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Even “WISE-R?”—an Update on the NHLBI-Sponsored Women’s Ischemia Syndrome Evaluation

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Abstract

Purpose of Review—For over 20 years, the Women’s Ischemia Syndrome Evaluation (WISE), a program sponsored by the National Heart, Lung, and Blood Institute, has explored diverse and important aspects of ischemic heart disease in women.

Recent Findings—*Women* with symptoms and signs of ischemia but no significant epicardial obstructive coronary artery disease (INOCA) were documented to be at elevated risk for recurrent angina hospitalization, major adverse cardiac events, death, and health resource consumption rivaling those with obstructive coronary disease.

Summary—WISE investigators have advanced our understanding of cardiovascular outcomes, systemic manifestations, psychological variables, socioeconomic factors, genetic contributions, hormonal status, advanced imaging, coronary functional findings, biomarkers, patient-reported outcomes, and treatments pertaining to women with this disease entity. This review delves into the

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WISE findings subsequent to a prior review¹, postulates directions for future research, and asks are we “Even ‘WISE-R?’”

Keywords

WISE; NHLBI; Non-obstructive coronary artery disease; Coronary microvascular dysfunction; Ischemic heart disease

Introduction

In 1996, the National Heart, Lung, and Blood Institute initiated the Women’s Ischemia Syndrome Evaluation (WISE), which has revolutionized our knowledge of the pathophysiological processes underlying heart disease in women and related outcomes. As described in our 2006 review [1•], the WISE collaboration explored anginal symptoms, diagnostic modalities for coronary micro- and macrovascular disease, and psychosocial and reproductive variable contributions to ischemic heart disease (IHD) in women. Ongoing WISE studies have targeted the development of innovative diagnostic and therapeutic options for IHD, both for women *and* increasingly men. But just how has all of this information made us “WISE-R?”

Evolution of WISE Cohorts

WISE research includes multiple cohorts over time (Fig. 1). The original WISE cohort, enrolled from 1997 to 2001 at four US sites, was comprised of women with suspected IHD, undergoing clinically indicated invasive coronary angiography, including women with and without obstructive coronary artery disease (CAD). The subsequent WISE Coronary Vascular Disease (CVD) cohort, enrolled from 2009 to 2012, enrolled exclusively women with suspected ischemia and no obstructive CAD (INOCA), defined as < 50% stenosis. The WISE-CVD cohort had fewer Caucasian women, higher levels of education, and a lower prevalence of cardiac risk factors than WISE, both cohorts showed similar patterns of disordered coronary reactivity, including a high prevalence of coronary microvascular dysfunction (CMD) [2]. Both cohorts had a high prevalence of non-obstructive CAD: however, CMD did not appear to be simply attributable to traditional atherosclerosis risk factors.

Currently, WISE is enrolling women and men in 2 new cohorts: WISE - Heart Failure with Preserved Ejection Fraction (HFpEF) ([NCT02582021](#)) enrolling women and men with INOCA undergoing clinically indicated invasive functional coronary angiography (FCA), and women and men with HFpEF, and WISE - Pre-HFpEF ([NCT03876223](#)), enrolling women and men specifically undergoing clinically indicated invasive FCA, to evaluate mechanistic links between CMD and HFpEF.

INOCA Cardiovascular Outcomes

WISE studies reveal the adverse results of the underrecognized INOCA, previously labeled as benign. WISE women with 0–49% stenosis have an increased 5-year cardiovascular event rate compared with asymptomatic women in the community and adjusted for CAD risk

factors [2]. In a recent analysis of 9-year mortality in the WISE cohort, 33% of the deaths occurred in women without obstructive CAD, reflecting a 13% mortality rate [3], further emphasizing the significant impact of INOCA. WISE investigations determined that CMD predicted major adverse cardiac events (MACE) including death, myocardial infarction, stroke, and heart failure hospitalization in these women [4]. Additionally, we documented that the majority of HF hospitalizations at extended follow-up were characterized by HFpEF and not associated with obstructive CAD [5].

These WISE INOCA outcomes studies underscore the critical need for further research into underlying pathophysiology, prognostic factors, diagnosis, and management strategies for INOCA and CMD.

