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Review

Beyond Coronary Stenosis: A Mechanism-Based Approach to Ischemic Heart Disease in Women

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Abstract

Despite major advances in cardiovascular medicine, ischemic heart disease (IHD) in women remains underrecognized and undertreated. A substantial proportion of symptomatic women have no flow-limiting epicardial stenosis, and ischemia may arise from coronary microvascular dysfunction, vasospasm, diffuse atherosclerosis, plaque-related mechanisms, spontaneous coronary artery dissection (SCAD), or combinations of these processes. Female-specific biological factors—including hormonal transitions, vascular aging, inflammation, metabolic changes, and reproductive cardiovascular risk enhancers—modify the coronary substrate across the life course. This review integrates these determinants with contemporary coronary phenotyping and proposes a clinically oriented, mechanism-based framework for IHD in women. Multimodality imaging, invasive coronary functional testing, and intracoronary imaging are considered complementary tools for identifying predominant and coexisting mechanisms. Management should combine guideline-directed cardiovascular prevention with mechanism-targeted antianginal therapy and women-specific considerations, including reproductive planning, pregnancy counseling, medication safety, and psychosocial care. This framework is intended as a practical synthesis rather than a validated classification system and aims to support more precise diagnosis and individualized treatment of women with ischemic symptoms.

Keywords: ischemic heart disease; coronary vascular dysfunction; coronary microvascular dysfunction; INOCA; MINOCA; spontaneous coronary artery dissection; multimodality imaging; women's cardiovascular health

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1. Introduction

Cardiovascular disease remains the leading cause of mortality among women worldwide despite substantial advances in cardiovascular prevention and treatment [1]. Nevertheless, important sex-related disparities in diagnosis, treatment, and clinical outcomes persist, reflecting the limitations of diagnostic paradigms historically developed in predominantly male populations with obstructive coronary artery disease [2,3].

Growing evidence demonstrates that myocardial ischemia in women frequently occurs despite the absence of flow-limiting coronary stenoses, indicating that obstructive coronary artery disease alone does not adequately explain the complexity of female ischemic heart disease. Female-specific biological factors shape a unique vascular substrate that interacts with structural and functional coronary abnormalities to determine disease expression and clinical presentation [4–9]. These observations have challenged the traditional stenosis-centered model and support a broader understanding of ischemic heart disease as a heterogeneous condition requiring a mechanism-based approach.

Recent advances in coronary physiology, multimodality imaging, coronary functional testing, and intracoronary imaging have enabled a shift from anatomy-based diagnosis toward mechanism-based characterization of myocardial ischemia, creating new opportunities for more accurate diagnosis and personalized treatment [4,10–12].

This review goes beyond a descriptive summary of sex differences by integrating female life-course biology, coronary functional and structural abnormalities, contemporary diagnostic phenotyping, and mechanism-directed management within a single clinical framework. Its purpose is not to introduce a new disease classification, but to provide a practical synthesis that helps clinicians move from a stenosis-only interpretation toward identification of predominant and coexisting mechanisms of ischemia in women.

2. Epidemiology

IHD remains the leading cause of morbidity and mortality among women worldwide and continues to represent a major public health challenge despite substantial advances in cardiovascular prevention and treatment [1]. Beyond mortality, the disease is associated with persistent symptoms, impaired quality of life, recurrent healthcare utilization, and considerable socioeconomic burden across a woman's lifespan [1,2].

The epidemiology of IHD in women is characterized by an apparent paradox. Compared with men, women generally have a lower prevalence of obstructive coronary artery disease but continue to experience a substantial burden of myocardial ischemia, recurrent angina, acute coronary syndromes, and adverse cardiovascular outcomes [2–4]. This discrepancy indicates that disease burden cannot be explained solely by the presence of obstructive coronary stenoses and highlights the contribution of multiple coronary mechanisms to disease expression and prognosis [4–6].

Age-related differences further distinguish the epidemiology of female IHD. Cardiovascular events generally occur later in women than in men, but younger women with acute myocardial infarction may experience disproportionately adverse outcomes. These differences cannot be attributed solely to delayed diagnosis or treatment. Hormonal status, menopausal transition, vascular aging, baseline cardiometabolic risk, and female-specific risk enhancers interact with health-care disparities and may influence both presentation and prognosis [2,5,8]. With aging and loss of ovarian hormonal exposure, endothelial dysfunction, arterial stiffness, adverse body-fat distribution, insulin resistance, and atherogenic lipid changes become increasingly relevant, while the cumulative impact of hypertension, diabetes, obesity, and inflammatory disorders progressively increases absolute cardiovascular risk [5,8].

