Review Article

Coronary Slow-Flow Syndrome: A Review on Natural History of Disease and Best Practices

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Highlights

- Prevalence and Diagnosis: Coronary Slow Flow (CSF) occurs in 1–7% of patients undergoing angiography, diagnosed via corrected TIMI frame count (cTFC) exceeding 21 ± 3 frames, alongside scintigraphy and ECG analysis.
- Key Risk Factors: CSF is linked to cardiovascular risks like hypertension, diabetes, and inflammation, with genetic and psychological factors also playing a role in its development.
- Clinical Management: Treatment focuses on symptom relief using nitrates calcium channel blockers, statins, and anti-inflammatory agents, alongside lifestyle modifications and stress management.
- Long-Term Outcomes: CSF can lead to complications like myocardial infarction and left ventricular dysfunction, with a 10-year mortality rate of 15.3%, emphasizing the need for early detection and tailored care.

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ABSTRACT

Coronary slow flow (CSF) poses significant clinical challenges, marked by delayed coronary blood flow despite angiographically normal epicardial arteries. With a prevalence of 1% to 7%, the underlying pathogenesis and clinical manifestations of this condition remain incompletely understood. This review examines the natural history of CSF, including its pathophysiological mechanisms, ranging from inflammatory cascades to microvascular dysfunction. Diagnostic approaches, such as corrected TIMI frame count, scintigraphy, and ECG analysis, provide valuable insights into its complex presentation. Further, the review outlines management strategies, focusing on pharmacological interventions like calcium channel blockers and anti-inflammatory agents. Understanding CSF's natural history is crucial for implementing effective preventive measures, spanning primary to tertiary prevention. Still, further research is essential to fully elucidate its pathophysiology and optimize therapeutic strategies for improving patient outcomes in this complex disorder.

Keywords: Angiography; Coronary Arterial Diseases; Coronary Slow Flow; Natural History of Disease; TIMI Frame Count

RHYTHM
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Introduction

Coronary slow flow (CSF) was initially recognized as a clinical manifestation of microvascular dysfunction, characterized by delayed contrast passage during coronary angiography in distal vessels of individuals with normal or near-normal epicardial coronary arteries.[1,2] First reported in 1% to 7% of patients undergoing coronary angiography (based on 1996 Italian data),[3] this phenomenon was formally described by Tambe et al.[4] in 1972 following observations of six patients with angina. Subsequent research has transformed our understanding of CSF from a mere angiographic observation to a distinct clinical entity with unique pathophysiological mechanisms, characteristic features, and established diagnostic criteria.

CSF represents a microvascular disorder characterized by delayed coronary contrast passage during angiography in the absence of significant obstructive coronary artery disease.[1,2] Affected patients demonstrate impaired coronary blood flow despite angiographically normal or near-normal epicardial arteries.[5] Current diagnostic criteria incorporate the thrombolysis in myocardial infarction (TIMI) frame count as a quantitative measure of coronary flow velocity. [6] This metric records the number of cine frames required for contrast to reach standardized distal coronary landmarks. For the left anterior descending artery (LAD), the corrected TIMI frame count (cTFC) is calculated by dividing the absolute frame count by 1.7. 6 CSF is formally defined as a cTFC exceeding two standard deviations above the normal range (21 ± 3).[7]

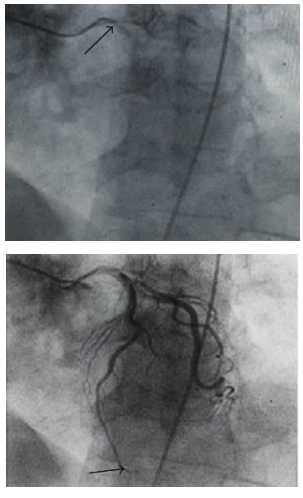
The Coronary Vasomotion Disorders International Study (COVADIS) group proposed these criteria as surrogate markers for coronary microvascular dysfunction[8,9] Nonetheless, subsequent evidence demonstrates limited diagnostic performance for microvascular dysfunction,[10] reinforcing CSF's distinction as a unique clinical entity.