INOCA Systemic Manifestations

Metabolic Syndrome

Recent WISE studies emphasize the association of IHD with systemic conditions. While the metabolic syndrome (MetS) is linked with CVD, WISE investigators have also observed relations with coronary atherosclerosis and arterial remodeling defined by intravascular ultrasound (IVUS) [6]. Further, this association does not depend on the full MetS cluster, but rather appears to be specifically driven by the individual factors of waist circumference and systemic blood pressure (BP). These findings support the hypothesis that dysmetabolic states and their associated inflammation may contribute to both INOCA and systemic disorders.

Renal Insufficiency

IHD has known associations with renal function, which WISE has further characterized. In WISE, the presence of mild chronic kidney disease (CKD) is an independent predictor of all-cause and cardiac mortality, regardless of CAD severity [7]. Renal insufficiency was also determined to be significantly associated with reduced coronary flow reserve (CFR) [8], lending insight into one of the possible pathogeneses for CMD.

Migraine Headache

While initial WISE analyses did not link migraine with CVD [9], subsequent longer-term follow-up showed an increased adjusted risk with MACE [10]. This higher risk was primarily driven by an associated two-fold increase in stroke risk. These findings suggest CKD, migraine, and possibly stroke may represent a broader spectrum of systemic microvascular functional disorders. CMD and these systemic diseases may also share common risk factors, which could warrant further investigation that could provide clues to better management and prevention.

Psychological Status

Higher State-Trait Anxiety Inventory scores correlate with more frequent angina and dyspnea in the WISE [11]. Depression and anxiety were also associated with elevated CVD costs [11, 12]. WISE investigators have proposed that somatic and not cognitive/affective symptoms of depression portended a worse CVD prognosis [13]. Further, negative

affectivity was uniquely associated with higher body mass index (BMI) values and hostility with increased frequency of MetS [14], although neither correlated with MACE. Finally, the predictive value of depression for MACE improves when the severity of comorbid anxiety is also accounted for [12], supporting the analysis of depression and anxiety together, instead of individually.

In addition to suggesting novel ways to study the links between psychological status and CVD, WISE investigators recently sought to elucidate the mechanisms underlying these associations. Among women with suspected IHD, those with comorbid depression had 70% higher circulating serum levels of C-reactive protein (hs-CRP) and 25% higher levels of IL-6 [15]. These findings suggest that inflammation may be at least partly contributory. Another possible mediating factor is the interval development of MetS. Among women diagnosed with depression, those with comorbid MetS were at 2.6 times higher risk of CVD [16]. Vascular processes may also be responsible. Mental stress peripheral vasoreactivity was elevated in patients with CMD, suggesting a mechanism and potential treatment target for stress-induced chest pain in CMD [17].

Treatment with antidepressants, alone and in combination with anxiolytics, correlates with higher risk of CVD events and all-cause mortality in WISE women compared with untreated women in the general population [18]. While treatment of anxiety disorders correlated with less obstructive CAD, anxiolytic use was associated with more frequent chest pain, nitroglycerin use, and hospitalizations for coronary catheterization [11]. Conversely, WISE women receiving lipidlowering therapy had higher aggressive responding subscores on the Cook-Medley Hostility Scale, indicating a higher inclination towards hostility in social situations [16].

Socioeconomic Status

Sex-Based Differences

In 2006, WISE investigators proposed key working hypotheses related to sex-specific IHD for women, which have arguably set the stage for much of the investigation conducted over the past decade. Because the original WISE design ([NCT00000554](#)) exclusively studied women, WISE investigation has encouraged other researchers to also investigate women, to provide a framework exploring sex-specific IHD development. WISE investigators [19] have stressed the importance of specific study of women rather than comparison to men, in order to uncover sex-specific mechanisms and ultimately treatment strategies.

Economic Impact

Income is a significant predictor of cardiovascular death and costs, including risk-adjusted models controlling for obstructive IHD, chest pain, and cardiac risk factors [20]. WISE women with an annual income below \$20,000 had the highest 5-year hospitalization and drug treatment costs. They were also more likely than higher-income women to require 2 or more anti-ischemia medications in the follow-up. When compared with women with obstructive CAD, INOCA women had more repeat catheterizations or angina

hospitalizations, higher drug treatment costs, and the greatest proportion of anti-ischemic therapy costs [21].