Non-obstructive coronary presentations are particularly relevant in women. Across angiographic and chest-pain cohorts, women are substantially more likely than men to have angina or objective ischemia without obstructive epicardial CAD, and contemporary ANOCA/INOCA literature reports non-obstructive disease in approximately one-half or more of women referred for evaluation of suspected ischemic syndromes, depending on referral setting and diagnostic definitions [4,9]. INOCA accounts for approximately 5–10% of acute myocardial infarction presentations and is more frequent in women than

in men [6,13]. In the VIRGO study of young patients with acute myocardial infarction, MINOCA was identified in 14.9% of women compared with 3.5% of men (odds ratio 4.84, 95% CI 3.29–7.13), highlighting the particularly strong female predominance of non-obstructive myocardial infarction in younger patients [14].

CAD is female-predominant, with women comprising more than 90% of many contemporary SCAD cohorts; it is an especially important cause of acute myocardial infarction in younger and middle-aged women [15,16]. These estimates vary according to population, age, and diagnostic strategy, but they illustrate why an obstructive-CAD-only model incompletely captures the burden of IHD in women.

Sex-related disparities also extend throughout the continuum of cardiovascular care. Women remain underrepresented in cardiovascular clinical trials and are less likely to undergo invasive coronary angiography, receive timely revascularization, or participate in cardiac rehabilitation despite presenting with comparable symptoms and cardiovascular risk profiles [2,3]. These inequalities continue to limit the generation of robust sex-specific evidence and may contribute to persistent differences in diagnosis, treatment, and clinical outcomes.

Collectively, these epidemiological observations demonstrate that the burden of IHD in women cannot be adequately interpreted through the prevalence of obstructive coronary artery disease alone. Rather, they underscore the need to understand the biological mechanisms that shape disease expression in women and provide the rationale for the mechanism-based pathophysiological framework discussed in the following section.

3. Biological Basis and Clinical Expression

3.1. Pathophysiology

Female cardiovascular biology changes across the life course through the interaction of sex hormones, reproductive history, vascular aging, metabolism, immune activation, and conventional cardiovascular risk factors. These determinants influence endothelial signaling, vascular smooth-muscle reactivity, coronary microvascular structure, thrombosis, and atherosclerotic plaque biology, thereby modifying both functional and structural mechanisms of myocardial ischemia [5,8,11,12,17].

During the reproductive years, estrogens contribute to vascular homeostasis through endothelial nitric oxide signaling, modulation of vascular tone, antioxidant effects, metabolic regulation, and anti-inflammatory pathways. Loss of estrogen exposure during the menopausal transition is accompanied by reduced endothelial resilience, increased oxidative stress, arterial stiffening, adverse lipid and glucose metabolism, and a shift toward a more pro-inflammatory vascular environment [5,8]. These changes are heterogeneous and interact with age and cumulative risk-factor exposure; menopause should therefore be understood as one component of vascular aging rather than as an isolated causal event.

Endothelial dysfunction is a central link between female-specific risk exposures and ischemic phenotypes. Reduced nitric-oxide bioavailability, increased reactive oxygen species, altered endothelin signaling, and inflammatory activation impair endothelium-dependent vasodilation and may facilitate both microvascular dysfunction and epicardial vasomotor abnormalities. At the microvascular level, impaired vasodilatory reserve may reflect functional dysregulation, structural remodeling with arteriolar wall thickening and luminal narrowing, capillary rarefaction, or combinations of these abnormalities [10,11,18]. Chronic inflammation and oxidative stress can further promote endothelial injury, microvascular remodeling, and atherosclerotic progression, providing a biological basis for overlap between coronary vascular dysfunction and structural disease [11,12,17].

