	0.9
Kenkre, 2017 ⁴⁰	Chest pain or noninvasive positive tests for ischemia	Coronary angiography	All-cause death	1	1.7
			Cardiac death	0.6	1.1
No Obstructive CAD—Functional Testing				Normal Test	Abnormal Test
Johnson, 2004 ¹⁰	Chest pain or noninvasive positive tests for ischemia	Magnetic resonance spectroscopy	All-cause death, MI, heart failure, stroke, other vascular events, and hospitalization for unstable angina	4.4	14
Schindler, 2005 ³⁸	Chest pain	Positron emission tomography	Cardiovascular death, acute coronary syndrome, MI, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, ischemic stroke, or peripheral revascularization	0.9	5–7
Doyle, 2010 ³⁹	Chest pain or noninvasive positive tests for ischemia	Cardiac magnetic resonance imaging	All-cause death, nonfatal MI, or hospitalization for worsening anginal symptoms	4	12
Murthy, 2014 ²⁶	Chest pain	Positron emission tomography	Cardiac death, nonfatal MI, late revascularization, and hospitalization for heart failure	2.7	6.7

CAD indicates coronary artery disease; INOCA, ischemia and no obstructive coronary artery disease; MACE, major adverse cardiovascular events; MI, myocardial infarction.

* Annual MACE rate from the reported mean follow-up events rate divided by the mean years of follow-up.

to the degree of luminal stenosis but also to the extent of the angiographic disease, increasing with the number of vessels affected in both nonobstructive and obstructive disease.^{4,47}

Primary Prevention Risk Scores

Current guidelines endorse use of primary prevention risk scores in asymptomatic patients. Related to the asymptomatic populations used to develop primary prevention scores, the Framingham Risk Score (FRS) appears to

underestimate risk in women,⁴⁸ while the Reynolds Risk Score may perform better in selected populations.⁴⁹ Among asymptomatic subjects enrolled in the MESA (Multi-Ethnic Study of Atherosclerosis), the current guideline Atherosclerotic Cardiovascular Disease score and 3 older FRS-based risk scores overestimate MACE by 37% to 154% in men and 8% to 67% in women, while the Reynolds Risk Score underestimated risk in women by almost one quarter.⁵⁰ Whether knowledge of the enrolled MESA subjects' coronary artery calcium score led to activities to reduce risk is not clear.⁵¹ The Atherosclerotic Cardiovascular Disease score accurately predicted risk in the