The Role of Social Relationships and Ethnicity

When compared with women with higher Social Network Inventory scores, more isolated women experienced strokes at more than twice the rate, even following covariate adjustment [22], demonstrating a possible protective effect of social relationships. In terms of ethnicity, black women more often presented with symptoms they attributed to stomach-based pain compared to white women, irrespective of their CAD severity [23]. This was associated with higher all-cause and cardiovascular mortality among black women, suggesting that this atypical presentation may result in impairment of diagnosis and care delivery, potentially facilitating worse outcomes.

Genetic Factors

In 2008, WISE women positive for two beta-adrenergic receptor polymorphisms, ADRB1 Gly389 and ADRB3 Arg64, were found to be at increased risk for adverse cardiac events [24]. Interestingly, this risk elevation was limited to women with suspected INOCA versus those with obstructive CAD. The homozygous short variant of the 5-HTTLPR serotonin transporter gene polymorphism was also associated with increased MACE among INOCA women [25], while one genetic marker, single nucleotide polymorphism (SNP) rs2301753 on chromosome 6 in RNF39, achieved chip-wide significance for non-obstructive CAD [26].

WISE also examined the role of SNPs in genes encoding antibodies against oxidized LDL cholesterol, known to contribute to atherosclerosis [27]. SNPs in two of these genes resulted in augmented levels of IgG and IgM oxidized LDL antibodies, which led to less severe IHD, while multiple pairs of epistatic quantitative trait loci were associated with body weight, BMI, and waist and hip circumferences and ratios, using statistical modeling [28].

Hormonal Status

Endogenous Estrogen

WISE women with early onset vasomotor symptoms have higher CVD mortality and lower flow-mediated dilation than those with later onset symptoms [29]. Hypothalamic hypoenestrogenism (HHE) results from inadequate ovarian stimulation by the hypothalamus in premenopausal women, resulting in low estrogen levels. HHE, specifically due to psychosocial stress, was prevalent among premenopausal WISE, which was the most powerful predictor of obstructive CAD [30]. Further, WISE women with both diabetes mellitus and HHE had higher prevalence and obstructive CAD severity [31] than those having diabetes alone. These findings further endorse that estrogen deficiency may precipitate atherosclerosis and endothelial dysfunction. However, investigators also found that estrogen exposure time has no association with angiographic CAD or other adverse outcomes [32].

Exogenous Estrogen

HT initiation before 55 years of age was associated with less obstructive CAD among WISE women with natural menopause [33]. Prior oral contraceptive (OC) use among postmenopausal women, correlated with decreased angiographic CAD severity score [34]. Also, low-dose estrogen therapy in a WISE ancillary randomized placebo-controlled trial resulted in improved chest pain, menopause symptoms, and quality of life but did not improve ischemia or endothelial dysfunction [35].

Other Hormones

Lower circulating levels of dehydroepiandrosterone sulfate (DHEA-S), associated with aging, were linked with increased cardiovascular and all-cause mortality in WISE women [36]. Phytoestrogens or dietary soy isoflavones investigation found that blood daidzein level was associated with lower triglyceride and higher high-density cholesterol (HDL-C) level, resulting in a beneficial total cholesterol/HDL-C ratio [37]. Alternatively, blood genistein levels were inversely associated with CFR, resulting in lower flow reserve with higher phytoestrogen level [38].

Menopause and Hypertension

Among premenopausal and postmenopausal women, systolic BP (SBP) and pulse pressure (PP) were found to be stronger CVD risk factors related to angiographic CAD, among premenopausal women when compared to postmenopausal women [39].

Advanced Cardiac Imaging

Cardiac Magnetic Resonance Imaging

The novel applications and limitations of imaging modalities are additional themes within recent WISE literature (Fig. 2) [40]. Due to its high spatial resolution, diagnostic accuracy, and lack of ionizing radiation, cardiac magnetic resonance imaging (CMRI) has become a powerful imaging technique for evaluating suspected IHD and other structural abnormalities among women [41].

WISE women with reduced CFR were found to have reduced time to peak filling rate (tPFR), a marker of diastolic dysfunction, on CMRI [41]. In addition, diminished coronary blood flow (CBF) change, a measure of endothelial-dependent CMD, was associated with elevated left ventricular end-diastolic pressure (LVEDP) and increased mass on CMRI. CMRI was also used to identify a previously unsuspected link between aortic flow conditions and left ventricular ejection fraction (LVEF), which may shed further light on a linkage between CMD and LV diastolic dysfunction [42].