Epidemiology

A study involving 3600 patients who underwent elective coronary angiography found that the prevalence of CSF was 2%.[11] This prevalence increased to 5.5% in a separate study of 1741 patients undergoing coronary angiography in the United States.[12] Moreover, a prospective study conducted in China involving 552 patients suffering from chronic total coronary occlusion reported that the prevalence of CSF could reach 16.1%.[13] An association also exists between CSF and cardiovascular risk factors, including advanced age, male sex, obesity, diabetes, hyperlipidemia, and hypertension.[11-13]

Diagnosis

The diagnosis of CSF involves various examination modalities, with the calculation of cTFC serving as the primary method. Patients are diagnosed with CSF when their cTFC value exceeds two standard deviations from the normal range. The diagnosis may also be supported by assessing changes in the TIMI frame count. For instance, a case series reported altered TIMI values before and after the intracoronary administration of adenosine (Figure 1).[14] Scintigraphy can identify myocardial perfusion abnormalities, which are frequently observed in CSF patients (approximately 28–75% of cases).[15,16] In addition, ECG parameters are assessed in CSF patients for ventricular repolarization disorders, as indicated by an increased Tp-Te interval and Tp-Te/QT ratio.[17] Nevertheless, in some instances, ECG parameters may not reveal abnormalities in CSF patients.[7]



(a)

(b)

Figure 1. Opacifications of the ostium (a) and the left anterior descending artery (b) during angiography to calculate the thrombolysis in myocardial infarction (TIMI) frame count in a 70-year-old man who presented with an episode of chest pain at rest. An intracoronary adenosine challenge was performed, resulting in a reduction of the TIMI frame count from 65 to 16. (Reproduced under the Creative Commons Attribution License.)[14]

Natural History of CSF

Pre-pathogenesis stage

The prepathogenesis stage focuses on evaluating individual risk factors and susceptibility to CSF. Epidemiologic studies stratify CSF risk by sex, cardiovascular risk factors, inflammatory markers, genetic predisposition, and psychological factors.

Current evidence indicates CSF occurs more frequently in men than women.[11–13,18] However, women with CSF often present with more severe cardiac involvement.[11–13,18] Modifiable cardiovascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and tobacco use, demonstrate significant associations with CSF development.[19,20]

Emerging data implicate chronic inflammation and immune dysregulation in CSF pathogenesis. Elevated inflammatory markers, particularly high-sensitivity C-reactive protein (CRP), correlate with CSF incidence.[21,22]

Genetic polymorphisms also contribute to microvascular dysfunction, including C677T variants (the methylenetetrahydrofolate reductase [MTHFR] gene),[23] -592A/C (IL10) gene,[24] or the -634C/G (IL6) gene.[25]

Psychological factors (chronic stress, depression, or anxiety) may further modulate CSF risk, although mechanistic insights remain limited.

Pre-symptomatic stage

The pre-symptomatic stage represents the phase when pathogenic mechanisms have been initiated but patients remain without perceptible symptoms, showing no subjective complaints or objective findings during clinical evaluation. In CSF, asymptomatic patients demonstrate no overt clinical manifestations yet reveal characteristic abnormalities through diagnostic testing. Coronary angiography may show a disproportionate delay in coronary artery filling relative to the degree of obstruction, manifested as prolonged contrast transit time or reduced blood flow velocity.[12, 14]

Endothelial function testing, particularly flow-mediated dilation of the brachial artery, frequently reveals endothelial dysfunction in these patients.[28]

Additional markers like increased carotid intima-media thickness often suggest concurrent systemic atherosclerosis and elevated cardiovascular risk, indicating broader vascular involvement beyond the coronary circulation.[29]

Early stages of clinical CSF

In the early stages of the disease, the pathogenesis commences, resulting in patients experiencing one or more clinical manifestations. Common clinical manifestations observed in CSF include symptoms such as chest pain associated with physical activity or emotional stress.[12, 26] The chest pain experienced in CSF often lasts longer than that associated with ischemic heart attacks. This pain may be described as pressure, heaviness, or tingling in the chest and can radiate to the left arm, jaw, or back. Furthermore, some patients may experience other symptoms, including shortness of breath, excessive fatigue, palpitations (irregular heartbeat), dizziness, or loss of consciousness. These symptoms may occur episodically, and they are often triggered by activities that require increased blood flow. Be that as it may, they may resolve after rest or the administration of anti-anginal medications such as nitrate agents.[2, 12, 30]

Several pathways contribute to the pathogenesis of CSF, including endothelial dysfunction, inflammatory response, microvascular dysfunction, and platelet abnormalities. [31] However, before delving into the pathogenesis of CSF, it is essential to recognize that this condition involves disturbances in coronary blood flow even in the absence of total coronary occlusion or severe ischemic heart attacks. This distinction sets CSF apart from traditional ischemic heart attacks.