The menopausal transition represents a progressive biological transformation rather than an abrupt increase in cardiovascular risk. As estrogen exposure declines, endothelial

dysfunction, arterial stiffening, oxidative stress, chronic low-grade inflammation, and metabolic dysregulation progressively reduce vascular resilience and reshape the coronary circulation. The timing and magnitude of this transformation vary considerably among individuals and largely reflect the cumulative interaction between hormonal aging and lifelong exposure to conventional cardiovascular risk factors [5,8].

Female-specific conditions represent important life-course determinants of cardiovascular health. Hypertensive disorders of pregnancy, gestational diabetes, premature ovarian insufficiency, polycystic ovary syndrome, and autoimmune diseases leave a persistent vascular imprint that frequently precedes clinical manifestations by many years. Although clinically heterogeneous, these conditions converge on common biological pathways characterized by endothelial injury, immune activation, chronic inflammation, oxidative stress, and metabolic dysfunction, accelerating vascular aging and increasing long-term susceptibility to myocardial ischemia [8,12,19].

As these life-course determinants accumulate over time, they progressively reshape the coronary circulation through the interplay of functional and structural abnormalities. Functional alterations initially predominate and include impaired endothelial regulation, reduced vasodilatory capacity, coronary microvascular dysfunction, and abnormal vasomotor responses, progressively limiting the ability of the coronary circulation to match myocardial perfusion to metabolic demand. With advancing vascular aging, these functional abnormalities coexist with diffuse atherosclerosis, positive arterial remodeling, plaque erosion, vascular fragility, and thrombotic pathways, creating a heterogeneous coronary substrate in which multiple mechanisms frequently interact within the same individual rather than occurring as isolated processes [4,10,11,13,15,17,20,21].

Overall, female IHD should be viewed as the consequence of progressive biological transitions that continuously reshape the coronary circulation throughout life. The evolving balance between functional and structural abnormalities generates distinct biological substrates from which different clinical phenotypes emerge, providing the biological foundation for the heterogeneous clinical expression of IHD discussed in the following section.

3.2. Clinical Spectrum

The mechanisms described above frequently coexist. For clinical organization, this review uses the terms functional-dominant, mixed-mechanism, and structural-dominant presentations. These labels are conceptual and have not been prospectively validated as diagnostic categories or risk strata. They are intended to describe the relative contribution of abnormalities demonstrated by anatomical imaging, ischemia testing, coronary physiology/vasoreactivity testing, and intracoronary imaging. A patient may move between categories as new information emerges, and coexistence of mechanisms should be expected rather than treated as an exception.

3.2.1. Functional-Dominant Clinical Presentations

Functional-dominant presentations are common in women with ANOCA/INOCA and include coronary microvascular dysfunction, endothelial dysfunction, and epicardial or microvascular spasm. These endotypes may overlap, and symptom burden can be substantial despite the absence of flow-limiting stenosis [4,9,10].

The relevant clinical task is therefore not simply to label the angiogram as "non-obstructive," but to determine whether impaired vasodilatory reserve, abnormal vasomotion, or another mechanism explains symptoms and objective ischemia.

3.2.2. Mixed-Mechanism Clinical Presentations

Mixed-mechanism presentations combine coronary vascular dysfunction with diffuse or focal atherosclerosis, plaque-related disease, or other structural abnormalities. The

presence of one mechanism does not exclude another; for example, microvascular dysfunction may contribute to persistent symptoms in a patient who also has obstructive CAD [10,17,20,21].

Recognition of overlap is clinically important because similar angiographic findings may produce different symptom and ischemic profiles depending on concomitant vascular dysfunction, and non-obstructive angiography does not exclude diffuse atherosclerotic or plaque-related disease.

3.2.3. Structural-Dominant Clinical Presentations

Structural-dominant presentations include obstructive atherosclerotic CAD, plaque-related acute coronary syndromes, and non-atherosclerotic structural disorders. SCAD must be distinguished explicitly from atherosclerotic disease: it is a non-atherosclerotic coronary arteriopathy caused by intramural hematoma and/or intimal disruption and has a strong female predominance [15,16].

Even when structural disease is clinically predominant, concomitant coronary vascular dysfunction may remain relevant to residual ischemia or persistent angina and can justify additional physiological assessment when symptoms are unexplained or disproportionate to anatomy [4,10,21].

Accordingly, these categories should be used as a pragmatic map of predominant mechanisms, not as mutually exclusive diagnoses. This distinction is central to the integrated diagnostic approach described below.