CMRI is multifaceted with the area of myocardial perfusion imaging (MPI) evolving. Among women with INOCA, global first-pass perfusion CMRI-determined measurements of normalized uptake slope and peak signal uptake, in conjunction with LVEF, were found to predict MACE [43]. However, when tested with the non-pharmacological cold pressor method for endothelial stress, MPI reserve index (MPRI) could not identify CMD among symptomatic women, potentially due to inadequate provocative stress [44]. Further, late

gadolinium enhancement (LGE) has emerged as a signal of myocardial damage and scar, now described in the setting of CMD [45]. WISE investigators developed and tested the Decisions Informed by Combining Entities (DICE) algorithm. Integrating CMRI and gated single-photon emission computed tomography (SPECT), DICE improves MPI interpretation, diagnostic, and prognostic outcomes [46]. The research benefit of evaluating CMRI and SPECT together was demonstrated by a study finding that internal energy utilization of the LV, determined independently by both modalities, has greater prognostic value than EF or the presence of a myocardial perfusion defect [47].

Positron Emission Tomography

Positron emission tomography, or PET, has emerged as another technology that can non-invasively detect and monitor CMD and its complications, in addition to subclinical and early stage atherosclerosis.

Due to its high spatial resolution, PET can accurately quantify myocardial blood flow in absolute terms and detect subtle differences in regional perfusion, critical to understanding certain cardiac disease pathologies, even in the earliest functional stages of disease before structural alterations manifest [48]. In a 2003 study [49], WISE investigators discovered that CFR was heterogeneously distributed throughout the vascular territories, suggesting that only one CFR measurement during catheterization may not accurately reflect all three vessels.

Since then, PET has become a widespread stress myocardial perfusion testing modality, which offers additional notable advantages when compared with SPECT [40]. In addition to its improved spatial and temporal resolution and optimal safety profile, PET demonstrates similar prognostic and higher diagnostic accuracy. The extent and severity of PET stress abnormalities have a directly proportional relationship with MACE. PET can also estimate both epicardial and subepicardial perfusion. The concordant use of CT with PET further allows for the correction of breast tissue attenuation, a noted limitation of SPECT among women.

The role of PET in the research of CMD treatment and associated disease pathologies has also become increasingly well-recognized. The serial measurement of MBF in response to cold exposure or pharmacologic vasodilation renders PET a useful tool for evaluating the effects of lifestyle modification and therapeutic interventions on the coronary circulation [50]. More recently, the ability for PET to concordantly measure regional myocardial blood flow patterns, myocardial oxygen, and glucose metabolism has allowed for analysis of the relationships between CMD and the development of infiltrative, hypertrophic, and other non-ischemic cardiomyopathies [48].

While PET can accurately identify changes in the coronary circulation, how these findings may affect clinical outcomes warrants further larger-scale prospective investigation.

Invasive Imaging Strategies

WISE investigation used IVUS to assess the coronary wall anatomy in a cohort of women with CMD, demonstrating preserved lumen size and evidence of positive remodeling in the

setting of coronary atherosclerosis [51]. In a selected case, IVUS combined with OCT successfully identified plaque rupture as the etiology for ST elevation myocardial infarction in a woman with apical wall motion abnormality [52]. Among women with suspected INOCA, corrected TIMI frame count, an invasive angiographically derived coronary flow imaging measure, independently predicted future angina hospitalizations [53]. In a 2013 prospective study, WISE researchers developed a modified Gensini angiographic score for women, based on the presence, location, and severity of vessel stenosis and collaterals, which effectively predicted long-term MACE [54].

Invasive Functional Coronary Angiography

Functional coronary angiography (FCA) has served as a fundamental tool throughout WISE history, specifically for detecting CMD within the INOCA population [55]. Recently, WISE researchers have expanded upon the array of FCA applications, highlighting the procedure's implications for INOCA assessment and treatment and reaffirming its diagnostic and predictive efficacy, with a published safety record [56].

