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CHAPTER 1

THE NO-REFLOW PHENOMENON IN ACUTE CORONARY SYNDROMES: PATHOPHYSIOLOGY, CLINICAL DETERMINANTS, AND CONTEMPORARY MANAGEMENT

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Introduction

Early and effective myocardial reperfusion remains the cornerstone of treatment in acute coronary syndromes (ACS). Despite successful restoration of epicardial coronary artery patency with primary or early percutaneous coronary intervention (PCI), a substantial proportion of patients exhibit inadequate myocardial tissue perfusion, a phenomenon known as no-reflow (Ito et al., 1996). This paradoxical dissociation between epicardial flow and microvascular perfusion has emerged as a critical determinant of infarct size and clinical outcomes.

The no-reflow phenomenon was first described in experimental models of myocardial ischemia and reperfusion, where irreversible microvascular damage persisted despite reopening of the infarct-related artery (Kloner, Ganote, & Jennings, 1974). Subsequent clinical studies confirmed that no-reflow is not a rare angiographic curiosity but a frequent complication, particularly in ST-segment elevation myocardial infarction (STEMI), with reported incidences ranging from 10% to 30% depending on diagnostic criteria and patient population (Reffelmann, & Kloner, 2002). Importantly, no-reflow has also been documented in non–ST-segment elevation myocardial infarction (NSTEMI), underscoring that microvascular dysfunction is not limited to complete coronary occlusion (Ndrepepa et al., 2010a).

Pathophysiologically, no-reflow represents a complex and multifactorial process involving microvascular obstruction, distal thromboembolization, ischemia–reperfusion injury, endothelial dysfunction, and inflammatory activation (Niccoli et al., 2009). These mechanisms interact dynamically and may be influenced by patient-related factors, lesion characteristics, and procedural aspects of PCI. As a result, no-reflow is increasingly viewed not as a single entity but as a spectrum of microvascular injury with variable clinical expression.

Clinically, the presence of no-reflow is strongly associated with larger infarct size, impaired left ventricular recovery, adverse remodeling, heart failure, malignant ventricular arrhythmias, and increased short- and long-term mortality (Niccoli et al., 2013). Given its prognostic significance, early recognition and prevention of no-reflow have become integral components of contemporary ACS management.

This narrative review aims to provide a comprehensive overview of the no-reflow phenomenon in ACS, focusing on its pathophysiological mechanisms, clinical and procedural determinants, diagnostic approaches, and current therapeutic strategies, with particular attention to both STEMI and NSTEMI settings.

Definition and Classification of No-Reflow

The no-reflow phenomenon is defined as inadequate myocardial perfusion despite successful mechanical reopening of the epicardial coronary artery, in the absence of angiographically evident obstruction such as dissection, spasm, or residual stenosis (Eeckhout, & Kern, 2001). This concept highlights the dissociation between epicardial coronary flow and microvascular tissue-level perfusion, which is the principal determinant of myocardial salvage.

From a clinical standpoint, no-reflow can be broadly categorized into angiographic no-reflow and myocardial no-reflow. Angiographic no-reflow is traditionally identified during coronary angiography by reduced Thrombolysis in Myocardial Infarction (TIMI) flow grade (≤2) following PCI, despite adequate stent deployment and absence of mechanical complications (Gibson et al., 1996). However, reliance on epicardial flow alone is insufficient, as normal TIMI 3 flow does not necessarily imply effective microvascular reperfusion.

To better assess myocardial perfusion, adjunctive angiographic tools such as myocardial blush grade (MBG) and corrected TIMI frame count have been introduced. Impaired myocardial blush (MBG 0–1) in the presence of TIMI 3 flow is widely accepted as a marker of myocardial no-reflow and has been consistently linked to worse clinical outcomes (van 't Hof et al., 1998).

No-reflow may also be classified according to its temporal behavior. Transient no-reflow refers to reversible impairment of microvascular flow that improves spontaneously or after pharmacological intervention, whereas persistent no-reflow reflects sustained microvascular obstruction and carries a particularly adverse prognosis (Morishima et al., 2000). In addition, the distinction between clinical no-reflow, associated with hemodynamic instability or malignant arrhythmias, and subclinical no-reflow, detectable only by imaging modalities, is clinically relevant.

The prevalence and expression of no-reflow differ between ACS subtypes. While STEMI is associated with a higher incidence due to prolonged ischemia and large thrombus burden, NSTEMI patients may also develop no-reflow as a consequence of distal embolization, microvascular dysfunction, or inflammation, even in the absence of total coronary occlusion (Niccoli et al., 2016).