3.3. An Integrated Mechanism-Based Framework

Figure 1 summarizes the conceptual framework. Female life-course determinants shape coronary vascular function and structure, from which different ischemic phenotypes emerge. The functional-dominant, mixed-mechanism, and structural-dominant labels are descriptive rather than validated categories and should be interpreted according to the totality of anatomical, physiological, and clinical findings. SCAD is represented as a non-atherosclerotic structural mechanism, separate from progressive atherosclerotic disease.

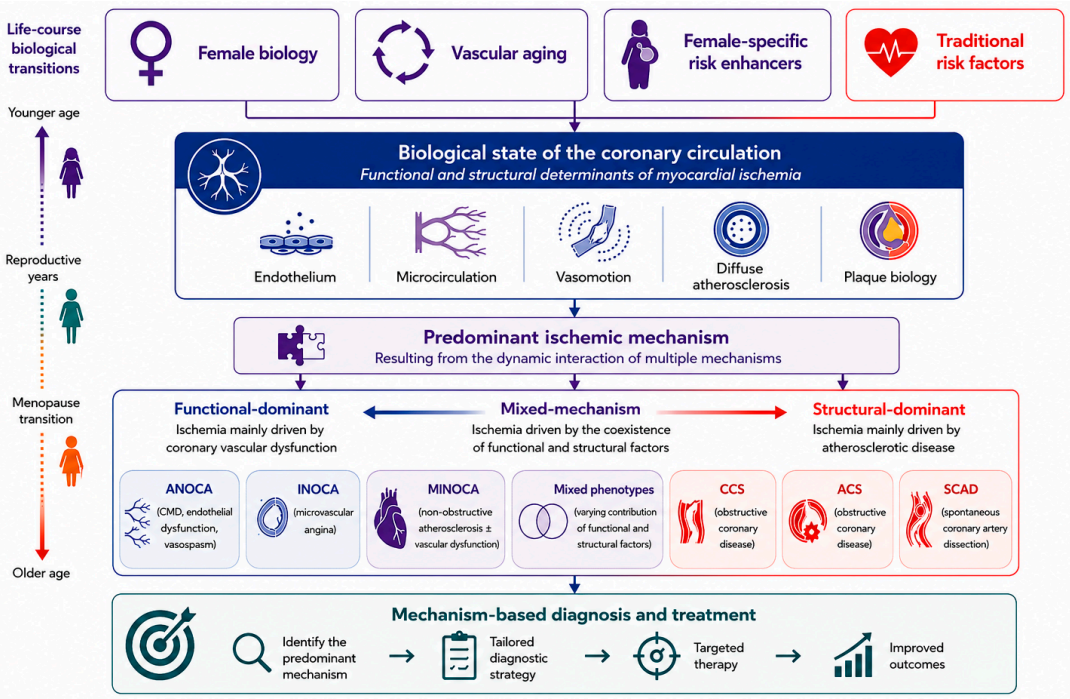


Figure 1. Mechanism-Based Framework of Female Ischemic Heart Disease.

4. Mechanism-Based Diagnostic Approach

Integrated Functional and Structural Phenotyping

The diagnostic evaluation of women with suspected IHD should characterize both structural coronary disease and functional abnormalities rather than follow a rigid, mutually exclusive sequence. Anatomical imaging, ischemia testing, coronary physiology, vasoreactivity testing, and intracoronary imaging answer different clinical questions and should be combined according to presentation, prior findings, pre-test likelihood, and residual diagnostic uncertainty [4,7,21,22]. Detection of obstructive CAD does not necessarily terminate evaluation: persistent or disproportionate symptoms and residual ischemia may justify assessment for coexisting coronary vascular dysfunction.

The integrated diagnostic strategy is summarized in Figure 2. The components are complementary rather than sequential gates; functional and structural assessments may proceed in parallel when clinically appropriate.