WISE elaborated on the relationship between CBF change and diastolic parameters, including tPFR, end-systolic volume, and LVEF [57]. Among women with INOCA and CVD risk factors, CMD diagnosed with intra-coronary adenosine CFR improved MACE prediction, in comparison with angiographic CAD severity and CVD risk factors [58]. In a 2015 study, the WISE team utilized FCA to characterize relationships between CFR and arterial properties [59]. CFR was inversely related to aortic systolic pressure and aortic pulse wave velocity (aPWV), an index of arterial stiffness. These findings revealed a novel mechanism by which changes in arterial properties increase afterload, requiring the LV to generate additional "wasted energy" that increases myocardial oxygen demand.

The presence of brachial artery constriction, measured by non-invasive ultrasound after release of occlusion, predicted almost double the risk for MACE, after adjusting for obstructive CAD and traditional risk factors [57]. Application tonometry recording of radial artery blood pressure waveforms, among WISE women with INOCA, identified modifications in systolic wave characteristics and diastolic timing, supporting the aforementioned relationship between CFR, afterload, myocardial efficiency, and ischemia [60]. Brachial PP is a stronger predictor of MACE and CVD mortality than SBP, diastolic BP (DBP), and mean arterial pressure (MAP), with an 18% excess mortality risk for every 10 mmHg increase in PP [61].

Recent WISE findings advised the 2019 European Society FCA Guidelines [62]. Namely, in patients with persistent symptoms but angiographically normal coronary arteries or non-obstructive CAD and preserved fractional flow reserve, guidewire-based CFR and/or microcirculatory resistance measurements should be considered. Further, if coronary arteries are not significantly stenosed on angiography, intra-coronary acetylcholine with electrocardiographic monitoring can be considered. Finally, transthoracic Doppler of the left anterior descending artery, CMRI, and positron emission tomography can be considered for non-invasive CFR measurement.

Serum Biomarkers

While imaging and the various aforementioned testing modalities have a central role in CVD diagnosis and prognostication, laboratory evaluation was not as well defined.

Inflammatory Markers

As inflammation is proven to contribute to CVD, the team recently evaluated the relationships between systemic inflammatory markers and CVD outcomes. While both elevated IL-6 and serum amyloid A (SAA) protein were associated with increased all-cause mortality, only elevated IL-6 correlated with increased hospitalization [63]. A combined multi-marker testing approach, including hs-CRP, IL-6, SAA, and hemoglobin, gave predictive information beyond that provided by the Framingham Risk Score [64]. The presence of 3 or more abnormal serum biomarkers was associated with substantially increased mortality.

WISE also examined how serologic evaluation may suggest CMD. Circulating bone marrow progenitor cells (CPCs), increased in IHD, are generated by the reparative response. Decreased CFR was significantly associated with elevated CD34+ CPC levels [65]. Further studies are required to characterize the role of CPCs in obstructive versus non-obstructive disease and CVD prognostication.

Cardiac Risk Markers

Contemporary studies have also elaborated on knowledge regarding other serologic cardiac risk markers. The triglyceride/HDL-C ratio was affirmed as a strong independent predictor of all-cause mortality and MACE [66]. Interestingly, despite the strong association between CMD and the development of HFpEF, BNP did not show predictive value in women with the disease [67].

Patient-Reported Measures

Remotely collected and self-reported patient data, whether acquired by survey or wearable device technology, are increasingly popular. WISE recently investigated the prognostic and diagnostic value of such data, for higher-risk individuals.

Duke Activity Status Index

Estimated functional capacity (EFC) has been shown to relate to several major CVD outcomes. Lower EFC, based on the Duke Activity Status Index (DASI), was associated with increased long-term mortality [68] and the development of HF [69] among WISE women. Functional impairment was also predictive of MACE and indeterminate exercise stress testing [70]. Furthermore, CFR correlated directly with the DASI score [71]. This finding supports the functional importance of DASI to risk stratify women undergoing ischemic evaluation.

Aside from using DASI for EFC, self-reported data also helps characterize the joint impact of smoking history and exercise capacity upon CVD outcomes. WISE women reporting both tobacco use history and low exercise capacity had the highest MACE risk [72]. Further, all

smokers had significantly greater risk, regardless of exercise capacity, even after controlling for preexisting CAD severity and other established risk factors. This study demonstrates the combined beneficial cardiovascular effects of maintaining a high exercise capacity and avoiding tobacco use, in addition to the value of information reported via validated questionnaires.

