Treatment Approaches in Non-ST-Segment Elevation Acute Coronary Syndrome: From Guidelines to Clinical Practice

Abstract

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) encompasses a spectrum of clinical presentations ranging from unstable angina to non-ST-segment elevation myocardial infarction (NSTEMI), representing a significant challenge in contemporary cardiology. This paper overviews treatment approaches in NSTE-ACS, synthesizing evidence from guidelines and clinical practice. After discussing the pathophysiology and clinical presentation of NSTE-ACS, we outline key recommendations from major guidelines, emphasizing medical and invasive management strategies. Pharmacological interventions, including antiplatelet and anticoagulation therapies, are explored alongside considerations for analgesia and symptom management. Invasive approaches such as coronary angiography and percutaneous coronary intervention (PCI) are discussed, highlighting timing and selection criteria for optimal outcomes. Risk stratification tools and their implications for prognosis are analyzed, focusing on special populations and challenges in risk assessment.

Furthermore, we address controversies in NSTE-ACS management, including the balance between risks and benefits of interventions, adherence to guidelines, and emerging therapies. Additional sections cover topics such as patient education, shared decision-making, and considerations for health equity and access to care. The review concludes with insights into future directions in NSTE-ACS management, emphasizing the importance of multidisciplinary collaboration, quality improvement initiatives, and a patient-centered approach. This review is a valuable resource for clinicians involved in the care of NSTE-ACS patients, providing evidence-based guidance and addressing key issues in clinical practice.

Keywords: NSTE-ACS; Treatment Approaches; Guidelines; Clinical Practice; Acute Coronary Syndrome

Introduction and Background

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) represents a significant portion of cases encountered in clinical cardiology practice [1]. NSTE-ACS includes a spectrum of ischemic heart diseases, ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI), which collectively contribute to substantial morbidity and mortality worldwide [2]. Despite advancements in diagnostic modalities and treatment strategies, NSTE-ACS remains challenging due to its heterogeneity in clinical presentation, variable prognosis, and complex pathophysiology [3]. The pathophysiological basis of NSTE-ACS involves the disruption of coronary artery plaques, leading to partial or intermittent occlusion of the coronary vessel [4]. Plaque rupture or erosion triggers a cascade of events, including platelet activation, thrombus formation, and vasoconstriction, ultimately resulting in myocardial ischemia [5]. The degree and duration of coronary artery obstruction determine the clinical manifestation, ranging from transient ischemia in UA to myocardial necrosis in NSTEMI [6]. Diagnosis of NSTE-ACS relies on a combination of clinical