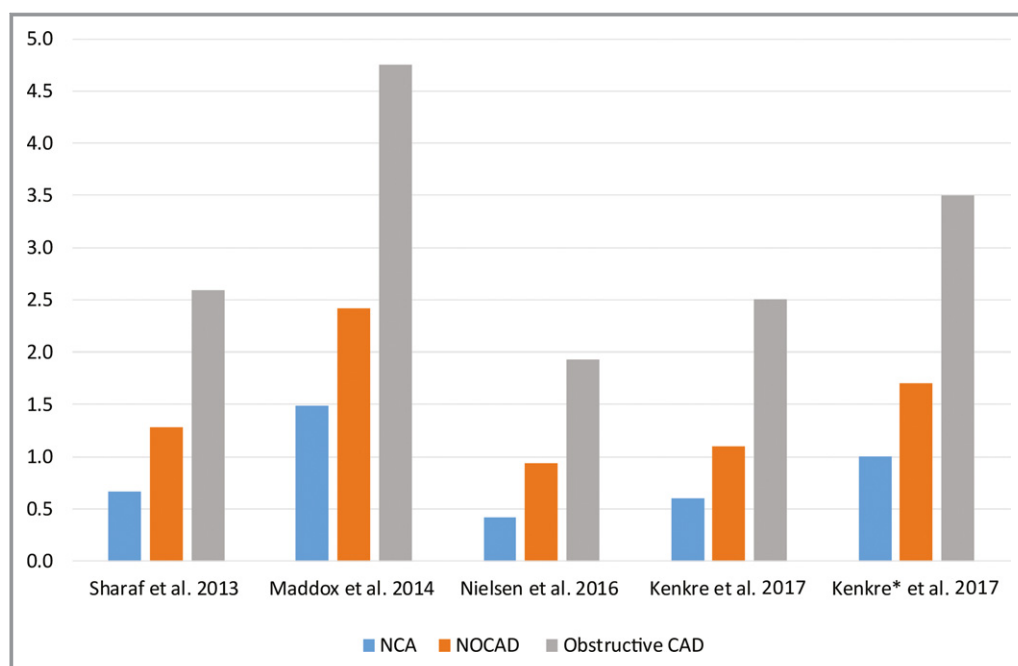


Figure 1. Annual MACE rate stratified by normal coronary arteries, nonobstructive CAD, and obstructive CAD. Annual MACE rates from the reported mean MACE rate divided by the mean years of follow-up. CAD indicates coronary artery disease; MACE, major adverse cardiovascular events; NCA, normal coronary arteries; NOCAD, nonobstructive coronary artery disease. Outcomes include: Sharaf⁴⁷: cardiovascular death or nonfatal MI; Maddox⁴: all-cause mortality or nonfatal MI; Nielsen⁴¹: all-cause death, MI, late coronary revascularization; Kenkre¹⁸: cardiac mortality; Kenkre^{18*}: all-cause death.

Reasons for geographic and racial differences in stroke, a contemporary US dataset that includes representative ethnicity and socioeconomic status.⁵² A recent study in stable INOCA patients undergoing Coronary Reactivity Testing (CRT) demonstrated that a majority were classified as intermediate risk by FRS, which did not accurately predict MACE, while the addition of coronary macro- and microvascular endothelial dysfunction to the FRS correctly reclassified 23%, with a net reclassification index of 0.23.⁵³ Coronary endothelial dysfunction, both micro- and macrovascular, added to the FRS in INOCA improved discrimination and risk stratification, further emphasizing the crucial role of functional assessment.

Obstructive CAD Likelihood Scores

In symptomatic patients, clinical likelihood scores (eg Diamond/Forrester, Morise, and CAD Consortium Pretest Probability score) assess the likelihood of obstructive CAD. Several analyses now indicate that these scores overestimate the likelihood of obstructive CAD in contemporary symptomatic patients undergoing noninvasive computed coronary tomography angiography. Although designed for predicting likelihood of obstructive CAD, the Diamond/Forrester and CAD Consortium Pretest Probability score were also tested for prediction of MACE in the PARTNERS Registry, and demonstrated that the CAD Consortium score had the highest

discriminatory ability (area under the curve 0.687; 95% confidence interval, 0.646–0.728) for MACE.⁵⁴ Similarly, the Morise pretest clinical score that includes 9 variables to estimate the likelihood of obstructive CAD effectively stratified WISE subjects according to the combined end point of cardiac death/MI during a mean follow-up of 3.4 years, with separation between the low-risk group and the others ($P=0.012$).⁵⁵ The intermediate- and high-risk groups were separable for as long as 1.5 years, but thereafter, became less clearly separable.⁵⁵ Other obstructive CAD prediction scores developed in stable or acute chest pain patients have not been tested for MACE prediction.

The newly developed PROMISE (Prospective Multicenter Imaging Study of Chest Pain) minimal risk tool was designed to identify “low-risk” patients in whom deferred noninvasive testing (noninvasive coronary angiography or functional stress testing) may be considered.⁵⁶ Subjects with minimal risk had a low-risk profile (0.5% risk of cardiovascular death and MI at a median 25 months). While this could be of use for risk stratification in INOCA, prior studies suggest that the majority of INOCA patients are classified in the “intermediate-risk” class.³⁶