Wearable Technology

WISE assessed the capacity of Fitbit technology to determine treatment response of women with CMD to ranolazine, a late sodium channel current inhibitor. In a randomized, double-blinded crossover trial, investigators examined the difference in daily step counts after 2 weeks of therapy with ranolazine versus placebo [73]. Overall, ranolazine correlated with reduced step count. However, those patients who reported improved angina had higher step counts, objectively confirming that improved daily life activity was associated with better angina control. The predictive utility of wearable digital monitoring technology continues to be evaluated, with current exploration focusing on its association with prognostically valuable serum biomarkers, including hs-CRP, N-terminal pro-brain natriuretic peptide (NT-proBNP), and ultra-high sensitivity cardiac-specific troponin (u-hs-cTnI).

CMD Treatment

Driven by developments in understanding about mechanistic pathways, the WISE team continues to evaluate CMD treatment alternatives, including multiple pharmacologic probes involving the WISE-CMD cohort (Fig. 3). Interestingly, all of the recently studied medication classes appear to be of greatest therapeutic benefit among women with significantly decreased CFR (Table 1) [74].

Renin-Angiotensin-Aldosterone System Agents

Agents that block products of the Renin-Angiotensin-Aldosterone System (RAAS) have been a significant contemporary focus. High-dose angiotensin-converting enzyme inhibitor (ACEI) quinapril correlated with improved CFR and reduced angina, over a 16-week treatment period, among women with CMD [75]. Another theory postulated that aldosterone blockade may provide a synergistic effect with ACEI upon endothelial function. However, WISE found no significant improvement when eplerenone was added to quinapril [76].

Phosphodiesterase-5 Inhibition

Phosphodiesterase-5 (PDE-5) inhibitors block degradation of cyclic GMP in vascular smooth muscle cells, thus promoting vasodilation, historically for pulmonary hypertension and erectile dysfunction. Recently, WISE investigators found that sildenafil may also acutely improve CFR among women with CMD [77].

Ranolazine

A randomized, double-blinded crossover trial of ranolazine versus placebo found that while patients with CFR under 2.5 had improved MPRI and anginal symptoms, ranolazine was not effective for milder CMD [78]. However, in a pre-specified follow-up analysis evaluating WISE women with low CFR, ranolazine improved angina and myocardial perfusion. Within

this subgroup, reduced LV end-diastolic volume predicted improvement in anginal symptoms [79]. This finding supports the hypothesis that late sodium channel current blockade may be beneficial among women with more severe CMD.

Statins

Aside from the WISE probes, outside investigators have demonstrated the emerging role of statins in ameliorating CMD. The beneficial effects of statin therapy on exercise-induced ischemia and flow-mediated dilation in CMD were first shown in 2003 [80]. More recent studies have sought to elucidate the mechanisms underlying these effects. While some suggested that statins inhibit dextrose-induced superoxide anion formation [81], others reported that they downregulate arginase activity, facilitating enhanced synthesis of vasoprotective nitric oxide [82].

Intensive Medical Therapy

Given the abundance of adverse outcomes and resource consumption associated with INOCA, WISE has initiated a study to evaluate the role of intensive medical therapy (IMT). Since women represent the fastest-growing minority population of the US military, the “Women’s Ischemia Trial to Reduce Events in Non-Obstructive CAD” (WARRIOR) trial was funded by the Department of Defense. Currently enrolling subjects, WARRIOR ([NCT03417388](#)) is a multicenter, prospective, randomized blinded outcome evaluating the influence of IMT with aspirin, a high potency statin and ACEI/ARB therapy compared with usual care on MACE in symptomatic women with INOCA, over a 3-year follow-up period. The results should facilitate clinical management guidelines for women with INOCA.

Conclusions

Based upon this review of the multifaceted endeavors of the WISE collaboration for over 2 decades, we are certainly “WISE-R”, in many ways. The knowledge shared and awareness raised by these efforts have stimulated global recognition, bringing INOCA to the forefront. Based on these results, the ESC [83] and American College of Cardiology [55] have issued position papers, outlining proposed diagnostic and treatment algorithms, as well as directions for future research. The American Heart Association has even developed a “traffic light” sequence, supporting a definitive diagnostic approach for INOCA [55].