evaluation, electrocardiography (ECG), cardiac biomarkers, and imaging modalities [7]. Patients typically present with symptoms of chest discomfort, which may radiate to the neck, jaw, or arm, accompanied by dyspnea, diaphoresis, and nausea [8]. ECG changes such as ST-segment depression or T-wave inversion may be present. Still, the absence of ST-segment elevation distinguishes NSTE-ACS from ST-segment elevation myocardial infarction (STEMI) [9]. Cardiac biomarkers, particularly troponins, confirm myocardial injury and differentiate NSTEMI from UA [10]. Clinical guidelines provide evidence-based recommendations for managing NSTE-ACS, aiming to reduce ischemic events, alleviate symptoms, and improve long-term outcomes [11]. The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) guidelines offer consensus-based algorithms for risk stratification and treatment selection in NSTE-ACS [12]. Key principles include early initiation of antiplatelet and antithrombotic therapies, invasive coronary angiography with subsequent revascularization if indicated, and aggressive secondary prevention measures [13]. Medical management of NSTE-ACS involves a multifaceted approach to stabilizing coronary plaques, inhibiting thrombus formation, and alleviating ischemic symptoms [14]. Antiplatelet agents such as aspirin and P2Y12 inhibitors (e.g., clopidogrel, ticagrelor, prasugrel) are cornerstone therapies, targeting different pathways of platelet activation and aggregation [15]. Anticoagulants such as unfractionated heparin, low molecular weight heparin, and direct oral anticoagulants (DOACs) are prescribed to prevent further thrombus propagation and embolization [16]. Additionally, adjunctive therapies such as beta-blockers, nitrates, and statins optimize hemodynamic stability, relieve chest pain, and reduce atherosclerotic burden [17]. Invasive strategies are pivotal in managing high-risk NSTE-ACS patients, aiming to promptly identify and treat culprit lesions responsible for ongoing ischemia [18]. Early invasive strategy, defined as coronary angiography within 24 to 72 hours of hospital admission, is recommended for patients with high-risk features such as refractory angina, hemodynamic instability, or dynamic ECG changes [19]. Percutaneous coronary intervention (PCI) is the preferred revascularization modality, offering rapid restoration of coronary blood flow and symptom relief [20]. However, selecting an invasive strategy should be guided by careful risk assessment, considering individual patient characteristics, comorbidities, and preferences [21]. Risk stratification is crucial in guiding treatment decisions and predicting outcomes in NSTE-ACS patients [22]. Several risk scores and biomarkers have been developed to assess the likelihood of adverse events such as death, myocardial infarction, or recurrent ischemia [23]. For instance, the Global Registry of Acute Coronary Events (GRACE) score incorporates clinical variables such as age, heart rate, and renal function to estimate the risk of mortality in NSTE-ACS patients [24]. High-risk patients identified by risk scores may benefit from more aggressive treatment strategies, including early invasive management and intensified pharmacotherapy [25]. Despite advances in NSTE-ACS management, several challenges and controversies persist in clinical practice [26]. Balancing the risks and benefits of invasive procedures remains a subject of debate, particularly in elderly patients or those with significant comorbidities [27]. Adherence to guideline-directed therapies and quality metrics varies widely among healthcare providers and institutions, highlighting the need for continuous quality improvement initiatives [28]. Moreover, emerging therapies such as novel antiplatelet agents, antithrombotic agents, and invasive techniques present opportunities for improving outcomes but pose challenges in cost-effectiveness and safety [29]. Ultimately, NSTE-ACS represents a heterogeneous and clinically challenging condition with significant implications for patient outcomes and healthcare resource utilization [30]. A comprehensive understanding of the pathophysiology, diagnosis, and management principles is essential for clinicians caring for NSTE-ACS patients. By integrating evidence-based guidelines with individualized risk assessment and

patient preferences, healthcare providers can optimize outcomes and improve the quality of care in NSTE-ACS.