The inflammatory process plays a crucial role in the pathogenesis of CSF.[31-33] During the subclinical stage of atherosclerotic plaque formation, inflammatory pathways can become activated within the vessel wall. Inflammatory cells, such as monocytes and macrophages, accumulate in the affected areas and release cytokines and other inflammatory mediators. This activity can result in

endothelial cell damage and the development of atherosclerotic lesions.[34] Initially, these atherosclerotic plaques may not produce clear clinical symptoms.[31,35] Nonetheless, over time, the plaques can progress and cause the narrowing of the coronary artery lumen. As a result, blood flow through the coronary arteries becomes impeded, even in the absence of total blockage that would lead to ischemic heart attacks. Patients may, consequently, experience chest pain (angina) and other ischemic symptoms.[36]

Activation of inflammatory pathways contributes significantly to endothelial and microvascular dysfunction in CSF. Proinflammatory cytokines, including interleukin-1 and tumor necrosis factor-alpha, disrupt endothelial homeostasis and promote pathological vasoconstriction.[37,38] This endothelial injury establishes a self-perpetuating cycle of inflammation, marked by elevated acute-phase reactants like CRP.[21,22] The inflammatory milieu further modulates vascular pathophysiology through increased expression of cellular adhesion molecules and enhanced platelet aggregability, collectively impairing microvascular perfusion. These pathological changes ultimately manifest clinically as exertional fatigue, dyspnea, or angina-equivalent symptoms during physical activity.

Advanced stages of clinical CSF

Clinical manifestations of CSF can evolve into more severe and complex conditions, particularly in cases of persistent coronary blood flow disorders and microvascular dysfunction. Patients with advanced CSF may experience more frequent and intense episodes of angina pectoris, which can adversely impact their quality of life and contribute to economic burdens due to repeated hospital admissions. [1] Additionally, symptoms such as shortness of breath, fatigue, and discomfort during physical activity may also become more common and severe. Furthermore, CSF can lead to serious complications, such as myocardial infarction. Myocardial infarction, albeit rare in CSF, has been observed in some cases with persistent blood flow disturbances.[39,40]

Other complications include structural and functional changes in the heart. Left ventricular enlargement (left ventricular hypertrophy) and impaired left ventricular contraction function (systolic dysfunction) have been associated with the progression of CSF.[30,41]

A cross-sectional study indicated that CSF may impair the left atrial reservoir and booster functions.[42] This impairment can lead to diastolic heart failure, characterized by the heart's difficulty in pumping blood.[41,43] A recent study suggested that individuals with CSF have a higher risk of major adverse cardiovascular events.[44]

End stages of clinical CSF
Residual disability

In general, after management and treatment, patients with CSF often experience residual disability related to cardiac function, which impacts their quality of life, making it lower than that in the general population.[31] Firstly, these patients may encounter recurrent symptoms and require long-term management, affecting their overall quality of life. A study reported long-term effects of CSF on left ventricular function in some patients even after intervention.[41] Persistent symptoms such as chest pain, fatigue, and mental disturbances are also observed in patients following treatment.[1,26] This residual disability influences the social, emotional, and physical aspects of patients' lives.

Chronicity

CSF can progress to a chronic stage. For instance, patients may experience ongoing inflammation, endothelial dysfunction, and chronic microvascular issues. The condition also has a high recurrence rate, which may cause patients to experience symptom relapses after treatment, necessitating repeated hospital admissions.[45] There is a correlation between chronic CSF and atherosclerosis and coronary artery disease.[12,13] A prior study reported that patients with chronic CSF had risk factors that contributed to faster disease progression than those with coronary artery disease in general.[12] The chronicity of CSF is influenced by several factors, including cardiovascular risk factors such as diabetes, hypertension, and chronic kidney disease.[32]

Death

Based on a prospective observational study involving 137 patients, the mortality rate among those with CSF reached 15.3% after a 10-year follow-up period, with 9.4% of the total patients experiencing cardiovascular-related deaths.[32] Factors contributing to significant mortality include advanced age, multivessel coronary artery disease, coronary obstruction, and decreased left ventricular function.[32,41] Furthermore, the multivariate regression analysis in another study indicated that age, poor left ventricular function, and multivessel coronary artery disease were independent factors associated with mortality in CSF patients.[40] The natural history of CSF is illustrated in (Figure 2).