While our understanding of INOCA has significantly advanced, many knowledge gaps and questions still remain (Fig. 4) [74]. For example, why do some individuals with certain risk factors develop INOCA, while others do not? Are there undiscovered imaging modalities that can identify INOCA earlier? Is INOCA the precursor of angiographic stenoses, or is it a separate mechanism? What processes are responsible for INOCA evolving into myocardial infarction (MINOCA) and HFpEF? According to WISE authors, further translational investigation will be necessary, specifically focused on developing a phenotypic classification for INOCA patients, generating diagnostic algorithms based upon this classification system and formulating universal guidelines [74].

Thanks to a collaborative group of investigators and inspiring research volunteer participants, we look forward to the opportunity to continue cultivating our “WISE-dom” to improve health for women and men, just on the horizon.

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Fig. 1.

The development of various WISE cohort subgroups over time, overlying the trend in cardiovascular death rate among women; NHLBI = National Heart, Lung and Blood Institute; WTH = “Women Take Heart”, UPgh = University of Pittsburgh, Pgh = Pittsburgh, CS = Cedars-Sinai Medical Center, UF = University of Florida, RAAS = renin angiotensin aldosterone system, PDE-5 = phosphodiesterase-5, CMR = cardiac magnetic resonance imaging; CANS = Cardiac Autonomic Nervous System Study (1K23HL105787-01A1); WARRIOR = Women’s Ischemia Trial to Reduce Events In Non-Obstructive Coronary Artery Disease ([NCT03417388](https://clinicaltrials.gov/ct2/show/study/NCT03417388))

Fig. 2.

A model describing the use of CT (computed tomography), cMRI (cardiac magnetic resonance imaging), and nuclear imaging modalities to characterize pathology and stratify risk among women with ischemic heart disease. Reprinted with permission from Ref 42.

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WISE CMD Randomized Pharmacologic PROBE Trials

Trial (n)	Intervention	Results
QWISE ¹ (n=20)	Quinapril	↑CFR; ↓Angina
FemHRT-WISE ² (n=35)	Ethinyl estradiol and norethindrone acetate	→MRS ; ↓Angina
EWIS ³ (n=41)	Eplerenone	→CFR; →Angina
SWIS ⁴ (n=23)	Sildenafil	→CFR; →Angina
RWIS PILOT ⁵ (n=20)	Ranolazine	↗MPRI; ↓Angina
RWIS ⁶ (n=128)	Ranolazine	→MPRI; →Angina

CFR= coronary flow reserve, MRS= magnetic resonance spectroscopy; MPRI= myocardial perfusion reserve index, WISE= Women's Ischemia Syndrome Evaluation. 1. Pauley AHJ 2011; 2. Bairey Merz AHJ 2010; 3. Bavry AHJ 2014; 4. Denardo Clin Card 2011; 5. Mehta JACC Imaging; 6. Bairey Merz EHJ 2015

Fig. 3.

A summary of the pharmacologic probes and the influence of various agents upon vascular behavior and imaging characteristics

Fig. 4.

The state of our current understanding and proposed future directions for INOCA research. MACE = major adverse cardiac events, HF = heart failure, CMD = coronary microvascular disease, IHD = ischemic heart disease, ACS = acute coronary syndrome, HFpEF = heart failure with preserved ejection fraction, CAD = coronary artery disease, PET = positron emission tomography, MRI = magnetic resonance imaging, ACEi = angiotensin-converting

enzyme inhibitor, ASA = aspirin, Rx = treatment. Reprinted with permission from Ref 74.
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Table 1**Coronary microvascular dysfunction (CMD) treatment options**

Abnormal coronary vasoconstriction or endothelial inflammation
Angiotensin-converting enzyme inhibitors (ACE-I)
HMG-CoA reductase inhibitors (statins)
L-Arginine supplementation
Aerobic exercise
Enhanced external counterpulsation (EECP)
Abnormal coronary vasodilation
Beta-blockers/alpha-beta-blockers
Nitrates
Anti-anginal
Ranolazine
Ivabradine
Xanthine derivatives
Abnormal smooth muscle function (Prinzmetal's angina)
Calcium channel blockers
Nitrates
Abnormal cardiac nociception
Low-dose tricyclic medication
Spinal cord stimulation
Cognitive behavioral therapy