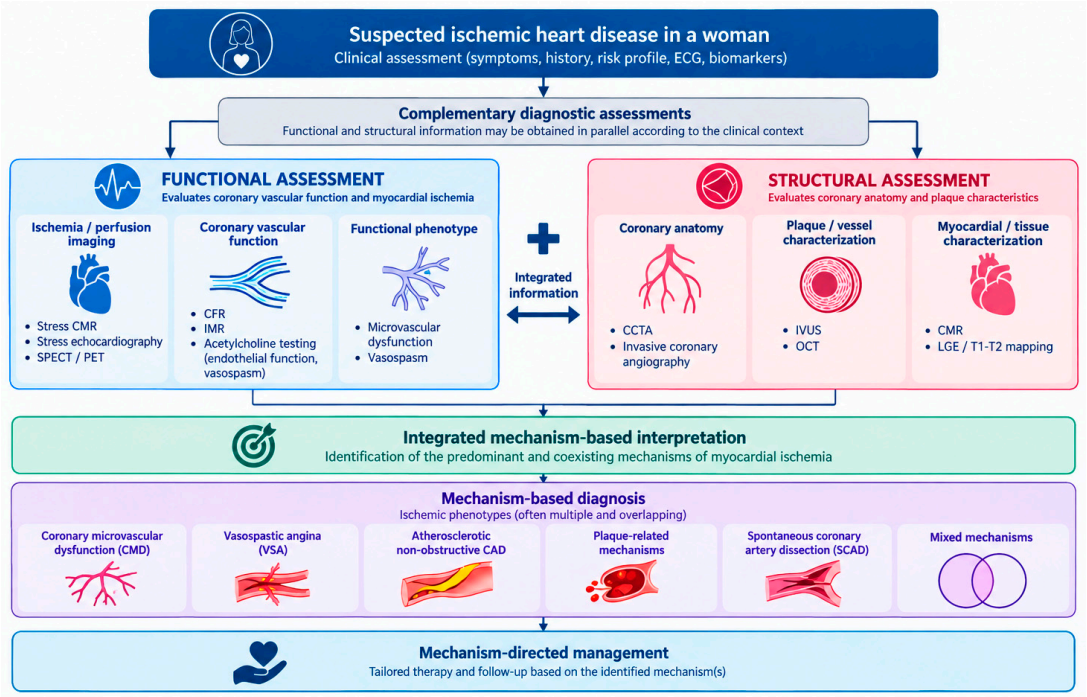


Figure 2. Integrated mechanism-based approach to the diagnosis of ischemic heart disease in women. Anatomical, ischemia/perfusion, coronary vascular functional, and structural/intracoronary assessments are complementary rather than sequential gates and may be used in parallel according to the clinical context.

The initial objective is to determine whether obstructive epicardial coronary artery disease represents the principal substrate of ischemia. Coronary computed tomography angiography is the preferred first-line anatomical test in patients with stable symptoms and low-to-intermediate pre-test probability because of its high negative predictive value and its ability to characterize coronary atherosclerosis beyond luminal stenosis, whereas invasive coronary angiography remains the reference standard in acute presentations or when obstructive disease is strongly suspected [2,7,23]. Nevertheless, anatomical imaging alone frequently fails to explain symptoms or objective evidence of ischemia in women, underscoring the limitations of relying exclusively on coronary stenosis to define ischemic heart disease [1,3,24,25].

When obstructive coronary disease is absent or insufficient to explain the clinical presentation, the diagnostic focus shifts toward confirming ischemia and identifying its underlying mechanism. Functional imaging techniques provide complementary informa-

tion by demonstrating inducible ischemia, evaluating its extent, and, in selected modalities, quantifying myocardial perfusion. Among these, positron emission tomography remains the reference non-invasive technique for quantitative assessment of myocardial blood flow and coronary flow reserve, whereas stress cardiovascular magnetic resonance uniquely combines functional evaluation with myocardial tissue characterization, facilitating the identification of alternative diagnoses and myocardial injury patterns [6,7,10,11,20,26].

When coronary vascular dysfunction is suspected, invasive coronary functional testing can combine pressure/flow measurements with pharmacological vasomotor testing. Coronary flow reserve (CFR) assesses the capacity to augment coronary flow during hyperemia; an impaired CFR ($\leq$2.5 when measured with intracoronary Doppler in the contemporary ESC ANOCA/INOCA framework) supports impaired vasodilatory reserve, while technique-specific thresholds should be respected. The index of microcirculatory resistance (IMR) provides a pressure- and thermodilution-based estimate of microvascular resistance, with IMR $\geq$ 25 units supporting coronary microvascular dysfunction. Acetylcholine provocation testing evaluates vasomotor function: epicardial spasm requires reproduction of symptoms and ischemic ECG changes with marked epicardial vasoconstriction (conventionally $\geq$ 90%), whereas microvascular spasm is characterized by symptoms and ischemic ECG changes without $\geq$90% epicardial constriction. Reduced CFR increased microvascular resistance, and vasospastic responses may coexist and should therefore be interpreted together [4,22,27].