Among patients with an intermediate pretest risk for obstructive CAD, with a normal ECG and who can exercise, guidelines recommend that exercise ECG stress testing be considered as the first test. In women evaluated for signs and

symptoms of ischemia undergoing clinically ordered coronary angiography in the WISE project, a pretest clinical score and an exercise test score designed for use in women with suspected CAD performed better than the commonly used Duke score in stratifying women with a low prevalence of obstructive CAD.^{41,55}

Nevertheless, treadmill ECG stress testing, stress echocardiography, and single photon emission computed tomography stress all have a limited sensitivity and specificity for detection of ischemia in INOCA patients.⁵⁷ This is not surprising given the lack of a large regional territory of ischemia, as in the obstructive CAD populations used to validate these techniques. Among subjects from the National Cardiovascular Data Registry's Cath Percutaneous Coronary Intervention (CathPCI) undergoing invasive coronary angiography for stable chest pain, while low- or intermediate-risk findings on noninvasive testing were associated with no obstructive CAD, the ability to predict MACE was not tested.⁵⁸ Notably, >50% of MACE occurred in subjects with normal stress testing in the PROMISE,⁵⁹ emphasizing the lower sensitivity and specificity to detect ischemia in less than obstructive CAD. An anatomical computed coronary tomography angiography approach offered better prognostic information once NOCAD was visualized.⁵⁹ Furthermore, mechanisms leading to acute coronary syndromes are not solely depending on degree of luminal stenosis. An ischemic event is the consequence of a complex interaction among plaque characteristics, endothelial dysfunction, coronary blood flow hemodynamics, hemostasis factors, and metabolic, inflammatory, neurohormonal, and environmental factors⁶⁰ that are not addressed by commonly used tests.

Secondary Prevention Risk Scores

The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (Syntax) II is a coronary angiographic-based score used to optimize outcomes relative to revascularization in obstructive CAD.¹² Other secondary prevention scores are relevant in early^{61,62} or longer-term⁶³ risk stratification after a vascular event. Scores using obstructive CAD variables are not applicable to INOCA patients. Recently, the Gensini score, which includes lesser-than-obstructive CAD (epicardial luminal diameter stenosis <50%), was found to be useful for prognosis in men and women referred for invasive coronary angiography with no obstructive CAD.⁶⁴ Previously, in women, a WISE coronary angiographic score that assigned points according to severity of stenosis, adjusted for the presence of collaterals and weighted by lesion location, predicted MACE in stable INOCA patients. Specifically, MACE risk was positively associated with increased coronary atherosclerosis scores in the absence of obstructive CAD.⁴⁷

Additional scores developed for secondary prevention in patients with established cardiovascular disease (CVD) do not include obstructive CAD as a variable, but were developed in populations dominated by obstructive CAD,^{63,65–71} and therefore are of unknown appropriateness for stable INOCA patients.

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)⁶³ score identifies higher-risk subjects on statin therapy, developed again in an obstructive CAD population. A score from the Guangdong Coronary Artery Disease Cohort (GCADC) study⁶⁵ had good predictive value for mortality among secondary prevention patients, and the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) score model predicted CVD mortality but not nonfatal outcomes or combined end points.⁷¹ Again, these studies addressed mostly obstructive CAD patients.

The Second Manifestation of Arterial Disease (SMART),⁶⁹ Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TIMI-TRS2°P),⁷⁰ and A Coronary Disease Trial Investigating Outcome with Nifedipine (ACTION) risk⁶⁶ scores, all showed substantial variability in risk among patients with stable CVD, but more importantly that aggressive guideline treatment in high-risk patients decreased their risk.⁶⁹ Similarly, the PREDICT CVD (New Zealand Primary Care Cohort Study) score developed for patients with previous CVD recognizes patient-specific risks of future events and how they may be reduced through therapeutic and behavioral strategies.⁶⁸