Management and Treatment

Currently, specific guidelines for the management and treatment of CSF are unavailable; consequently, a symptom-based approach is generally employed to alleviate ischemic symptoms and prevent complications. The European Society of Cardiology has published guidelines for the diagnosis and management of syndrome X and microvascular dysfunction, which encompass CSF.[46] This strategy advocates for controlling risk factors such as hypertension, hyperlipidemia, diabetes, and obesity, aiming to improve vascular conditions and reduce complication risk.

Pharmacologically, the oral administration of calcium channel blockers (CCBs), including diltiazem, nifedipine, and nicardipine, has been reported to relieve ischemic symptoms and enhance coronary blood flow. These agents decrease microvascular tone, inhibit vascular smooth muscle contraction, and promote vasodilation.[47] Multiple studies have documented the efficacy of CCBs in mitigating CSF-related symptoms and improving patients' quality of life.[48-51]

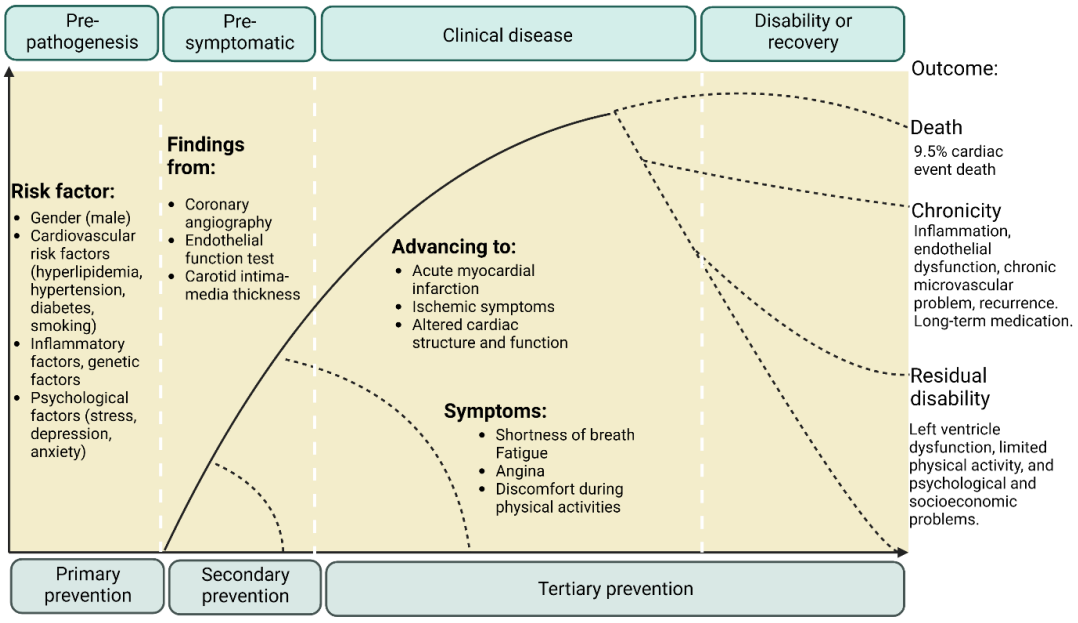


Figure 2. The summary of the natural history of coronary slow flow (CSF) encompasses several stages: pre-pathogenesis, pre-symptomatic, clinical disease, and disability or recovery.

Other drug classes employed for CSF management include statins, beta-blockers, and nitrates.[33] Statins are generally administered in cases of CSF to reduce blood cholesterol levels, which constitute a risk factor for ischemic symptoms.[52] Furthermore, statins exert direct effects on endothelial function and possess antithrombotic and anti-inflammatory properties.[53] Some studies have indicated that the use of statins, such as simvastatin, can improve myocardial perfusion in patients with CSF.[54] Nebivolol, a beta-blocker, has been shown to enhance endothelial function in CSF patients effectively.[55] Additional beneficial effects of nebivolol include prolonged QTc-interval, reduced chest pain, improved brachial artery dilation, and diminished oxidative

stress.[56,57] Although the use of nitrates in patients with CSF has been reported, it remains a subject of controversy. While some studies have found that intracoronary nitrate administration can increase coronary blood flow in patients with CSF[3] other investigations have not demonstrated significant effects.[58,59]

Antiplatelet agents, such as aspirin or clopidogrel, may also be administered to patients to reduce the risk of thrombosis and blood clot formation.[60] In some instances, anti-inflammatory therapy, employing nonsteroidal anti-inflammatory drugs or corticosteroids, may be considered to alleviate inflammation and reduce inflammation-associated CSF symptoms.[32] Regular cardiac monitoring is crucial to evaluate cardiac function, identify potential changes, and assess treatment response.