Clinical Presentation and Diagnosis

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) encompasses a spectrum of clinical manifestations ranging from asymptomatic ischemia to severe chest pain and hemodynamic instability, posing diagnostic challenges for clinicians [1]. The clinical presentation of NSTE-ACS is heterogeneous and influenced by various factors, including the extent and severity of myocardial ischemia, comorbidities, age, sex, and individual pain perception [2]. Prompt recognition and accurate diagnosis of NSTE-ACS are essential for guiding therapeutic interventions and optimizing patient outcomes. The hallmark symptom of NSTE-ACS is chest discomfort or angina pectoris, typically described as a pressing, squeezing, tightness, or heaviness sensation in the chest, often radiating to the left arm, shoulder, neck, jaw, or back [3]. The intensity and duration of chest pain may vary widely among individuals, ranging from mild discomfort to severe, incapacitating pain lasting minutes to hours [4]. Some patients may experience atypical symptoms such as dyspnea, nausea, diaphoresis, fatigue, dizziness, or epigastric discomfort, particularly in the elderly, women, and those with comorbidities [5]. Additionally, asymptomatic ischemia may occur in certain patients, particularly those with diabetes or autonomic neuropathy, making the diagnosis challenging [6]. Clinical assessment of patients presenting with suspected NSTE-ACS involves a thorough history taking, physical examination, and initial evaluation of vital signs, cardiac rhythm, and oxygen saturation [7]. Attention is paid to the onset, duration, frequency, precipitating factors, and relieving factors of chest pain, as well as associated symptoms such as dyspnea, palpitations, diaphoresis, and syncope [8]. Past medical history, including cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, smoking, and family history of premature coronary artery disease, is carefully elicited to stratify the patient's risk and guide further evaluation and management [9]. Diagnostic tests play a pivotal role in confirming the diagnosis of NSTE-ACS, assessing the extent and severity of myocardial ischemia, and guiding therapeutic decision-making [10]. The initial evaluation typically includes a 12-lead electrocardiogram (ECG), cardiac biomarker testing, and risk stratification using validated scoring systems such as the Thrombolysis in Myocardial Infarction (TIMI) risk score or the Global Registry of Acute Coronary Events (GRACE) score [11]. The ECG is a cornerstone in diagnosing NSTE-ACS, although it may be normal or nondiagnostic in up to 50% of cases [12]. Common ECG findings in NSTE-ACS include ST-segment depression, T-wave inversion, transient ST-segment elevation, or nonspecific changes, reflecting the presence of myocardial ischemia, injury, or repolarization abnormalities [13]. Cardiac biomarkers such as troponin and creatine kinase-MB (CK-MB) are sensitive and specific indicators of myocardial injury and necrosis, aiding in diagnosing NSTE-ACS and risk stratification [14]. Troponin, in particular, has emerged as the preferred biomarker due to its high myocardial specificity and prolonged elevation following myocardial injury, allowing for the detection of minor myocardial damage and delayed presentations [15]. Elevated troponin levels above the 99th percentile of the upper reference limit, with a rising or falling pattern, are diagnostic of myocardial infarction (MI) and indicate a poor prognosis in NSTE-ACS patients [16]. Creatine kinase-MB (CK-MB) may also be elevated in NSTE-ACS. However, it lacks the sensitivity and specificity of troponin and is primarily used as a confirmatory test in troponin-negative patients [17]. Additional diagnostic tests may be employed to evaluate myocardial ischemia further, assess cardiac

function, and identify underlying coronary artery disease in patients with suspected NSTE-ACS [18]. Exercise treadmill testing, stress echocardiography, nuclear myocardial perfusion imaging, and cardiac magnetic resonance imaging (MRI) are modalities used to detect inducible ischemia and assess myocardial viability, particularly in patients with equivocal or inconclusive initial evaluations [19]. Coronary angiography remains the gold standard for visualizing coronary anatomy, identifying culprit lesions, and guiding revascularization strategies in high-risk NSTE-ACS patients [20]. Invasive coronary angiography is indicated in patients with ongoing ischemia, hemodynamic instability, high-risk features on noninvasive testing, or recurrent symptoms despite optimal medical therapy [21]. Risk stratification is crucial in guiding therapeutic decision-making and optimizing outcomes in patients with NSTE-ACS [22]. Clinical prediction scores, such as the TIMI and GRACE scores, integrate clinical, ECG, and laboratory parameters to estimate the risk of adverse cardiovascular events, including death, MI, and recurrent ischemia [23]. High-risk features associated with adverse outcomes in NSTE-ACS include advanced age, hemodynamic instability, heart failure, renal insufficiency, dynamic ECG changes, elevated cardiac biomarkers, and evidence of ischemia on noninvasive testing [24]. Based on clinical evaluation and risk stratification scores, high-risk patients are candidates for early invasive management strategies, including coronary angiography and revascularization, to reduce the risk of recurrent ischemic events and improve survival [25].