Structural coronary abnormalities should also be considered when clinical findings remain unexplained despite the absence of significant angiographic stenosis. In these patients, intracoronary imaging with optical coherence tomography or intravascular ultrasound can identify plaque disruption, spontaneous coronary artery dissection, and other subtle abnormalities frequently missed by conventional angiography, particularly in patients presenting with myocardial infarction and non-obstructive coronary arteries [6,13,15,16,20].

Only the integration of these complementary diagnostic modalities allows identification of the underlying mechanism responsible for myocardial ischemia, providing the foundation for personalized therapeutic management. Anatomical imaging, functional testing, coronary physiology, and intracoronary imaging should therefore be viewed as complementary rather than competing tools, each contributing unique information to a mechanism-based diagnostic strategy [4,7,10,13,21].

No single modality comprehensively characterizes IHD in women. Anatomical, physiological, and morphological findings should therefore be integrated to identify predominant and coexisting mechanisms and to avoid interpreting an isolated test result outside its clinical context [4,21,22].

This is particularly relevant when obstructive CAD coexists with coronary vascular dysfunction, when diffuse non-obstructive atherosclerosis contributes to impaired perfusion, or when plaque disruption or SCAD is suspected despite non-obstructive angiography.

A mechanism-based interpretation can improve diagnostic precision while limiting unnecessary testing by directing investigations toward clinically meaningful uncertainty.

The practical endpoint is a sufficiently specific mechanistic diagnosis to support evidence-based prevention, symptom control, and targeted treatment.

5. Personalized Therapeutic Strategies

5.1. Targeting the Predominant Mechanism

Treatment should combine contemporary guideline-directed cardiovascular care with therapy targeted to the documented mechanism(s). For chronic coronary syndromes and ANOCA/INOCA, the 2024 ESC guideline emphasizes risk-factor control, antianginal therapy tailored to the clinical endotype, and invasive coronary functional testing in selected

persistently symptomatic patients [22]. For acute coronary syndromes, management and secondary prevention should follow contemporary ACS guidance [28].

For coronary vascular dysfunction, treatment should be matched to the endotype and individualized according to blood pressure, heart rate, comorbidities, and tolerance. Beta-blockers may be useful in patients with microvascular angina characterized by impaired vasodilatory reserve, whereas calcium-channel blockers are central to treatment of vasospastic angina; long-acting nitrates and other antianginal agents may be added when symptoms persist [4,22,27,29,30]. ACE inhibitors/ARBs and lipid-lowering therapy are appropriate when indicated for risk reduction and may also favor endothelial function. Non-selective beta-blockers should be avoided in documented vasospastic angina because of concern for worsening vasoconstriction. Evidence for several endotype-specific pharmacological strategies remains limited, and treatment response should be reassessed rather than assumed from the initial label.

Patients with mixed functional and structural mechanisms often require a combined therapeutic approach. In these patients, symptom control should be integrated with aggressive cardiovascular prevention, including lipid lowering, blood pressure optimization, diabetes management, smoking cessation, weight control, and regular physical activity according to current prevention guidelines [1,31,32]. Rather than prioritizing one mechanism over another, treatment should address both coronary vascular dysfunction and underlying atherosclerotic disease, recognizing that simultaneous targeting of multiple pathological processes is frequently necessary to optimize clinical outcomes [4,10,17].

When structural abnormalities predominate, management should follow the underlying etiology. Obstructive atherosclerotic CAD and plaque-related ACS require guideline-directed secondary prevention, antianginal treatment, and revascularization when indicated [22,28]. MINOCA is a working diagnosis rather than a single disease entity; therapy should therefore be directed to the mechanism identified by imaging, coronary physiology, or other targeted testing [6,13,33]. SCAD is a distinct non-atherosclerotic disorder and is generally managed conservatively when the patient is clinically stable because spontaneous healing is common and PCI can be technically challenging [15,16]. Evidence is insufficient to support a uniform antiplatelet regimen after conservatively managed SCAD; antithrombotic treatment should be individualized, while standard antiplatelet therapy applies after PCI/stenting or when another established indication is present.