The "Cardiovascular Disease Research Using Linked Bespoke Studies and Electronic Health Records" (CALIBER) score⁶⁷ used real-world commonly available data that contributed to important prognostic information in unselected patients with a wide phenotype of stable ischemic heart disease. The CALIBER models had good calibration and discrimination in internal and external validation with C-index 0.811 (0.735) for all-cause mortality and 0.778 (0.718) for nonfatal MI or coronary death in established stable ischemic heart disease.⁶⁷

Primary and Secondary Prevention Risk Versus Observed INOCA Risk

Comparison of primary, secondary prevention risk versus observed risk in an example of stable INOCA patient is presented in Figure 2.^{40,47,56,63,65–71} The primary prevention scores, developed in asymptomatic populations, predicted that risks vary between 1% and ≈5% and underestimate the observed INOCA risk. The related primary prevention risk guidelines for these low-risk scores would include therapeutic lifestyle change and not statin therapy. Among secondary risk scores, developed in symptomatic but mainly obstructive CAD patients, the predicted risk varied widely, either over- or underestimating the observed INOCA risk.

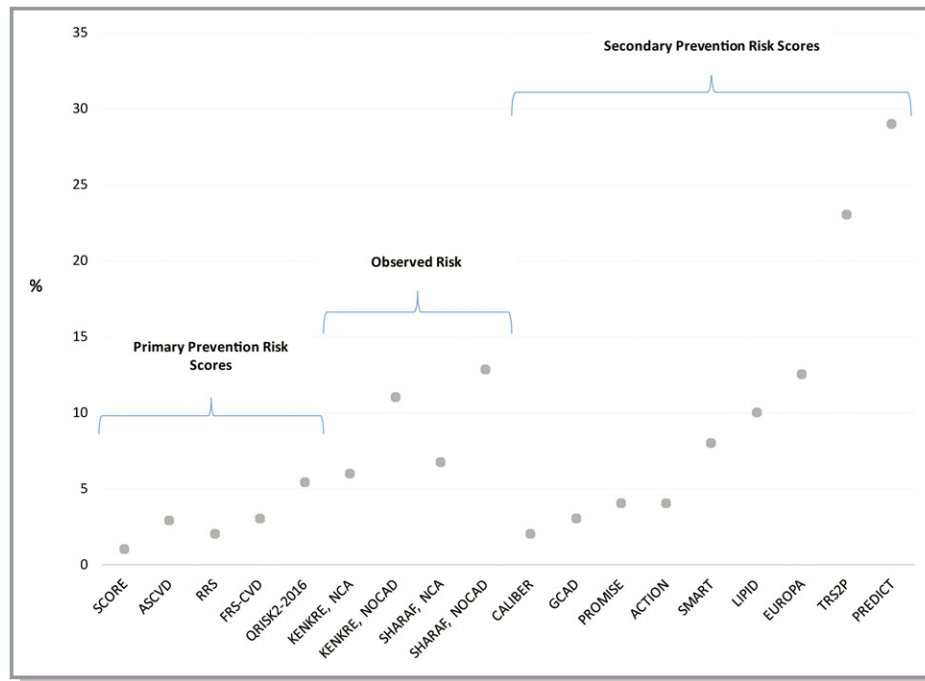


Figure 2. Predicted primary and secondary prevention scores risk vs observed 10-year risk in an example INOCA patient. Model variables used: female, 55 years, hypertension, systolic blood pressure 139 mm Hg on treatment, heart rate 80 bpm, total cholesterol 200 mg/dL (5.17 mmol/L); low-density lipoprotein 80 mg/dL (2.068 mmol/L), high-density lipoprotein 60 mg/dL (1.55 mmol/L), high-sensitivity C-reactive protein (hs-CRP) 2 mg/dL, creatinine 0.9 mg/dL (79 μ mol/L), white blood cell count 10 K^3 /mL, hemoglobin 12 g/dL, no family history, height 5' 67" (170 cm), weight 158 pounds (72 kg), body mass index 24.9, low-risk country, chest pain related to physical/mental stress, glomerular filtration rate 60 mL/min per 1.73 m². Predicted 10-year Risk: Primary Prevention Risk Scores: ASCVD—risk of cardiovascular death, nonfatal MI, nonfatal stroke; SCORE—risk of fatal cardiovascular disease; Reynolds (RRS)—risk of myocardial infarction, ischemic stroke, coronary revascularization and cardiovascular death; QRISK2—risk of MI or Stroke; FRS CVD—risk of CHD or coronary insufficiency death, MI, or angina; Secondary Prevention Risk Scores: CALIBER—myocardial infarction, cardiovascular death; GCAD—cardiovascular death; PROMISE—myocardial infarction, cardiovascular death; ACTION—myocardial