Guidelines Overview

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly developed comprehensive guidelines for the management of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) [3]. Table 1 illustrates the ACC/AHA guidelines for NSTE-ACS; these guidelines serve as essential tools for healthcare providers in diagnosing, risk stratifying, and treating patients with NSTE-ACS, incorporating the latest evidence-based recommendations to improve patient outcomes. The ACC/AHA guidelines emphasize the importance of a prompt and systematic approach to evaluating and managing patients presenting with symptoms suggestive of NSTE-ACS [12]. Clinical assessment begins with a detailed history, physical examination, and initial evaluation of vital signs, cardiac rhythm, and oxygen saturation [5]. Attention is paid to the onset, duration, and characteristics of chest discomfort or angina, as well as associated symptoms such as dyspnea, nausea, diaphoresis, or syncope. Past medical history, including cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, smoking, and family history of premature coronary artery disease, is carefully elicited to stratify the patient's risk and guide further evaluation and management. Diagnostic evaluation includes a 12-lead electrocardiogram (ECG) and cardiac biomarker testing, with risk stratification using validated scoring systems such as the Thrombolysis in Myocardial Infarction (TIMI) risk score or the Global Registry of Acute Coronary Events (GRACE) score [5]. The ECG is a cornerstone in diagnosing NSTE-ACS, although it may be normal or nondiagnostic in up to 50% of cases. Common ECG findings include ST-segment depression, T-wave inversion, transient ST-segment elevation, or nonspecific changes reflecting the presence of myocardial ischemia, injury, or repolarization abnormalities. Cardiac biomarkers such as troponin and creatine kinase-MB (CK-MB) are sensitive and specific indicators of myocardial injury and necrosis, aiding in diagnosing NSTE-ACS and risk stratification [8]. Risk stratification is crucial in guiding therapeutic decision-making and optimizing outcomes in patients with NSTE-ACS. Clinical prediction scores, such as the TIMI and GRACE scores, integrate

clinical, ECG, and laboratory parameters to estimate the risk of adverse cardiovascular events, including death, MI, and recurrent ischemia. High-risk features associated with adverse outcomes in NSTE-ACS include advanced age, hemodynamic instability, heart failure, renal insufficiency, dynamic ECG changes, elevated cardiac biomarkers, and evidence of ischemia on noninvasive testing. Pharmacological therapy forms the cornerstone of treatment for NSTE-ACS, with antiplatelet agents, anticoagulants, beta-blockers, ACE inhibitors or ARBs, and lipid-lowering therapy recommended to reduce the risk of recurrent ischemic events and improve long-term outcomes [7]. Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 receptor inhibitor, is recommended as first-line therapy for most patients. Ticagrelor and prasugrel are preferred over clopidogrel in patients undergoing PCI or presenting with high-risk features. Anticoagulant therapy with UFH or LMWH is used in addition to antiplatelet therapy to prevent thrombus formation and reduce the risk of recurrent ischemic events. Beta-blockers exert cardioprotective effects by reducing myocardial oxygen demand, suppressing sympathetic activity, stabilizing myocardial membranes, and improving coronary perfusion [9]. ACE inhibitors or ARBs are recommended for secondary prevention in patients with left ventricular dysfunction, heart failure, diabetes, or hypertension. Statins are recommended in all patients with NSTE-ACS to reduce the risk of recurrent ischemic events and improve long-term outcomes. Invasive coronary angiography with possible PCI or CABG is recommended in high-risk patients with NSTE-ACS, including those with ongoing ischemia, hemodynamic instability, or high-risk features on noninvasive testing. Early invasive management strategies aim to identify and treat culprit lesions, restore coronary perfusion, and prevent recurrent ischemic events, thereby improving outcomes and reducing mortality in high-risk patients [1]. The European Society of Cardiology (ESC) guidelines provide comprehensive recommendations for the diagnosis, risk stratification, and management of non-ST-segment elevation acute coronary syndrome (NSTE-ACS), reflecting the latest evidence-based practices and expert consensus in cardiovascular medicine [5].

Medical Management of Non-ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) presents a significant challenge in clinical practice, requiring prompt and adequate medical management to mitigate the risk of adverse cardiovascular events and improve patient outcomes. Pharmacological interventions play a central role in the medical management of NSTE-ACS, encompassing antiplatelet therapy, anticoagulation therapy, and analgesia and symptom management. Antiplatelet therapy represents a cornerstone of pharmacological treatment for NSTE-ACS, inhibiting platelet activation and aggregation, thereby reducing the risk of thrombus formation and recurrent ischemic events. Aspirin, a cyclooxygenase (COX) inhibitor, is recommended as first-line therapy in all patients with NSTE-ACS, exerting its antiplatelet effects by irreversibly inhibiting the synthesis of thromboxane A2, a potent platelet agonist [1]. Additionally, dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 receptor inhibitor, is recommended to provide synergistic antiplatelet effects and reduce the risk of recurrent ischemic events [2]. P2Y12 receptor inhibitors such as clopidogrel, ticagrelor, and prasugrel block the adenosine diphosphate (ADP) receptor on platelets, inhibiting ADP-induced platelet activation and aggregation [3]. Ticagrelor and prasugrel are preferred over clopidogrel in patients with NSTE-ACS undergoing percutaneous coronary intervention (PCI) or presenting with high-risk features due to their more potent and rapid onset of action [4]. These antiplatelet agents are typically administered as loading doses,