In women, mechanism-directed treatment should be accompanied by sex- and life-stage-specific counseling. Reproductive planning and pregnancy counseling are particularly important after SCAD and in women with established CAD or previous ACS. Medication regimens should be reviewed before conception and during pregnancy or breastfeeding because several standard cardiovascular drugs may be contraindicated or require modification. Menopausal hormone therapy should not be initiated for the purpose of primary or secondary cardiovascular prevention [8]. Psychosocial assessment is also important, particularly after acute coronary events or SCAD, because anxiety, depression, fear of recurrence, and impaired quality of life can affect recovery and adherence. Shared decision-making should integrate cardiovascular risk, reproductive goals, symptom burden, and patient preferences.

5.2. Long-Term Follow-Up and Therapeutic Reassessment

Long-term management of women with ischemic heart disease should extend beyond treatment initiation and focus on continuous clinical reassessment. Because the predominant mechanism responsible for myocardial ischemia may evolve over time, follow-up should not only evaluate therapeutic adherence and cardiovascular risk factor control but

also determine whether the initial therapeutic strategy remains appropriate for the patient's current clinical profile [1,4,7,13].

At each follow-up visit, clinicians should reassess symptom burden, angina frequency, functional capacity, quality of life, medication adherence, treatment tolerance, and optimization of modifiable cardiovascular risk factors, including blood pressure, lipid profile, glycemic control, smoking cessation, body weight, and physical activity [1,7,31,32]. Changes in symptom characteristics, recurrent ischemic events, or discordance between clinical presentation and previous diagnostic findings should prompt reconsideration of the predominant ischemic mechanism and, when clinically appropriate, additional diagnostic evaluation [4,7,21].

Beyond pharmacological therapy, structured cardiovascular prevention programs should be considered an integral component of long-term management. Cardiac rehabilitation plays a central role by combining supervised exercise training, optimization of medical therapy, cardiovascular risk factor management, patient education, lifestyle modification, and psychosocial support. Although traditionally recommended after myocardial infarction or coronary revascularization, its benefits may also extend to selected patients with coronary microvascular dysfunction, vasospastic angina, spontaneous coronary artery dissection, and persistent ischemic symptoms, in whom improving functional capacity and quality of life represents a major therapeutic objective [15,16,31,32].

Long-term follow-up should therefore be viewed as a dynamic process rather than a scheduled series of clinical visits. Periodic therapeutic reassessment allows treatment to evolve according to changes in symptoms, disease progression, and the relative contribution of different ischemic mechanisms, ensuring that management remains aligned with the patient's clinical status throughout the course of the disease (Table 1).

Table 1. Treatment and follow-up according to the predominant mechanism of myocardial ischemia.

Mechanistic Domain	Endotype/Substrate	Diagnostic Features	Management Principles	Follow-Up Considerations
Coronary vascular dysfunction	Impaired vasodilatory reserve/CMD	Reduced CFR and/or increased microvascular resistance (e.g., IMR $\geq$ 25 U), interpreted by technique	Risk-factor control; beta-blocker or other antianginal therapy according to phenotype; ACEi/ARB and lipid-lowering therapy when indicated	Symptoms, exercise capacity, treatment response; reconsider endotype if persistent symptoms
Coronary vascular dysfunction	Epicardial or microvascular vasospasm	Acetylcholine-provoked symptoms + ischemic ECG changes; severe epicardial constriction for epicardial spasm, absent severe constriction for microvascular spasm	Calcium-channel blocker; long-acting nitrate/other antianginal therapy if needed; avoid non-selective beta-blockers in documented VSA	Trigger control, symptom recurrence, treatment tolerance
Structural coronary abnormality	Obstructive atherosclerotic CAD/plaque-related ACS	Anatomically and/or physiologically significant CAD; plaque-related ACS mechanism	Guideline-directed secondary prevention and antianginal therapy; PCI/CABG when indicated	LDL-C, BP, glycemia, symptoms, adherence, recurrent events; CR after ACS
Structural coronary abnormality	MINOCA with identified structural mechanism	Mechanism defined by CMR, OCT/IVUS, physiology or targeted testing	Etiology-specific therapy rather than uniform MINOCA treatment	Reassess mechanism if recurrent symptoms/events