CSF management may also involve nonpharmacological approaches, including stress management and lifestyle modifications. [7,61-64] Stress management is particularly indicated if patients experience exacerbation of chest pain during stress episodes.[7,62-64] Combining pharmacological and nonpharmacological strategies has reportedly achieved successful outcomes in patients with CSF.[7,61-64] Cardiac rehabilitation, in conjunction with statins and aspirin, has been reported as efficacious for improving lipid profiles and arterial blood flow velocity.[65]

A summary of clinical management strategies for CSF is presented in (Table 1). Findings from diagnostic and interventional studies on CSF are detailed in (Table 2).

Preventive Measures

Primary prevention

Primary prevention strategies for CSF focus on controlling modifiable cardiovascular risk factors in at-risk individuals, given their well-documented association with CSF development.[66] As outlined by the Canadian Cardiovascular Society, these key risk factors include hypertension, diabetes mellitus, dyslipidemia, obesity, and a history of heart failure.[67] Targeted screening and management of elevated blood pressure, glycemic control, abnormal cholesterol levels, and excess body weight may help reduce the likelihood of early CSF onset. Preventive guidelines show some variation in their emphasis: while the American Heart Association/American College of Cardiology primarily address hypertension, diabetes, and hyperlipidemia management,[68] the European Society of Cardiology additionally identifies smoking cessation as a critical preventive intervention.[69]

Table 1. Clinical manifestation and treatment of coronary slow flow in cases with symptom relief outcomes

Author, year [ref]	Country	Sex	Age (years)	Past History	Chief Complaints	Clinical Manifestations	Treatment/ Drugs
Amasyali et al. 2006[70]	Turkey	Male	20	Chest pain and smoking	Recurrent chest pain during exercise	Exercise-induced angina	Nitrates and CCBs
		Male	33	Hypertension and hyperlipidemia	Chest pain radiating to the left arm	Angina with radiation	Beta-blockers and statins
Azzarelli et al., 2005[71]	Italy	Female	53	Cerebrovascular disease, moderate ponderal excess, and a normofunctional thyroid nodule	Effort chest pain	Acute chest pain	Beta-blockers, CCBs, and aspirin
		Female	39	Hyperlipidemia and smoking	Effort chest pain	Mild hypokinesia of the apex	Beta-blockers and statins
Barutcu et al., 2005[72]	Italy	Male	55	Hypertension	Persistent chest pain	Chronic angina	Statins and antiplatelets
Camsari et al., 2003[73]	Turkey	Male	55	Diabetes and smoking	Persistent chest pain	Chronic angina	CCBs and lifestyle modifications