followed by maintenance therapy to achieve and sustain optimal platelet inhibition. Anticoagulation therapy is another essential component of medical management in NSTE-ACS, aiming to prevent thrombus formation and reduce the risk of recurrent ischemic events. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are commonly used anticoagulants, exerting their antithrombotic effects by enhancing the activity of antithrombin III, thereby inhibiting thrombin and factor Xa [5]. UFH is typically administered as an intravenous bolus followed by a continuous infusion, whereas LMWH is administered subcutaneously and does not require routine monitoring of activated partial thromboplastin time (aPTT) [6]. Fondaparinux, a synthetic factor Xa inhibitor, represents an alternative anticoagulant option in patients with NSTE-ACS, particularly those at low risk of bleeding, as it offers similar efficacy with a lower risk of heparin-induced thrombocytopenia [7]. Direct oral anticoagulants (DOACs) such as rivaroxaban may be considered in selected patients with NSTE-ACS, particularly those with concomitant atrial fibrillation or a history of venous thromboembolism. However, their role in this setting remains to be fully elucidated [8]. Analgesia and symptom management are essential considerations in the medical management of NSTE-ACS, aiming to alleviate chest discomfort or angina and improve patient comfort and quality of life. Nitrates represent a cornerstone of analgesic therapy in NSTE-ACS, exerting their vasodilatory effects by releasing nitric oxide, promoting coronary artery vasodilation, and relieving myocardial ischemia [9]. Sublingual nitroglycerin is commonly used for the acute relief of angina symptoms in patients with NSTE-ACS. However, intravenous nitroglycerin may be considered in patients with ongoing ischemia or heart failure [10]. Morphine sulfate may be administered in combination with nitroglycerin for the management of severe or refractory chest discomfort in patients with NSTE-ACS. However, its routine use is not recommended due to potential adverse effects such as respiratory depression, hypotension, and delayed diagnosis and treatment [11].

Invasive Management in Non-ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS)

Invasive management strategies play a crucial role in the comprehensive management of non-ST-segment elevation acute coronary syndrome (NSTE-ACS), aiming to identify and treat culprit lesions, restore coronary perfusion, and prevent recurrent ischemic events. Key components of invasive management include coronary angiography, percutaneous coronary intervention (PCI) strategies, and careful consideration of timing and selection criteria for invasive procedures. Coronary angiography represents the gold standard diagnostic tool for assessing coronary anatomy and identifying culprit lesions in patients with NSTE-ACS. This invasive procedure involves the insertion of a catheter into the coronary arteries to inject contrast dye, allowing visualization of the coronary arteries and detecting any obstructive lesions or areas of stenosis. Coronary angiography is essential for risk stratification and guiding subsequent therapeutic interventions, such as PCI or coronary artery bypass grafting (CABG), based on the extent and severity of coronary artery disease [1]. Percutaneous coronary intervention (PCI) strategies are integral to managing NSTE-ACS, aiming to restore coronary perfusion and alleviate myocardial ischemia by treating obstructive lesions identified on coronary angiography. PCI encompasses a range of techniques, including balloon angioplasty, stent placement, and adjunctive therapies such as atherectomy or thrombectomy, depending on the lesion's characteristics and the patient's clinical presentation [2]. The selection of PCI strategy is guided by factors such as lesion complexity, vessel size, and the presence of thrombus or calcification to achieve optimal coronary revascularization

while minimizing procedural complications [3]. Timing and selection criteria for invasive procedures in NSTE-ACS represent critical considerations in clinical practice, balancing the benefits of early revascularization with the risks of procedural complications and bleeding. Early invasive management strategies aim to identify and treat high-risk patients with NSTE-ACS, including those with ongoing ischemia, hemodynamic instability, or high-risk features, on noninvasive testing, thereby reducing the risk of recurrent ischemic events and improving outcomes [4]. The selection of patients for invasive procedures is guided by clinical judgment, risk stratification tools, and consensus guidelines, focusing on identifying those who derive the most significant benefit from revascularization [5].