Table 1. *Cont.*

Mechanistic Domain	Endotype/Substrate	Diagnostic Features	Management Principles	Follow-Up Considerations
Structural coronary abnormality	SCAD (non-atherosclerotic)	Angiographic/intracoronary imaging features of spontaneous dissection/intramural hematoma	No uniform antiplatelet regimen is established after conservatively managed SCAD; antithrombotic therapy should be individualized according to clinical context. Standard antiplatelet therapy applies after PCI/stenting or for another established indication.	Recurrence counseling, individualized exercise, reproductive/pregnancy counseling
Mixed/overlapping mechanisms	Coexisting functional and structural abnormalites	Evidence of >1 relevant mechanism	Treat each clinically relevant mechanism; avoid assuming revascularization resolves vascular dysfunction	Dynamic reassessment according to residual symptoms, ischemia and treatment response

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CMD, coronary microvascular dysfunction; CR, cardiac rehabilitation; LDL-C, low-density lipoprotein cholesterol; MINOCA, myocardial infarction with non-obstructive coronary arteries; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; VSA, vasospastic angina.

5.3. Cardiac Rehabilitation

Cardiac rehabilitation (CR) is a core component of secondary prevention after acute coronary syndromes and should be offered before hospital discharge when indicated. Contemporary ACC/AHA guidance gives outpatient CR a Class 1 recommendation after ACS because it reduces recurrent events and hospitalizations and improves functional status and quality of life; home-based programs are a reasonable alternative for selected patients [28]. CR combines structured exercise, risk-factor management, medication optimization, education, nutritional counseling, and psychosocial support. Its relevance to women is particularly important because referral, enrollment, and completion remain lower in women than in men. For patients with SCAD, exercise prescription should be individualized and avoid extreme or poorly controlled exertion, while supporting safe return to physical activity [15,16]. In ANOCA/INOCA, structured exercise and multidisciplinary prevention may improve functional capacity and quality of life, although the evidence base is less robust than after ACS.

6. Conclusions

IHD in women cannot be understood solely by the presence or absence of obstructive epicardial stenosis. Coronary vascular dysfunction, atherosclerotic disease, plaque-related mechanisms, and non-atherosclerotic structural disorders such as SCAD may occur alone or coexist, and their relative contribution should guide diagnostic reasoning.

A mechanism-based approach integrates anatomy, ischemia assessment, coronary physiology, vasoreactivity testing, and intracoronary imaging according to the clinical question. The functional-dominant, mixed-mechanism, and structural-dominant labels proposed in this review are conceptual aids, not validated diagnostic classes.

The clinical objective is to identify the mechanism or combination of mechanisms that best explains ischemia and symptoms, then align treatment with contemporary guidelines, mechanism-specific evidence, and women-specific considerations.

This sex-informed and mechanism-oriented strategy may improve diagnostic precision, reduce therapeutic mismatch, and provide a more clinically useful framework for future research in women with IHD.

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Abbreviations

The following abbreviations are used in this manuscript:

ACEi	Angiotensin-converting enzyme inhibitor
ANOCA	Angina with non-obstructive coronary arteries
ARB	Angiotensin receptor blocker
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
CCB	Calcium-channel blocker
CCTA	Coronary computed tomography angiography
CFR	Coronary flow reserve
CMD	Coronary microvascular dysfunction
CMR	Cardiac magnetic resonance
CR	Cardiac rehabilitation
ECG	Electrocardiogram
ICA	Invasive coronary angiography
IHD	Ischemic heart disease
IMR	Index of microcirculatory resistance
INOCA	Ischemia with non-obstructive coronary arteries
IVUS	Intravascular ultrasound
LDL-C	Low-density lipoprotein cholesterol
MINOCA	Myocardial infarction with non-obstructive coronary arteries
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
SCAD	Spontaneous coronary artery dissection
SPECT	Single-photon emission computed tomography
VSA	Vasospastic angina

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