infarction, stroke, all-cause death; SMART—myocardial infarction, stroke, vascular death; LIPID—myocardial infarction, cardiovascular death; EUROPA—cardiovascular death; TRS2P—myocardial infarction, stroke, cardiovascular death; PREDICT—myocardial infarction, stroke, cardiovascular death. The 10-year risk was calculated from the reported risk divided by the numbers of follow-up years and then projected to 10 years. Observed 10-year Risk: Sharaf—cardiovascular death or MI (median follow-up of 9.3 years); Kenkre—cardiac mortality (median follow-up 9.5 years). ACTION indicates A Coronary disease Trial Investigating Outcome with Nifedipine; ASCVD, Atherosclerotic Cardiovascular Disease; CAD, coronary artery disease; CALIBER, Cardiovascular disease research using Linked Bespoke studies and Electronic Health Records; EUROPA, European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease; FRS-CVD, Framingham Risk Score Cardiovascular Disease; GCAD, Guangdong Coronary Artery Disease Cohort; INOCA, ischemia and no obstructive coronary artery disease; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; NCA, normal coronary arteries; NOCAD, nonobstructive coronary artery disease; PREDICT, Patients with Renal Impairment and Diabetes undergoing Computed Tomography; PROMISE, Prospective Multicenter Imaging Study of Chest Pain; QRISK2, QRESEARCH cardiovascular disease risk score; RRS, Reynolds Risk Score; SMART, Second Manifestation of Arterial Disease; SCORE, Systematic Coronary Risk Evaluation; TRS2P, Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention.

Table 2. Cardiovascular Treatment Rates in INOCA Patients

Author, Publication Year (n)	Hypertension/ Angina Therapy (%)	Statin Therapy (%)
Maddox, 2010 ⁷² (n=237 167)	51	47
Johnston, 2011 ⁷³ (n=5386)	21–56	51
Shaw, 2011 ⁷⁴ (n=824)	10–20	32
Jespersen, 2012 ¹⁵ (n=5183)	44	50
Sedlak, 2012 ⁷⁵ (n=1864)	34	32
Sharaf, 2013 ⁴⁷ (n=567)	2–39	10*/31 [†]
Chow, 2015 ⁷⁶ (n=10 418)	N/A	33.3
Nielsen, 2017 ⁴¹ (n=14 205)	11.8–32.3	25–39.2
Galway, 2017 ⁷⁷ (n=2642)	18–46	34–59

Hypertension/Angina therapy includes: angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, β -blocker, and calcium channel blocker medication. INOCA indicates ischemia and no obstructive coronary artery disease; N/A, not applicable.

*Normal coronary arteries.

[†]Nonobstructive coronary artery disease.

Cardiovascular Treatment Rates in INOCA Patients

Registry data demonstrate that half or less of stable INOCA patients are treated with cardiovascular medication effective for ischemic heart disease, such as angiotensin-converting enzyme