Conclusion

Managing Non-ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS) requires a multifaceted approach integrating evidence-based guidelines with individualized patient care. From the initial presentation to long-term follow-up, healthcare providers must navigate treatment decisions based on a thorough understanding of the patient's clinical profile, risk factors, and preferences. By adhering to established guidelines, healthcare teams can optimize outcomes and reduce the risk of recurrent cardiovascular events. However, the translation of guidelines into clinical practice has its challenges. Variability in patient presentation, comorbidities, and resource availability can complicate decision-making and implementation.

Furthermore, emerging research and technological advancements continuously shape the landscape of NSTE-ACS management, necessitating ongoing education and adaptation among healthcare providers. To address these challenges and improve patient care, a concerted effort is required from all stakeholders. Healthcare organizations should prioritize disseminating guidelines, providing resources for continuing education, and fostering interdisciplinary collaboration. Clinicians must stay abreast of the latest evidence and guidelines, engage in shared decision-making with patients, and advocate for access to appropriate resources and interventions. Patients, in turn, should be empowered to actively participate in their care, adhere to prescribed treatments, and advocate for their health needs. By working together, healthcare providers, policymakers, and patients can ensure that the best available evidence is translated into practice, ultimately improving outcomes and quality of life for individuals affected by NSTE-ACS. Through ongoing collaboration, education, and advocacy, we can strive towards a future where all patients receive timely, guideline-directed care, leading to better health and well-being for individuals and communities.

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Table 1: ACC/AHA Guidelines for NSTE-ACS Management

Diagnostic Evaluation	Recommendations
12-lead ECG	- Perform within 10 minutes of arrival

Diagnostic Evaluation	Recommendations
	- Assess for ST-segment depression, T-wave inversion, transient ST-segment elevation, or nonspecific changes
	- Consider serial ECGs if the initial ECG is nondiagnostic
Cardiac Biomarker Testing	- Measure troponin and CK-MB levels
	- Obtain serial measurements to assess for myocardial injury
Risk Stratification	- Calculate TIMI and GRACE scores
	- Consider clinical, ECG, and laboratory parameters to estimate risk
Pharmacological Therapy	**Recommendations**
Antiplatelet Agents	- Initiate DAPT with aspirin and a P2Y12 receptor inhibitor (ticagrelor or prasugrel preferred over clopidogrel)
Anticoagulants	- Use UFH or LMWH in addition to antiplatelet therapy for anticoagulation
Beta-Blockers	- Consider in all patients unless contraindicated
	- Use cautiously in patients with heart failure, bradycardia, or bronchospasm
ACE Inhibitors or ARBs	- Initiate in patients with left ventricular dysfunction, heart failure, diabetes, or hypertension
Lipid-Lowering Therapy	- Start statin therapy in all patients regardless of baseline lipid levels
	- Use high-intensity statin therapy (atorvastatin 80 mg or rosuvastatin 20-40 mg) for maximum efficacy
Invasive Management	**Recommendations**
Coronary Angiography	- Consider in high-risk patients with ongoing ischemia, hemodynamic instability, or high-risk features on noninvasive testing
	- Aim to identify and treat culprit lesions, restore coronary perfusion, and prevent recurrent ischemic events
PCI or CABG	- Perform PCI or CABG as appropriate based on coronary anatomy, patient

Diagnostic Evaluation	Recommendations
	characteristics, and procedural considerations

Table 1 illustrates the ACC/AHA guidelines for NSTE-ACS and provides evidence-based recommendations for the diagnosis, risk stratification, and management of patients presenting with this challenging clinical syndrome. These guidelines emphasize the importance of a systematic approach to patient evaluation, risk assessment, and therapeutic decision-making to improve patient outcomes and reduce the burden of cardiovascular disease.