Chalikias 2021[1]	Greece	Male	55	Smoking and hypercholesterolemia	Progressive chest pain over 3 months	Progressive angina	Statins and antiplatelets
Fragasso et al., 2009[74]	Italy	Male	60	History of ischemic heart disease	Unstable angina	Transient myocardial hypoperfusion	Nitrates and CCBs
Hawkins et al., 2012[75]	USA	Male	50	Hyperlipidemia	Recurrent chest pain, particularly postprandial	Post-prandial angina	Nitrates and CCBs
Horjeti and Goda 2012[76]	Albania	Male	60	Ischemic heart disease	Unstable angina	Unstable angina	Nitrates and beta-blockers
İzgi, 2022[77]	Turkey	Female	47	No significant past medical history	Exercise-induced chest pain	Exercise-induced angina	Nitrates and lifestyle modifications
Jaffe et al., 2008[78]	Canada	Male	50	Diabetes and hypertension	Persistent chest pain	Chronic angina	Statins and antiplatelets
Li et al., 2007[79]	China	Male	50	Hyperlipidemia	Chest pain during physical activity	Effort angina	Statins and nitrates
Sanghvi et al., 2018[61]	India	Female	46	Smoking	Sudden onset of chest pain	Acute chest pain	Beta-blockers and lifestyle modifications
Saya et al. 2008[7]	USA	Male	59	Left-sided chest tightness, along with shortness of breath and diaphoresis	Episodes of syncope preceded by palpitations	Acute chest pain	Nitrates, CCBs, and aspirin
Sezgin et al. 2003[62]	Turkey	Female	42	No significant past medical history	Recurrent chest pain, especially during stress	Stress-induced angina	Beta-blockers and stress management
Sucu et al., 2018[63]	Turkey	Female	40	No major risk factors	Chest pain and shortness of breath	Angina and dyspnea	Beta-blockers and stress management
Veerakul et al., 2015[80]	Thailand	Male	58	Non–insulin-dependent diabetes mellitus, hypercholesterolemia, and chronic low back pain	None	Chest heaviness, radiating to both jaws	Aspirin, statins, antiplatelets, CCBs, and metformin
Wang and Nie 2011[81]	China	Male	60	Diabetes and hypertension	Persistent chest pain and dyspnea	Effort angina	Statins and antiplatelets
Yilmaz et al., 2008[64]	Turkey	Female	39	Stress-related issues	Recurrent chest pain, more frequent with stress	Stress-induced chest pain.	CCBs and stress management
Zhu et al. 2022[31]	China	Female	40	No major risk factors	Chest pain and shortness of breath	Angina and dyspnea	Beta-blockers and stress management

CCBs: calcium channel blockers

Table 2. Summary of published studies on the risk factors and predictors of CSF

Reference	Study Design	Sample Size[a]	Primary Findings
Yu et al., 2024[44]	Retrospective cohort	614 vs. 428	There are higher risks for major adverse cardiovascular events.
He et al., 2018[65]	Prospective cohort	15 vs. 15	Cardiac rehabilitation improves lipid profiles, coronary and arterial blood flow velocity
Dutta et al., 2023[10]	Cross-sectional	46 vs. 106	Despite the association between the two conditions, CSF is not diagnostic for CMD.

Dai et al., 2022[82]	Cross-sectional	89 vs. 167	CSF can be predicted by the platelet × neutrophil/lymphocyte ratio.
Shui et al., 2021[42]	Cross-sectional	101 vs. 411	There is a negative association with left atrial reservoir and booster functions.
Zhang et al., 2024[83]	Case control	79 vs. 158	UAR could predict CSF in patients with CCS.
Mohammadzad et al., 2021[43]	Cross-sectional	53 vs. 69	There is an association with mild diastolic dysfunction and low global longitudinal strain.

CCS: chronic coronary syndrome, CMD: coronary microvascular dysfunction, CSF: coronary slow flow, UAR: uric acid to albumin ratio
[a]case/experiment vs. control

Secondary Prevention

Early detection of CSF is crucial, and individuals with cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, smoking, or a family history of heart disease are advised to undergo regular screenings.[66] Furthermore, a history of coronary artery disease, including heart attacks or unstable angina, should be considered due to its high-risk nature.[12] Comorbidities also play a role in increasing the risk of CSF, such as metabolic syndrome, chronic kidney disease, and obstructive sleep apnea syndrome.[84,85] Novel biomarker-based screening strategies, like platelet × neutrophil/lymphocyte ratio and uric acid to albumin ratio, can be developed to support prevention efforts.[82,83] Patients identified with CSF should receive appropriate management and treatment as previously discussed. (See the "Management and Treatment" section).

Tertiary Prevention

Following the diagnosis of CSF and the initiation of appropriate management, continued treatment is advised for patients to prevent disease progression and minimize potential disabilities. This treatment may include antiplatelet therapy, vasodilators, or anti-inflammatory medication, as indicated.[33] Currently, guidelines for pharmacological approaches to tertiary prevention in CSF cases are unavailable; therefore, medication administration is determined on a case-by-case basis.[33]

After symptom resolution, the decision to continue or discontinue treatment should be made by the managing physician following a comprehensive evaluation.[86] Generally, treatment may be discontinued when the patient's symptoms are well controlled and there are no signs of complications or disease progression.[48] Nonetheless, in certain cases, particularly if persistent risk factors or chronic symptoms are present, continued treatment may be necessary to manage the condition and prevent recurrence.[86,87] Regular cardiac monitoring, including ECG, echocardiography, and blood pressure and heart rate assessment, is also recommended to evaluate intervention efficacy and prevent potential complications.