inhibitor or angiotensin II receptor blocker, β -blocker, calcium channel blocker, or statin therapies (Table 2).^{15,41,47,72–77} Furthermore, the intensity of treatment, specifically for the maximally tolerated angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker and potent statin categories, is unknown in these registries. These findings suggest that the presence of normal coronary arteries or NOCAD at coronary angiography may be associated with diagnostic and therapeutic uncertainty, resulting in patients being less often treated with either primary prevention or secondary prevention guidelines therapy. This practice seems unchanged despite knowledge about adverse outcome in this population. The current ACC/AHA guidelines for patients with stable CAD echoes the ACC/AHA recommendations for patients with unstable angina/non–ST-segment–elevation MI for subgroups of patients with no obstructive CAD, which was defined as CSX.^{22,78} While there have been studies evaluating therapy in patients with CSX,^{79–82} these studies are limited in their characterization of coronary vasomotor function. Indeed, this emerging INOCA patient population remains underdiagnosed and undertreated, likely perseverating this observed therapeutic equipoise. The observed elevated MACE rate endorses this as a knowledge gap. Even mild degrees of atherosclerosis or abnormal coronary vasoreactivity are related to increased health risk.^{4,26,83,84} Furthermore, the majority of MIs result

Table 3. Knowledge Gaps in Stable INOCA

	CVD Primary Prevention Guidelines	Stable CAD Guidelines		Secondary CVD Prevention Guidelines	Knowledge Gaps
Detection	N/A	Likelihood of CAD score	Limited to the presence of obstructive CAD	Limited to established coronary or other atherosclerotic vascular disease	Evidence regarding the utility, benefits, and risks of invasive and noninvasive detection strategies in INOCA patients is needed to develop evidence-based detection guidelines
		Stress testing	Limited to the presence of obstructive CAD		
		CCTA	Limited to anatomical coronary plaque/stenosis and obstructive CAD flow		
		Coronary angiography	Limited to anatomical stenosis and obstructive CAD flow; no evidence-based guidelines for less than obstructive CAD		
Risk assessment	Limited to asymptomatic patients	Limited to stable known or suspected obstructive CAD		Risks scores limited to prior MI and established CAD	Risk scores developed in INOCA populations to develop evidence-based risk assessment guidelines are needed
Treatment	Limited to asymptomatic patients	Echoes treatment recommendations for specific subgroups of patients from UA/NSTEMI guidelines. Emphasis on the lack of dedicated treatment trials for INOCA		Limited to established coronary or other atherosclerotic vascular disease	MACE trials to inform evidence-based guidelines for treatment strategies are needed

CAD indicates coronary artery disease; CCTA, computed coronary tomography angiography; CVD, cardiovascular disease; INOCA, ischemia and no obstructive coronary artery disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not applicable; NSTEMI, non–ST-segment–elevation myocardial infarction; UA, unstable angina.

from rupture of nonobstructive plaque, highlighting the importance of optimizing therapy in these patients.^{85,86} To date, limited data exist about the effectiveness of therapy in stable patients with no CAD and high prevalence of CMD. Nevertheless, prior work in obstructive CAD has demonstrated that atherosclerotic progression can be slowed and MACE reduced with optimal medical therapy,⁶⁹ while surrogate outcome trials in CMD patients indicate improvement in endothelial function, CFR, and angina with optimal medical therapy, as well.⁸⁷ Patients with INOCA deserve to receive optimal treatment as per current guidelines while awaiting future dedicated trials.

Implications and Conclusions

An increasing number of stable INOCA patients and observed elevated MACE rate calls attention to several important knowledge gaps (Table 3). Existing primary and secondary prevention risk assessment tools do not appear to predict MACE risk in INOCA patients; investigation is needed to specifically address tools to accurately assess risk in these patients. Furthermore, there appears to be diagnostic and therapeutic uncertainty in INOCA patients with potentially inappropriately low rates of cardiovascular therapy given the documented atherosclerotic and ischemia burden. Evidence-based primary or secondary treatment guidelines do not specifically address this population, which is indicative of the absence of cardiovascular outcome trials in INOCA subjects. This important knowledge gap must be addressed to get ahead of this emerging issue. Clinical trials designed to test the impact of optimal medical therapy in INOCA patients are needed.

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Disclosures

None.

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