Conclusion

In summary, CSF is a complex clinical condition marked by delayed contrast agent passage through coronary vessels without significant obstruction. Originally characterized as a microvascular disorder, CSF is now recognized as a multifactorial condition involving diverse pathophysiological mechanisms. The reported prevalence varies significantly among different populations, with strong epidemiological associations observed between CSF and both traditional cardiovascular risk factors and systemic inflammatory markers. Diagnosis necessitates a comprehensive approach, employing modalities like coronary angiography, endothelial function tests, and electrocardiography. Management primarily focuses on symptom relief, risk factor control, and pharmacological interventions, despite the lack of definitive tertiary prevention guidelines. Long-term monitoring emphasizes the need to assess treatment efficacy and prevent complications, reinforcing the importance of personalized care in CSF management. (Figure 3) provides an overview of the risk factors, diagnosis, and management of CSF.

Comprehending the natural history of CSF is vital for numerous reasons, as it offers valuable

insights into the progression of the condition, including symptom development, complications, and long-term outcomes. Our review provides clinicians with critical information to predict disease trajectories, identify high-risk patients, and devise tailored management strategies. Additionally, this review paves the way for establishing prognostic indicators and risk stratification tools, enabling informed clinical decision-making and enhancing patient care. Further research is paramount to deepen our understanding of CSF pathogenesis and refine therapeutic approaches.

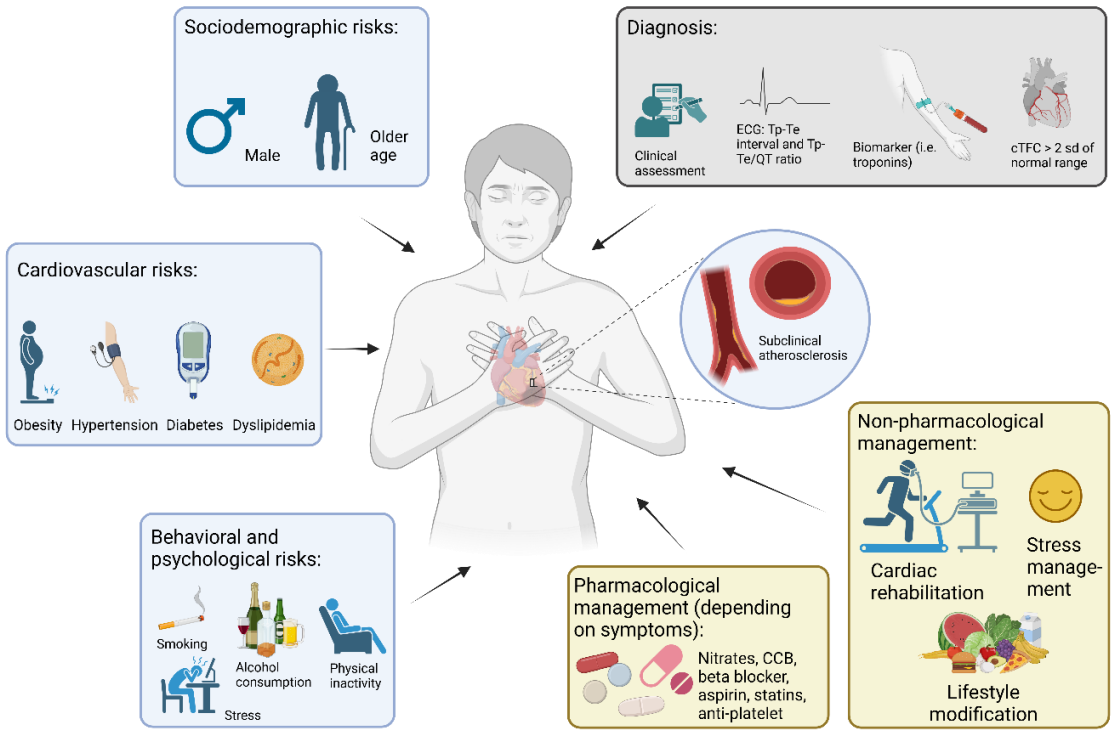


Figure 3. Risk factors, diagnosis, and treatment options for coronary slow flow.

Declarations:

Authors' Contributions

M.I.: conceptualization, data curation, writing the original draft, and visualization D.D.C.H.R.: writing (review and editing).

All the authors have read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No new data were created or analyzed in this study.

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