Pathophysiology of No-Reflow

The pathophysiology of the no-reflow phenomenon is complex and multifactorial, reflecting the cumulative impact of ischemic injury, reperfusion-related damage, and microvascular dysfunction. Rather than a single mechanism, no-reflow represents the final common pathway of several interrelated processes affecting the coronary microcirculation.

A central component of no-reflow is microvascular structural damage. Prolonged ischemia leads to endothelial cell swelling, capillary narrowing, and disruption of the capillary basement membrane. These changes increase microvascular resistance and impair erythrocyte transit even after restoration of epicardial coronary flow (Hollander et al., 2016). The severity of microvascular injury is closely related to ischemic duration, which explains the higher incidence of no-reflow in patients with delayed reperfusion.

Distal embolization of atherothrombotic material during PCI is another major contributor. Plaque fragments, cholesterol crystals, and platelet-rich thrombi can embolize into the downstream microcirculation, mechanically obstructing arterioles and capillaries. This mechanism is particularly relevant in lesions with a high thrombus burden and during aggressive interventional maneuvers such as balloon predilatation or high-pressure stent deployment (Topol, & Yadav, 2000). Distal embolization not only causes physical obstruction but also triggers local inflammation and vasoconstriction.

Ischemia–reperfusion injury plays a pivotal role in amplifying microvascular dysfunction. The sudden restoration of blood flow results in the generation of reactive oxygen species, calcium overload, and mitochondrial dysfunction within endothelial and myocardial cells. These processes promote endothelial apoptosis, increased vascular permeability, and interstitial edema, further compromising capillary patency (Yellon, & Hausenloy, 2007). Reperfusion injury also exacerbates myocardial stunning and contributes to irreversible myocyte death. The principal mechanisms contributing to the no-reflow phenomenon, including microvascular structural damage, distal embolization, ischemia–reperfusion injury, and inflammatory activation, are summarized in Table 1.

Table 1. Pathophysiological Mechanisms of the No-Reflow Phenomenon in Acute Coronary Syndromes

Mechanism	Key Pathological Features	Clinical/Procedural Context
Microvascular structural damage	Endothelial swelling, capillary compression, basement membrane disruption	Prolonged ischemia, delayed reperfusion
Distal thromboembolization	Plaque debris, platelet-rich thrombi obstructing arterioles	High thrombus burden, balloon predilatation, stent deployment
Ischemia–reperfusion injury	Oxidative stress, calcium overload, mitochondrial dysfunction	Sudden restoration of flow after prolonged occlusion
Inflammation and leukocyte plugging	Neutrophil adhesion, cytokine release, microvascular obstruction	STEMI, systemic inflammatory activation
Endothelial dysfunction and microvascular spasm	Reduced nitric oxide bioavailability, vasoconstriction	NSTEMI, diabetes mellitus, chronic microvascular disease
Interstitial edema	Increased vascular permeability, extravascular compression	Large infarct size, severe reperfusion injury

Abbreviations: ACS: acute coronary syndromes, PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non–ST-segment elevation myocardial infarction, NO: nitric oxide

Inflammation and leukocyte-mediated microvascular plugging constitute another key mechanism. Activated neutrophils adhere to the damaged endothelium via upregulated adhesion molecules, leading to capillary plugging and release of proteolytic enzymes and pro-inflammatory cytokines. This inflammatory cascade perpetuates endothelial dysfunction and worsens microvascular obstruction. Experimental and clinical data have demonstrated a strong association between systemic inflammatory activation and the extent of no-reflow (Fajar, Heriansyah, & Rohman, 2018).

Finally, functional abnormalities of the coronary microvasculature contribute to no-reflow independently of structural obstruction. Endothelial dysfunction results in impaired nitric oxide bioavailability and an imbalance between vasodilatory and vasoconstrictive mediators. Microvascular spasm and heightened vasoreactivity may further limit tissue perfusion despite an anatomically patent microcirculation. These functional disturbances are particularly relevant in NSTEMI, where ischemia may be intermittent and microvascular dysfunction may precede irreversible structural damage (Camici, & Crea, 2007).

Collectively, these mechanisms interact dynamically and may coexist within the same patient. The relative contribution of each pathway varies according to clinical presentation, ischemic time, thrombus burden, and procedural factors. Understanding the multifaceted pathophysiology of no-reflow is essential for developing targeted preventive and therapeutic strategies in ACS.

Clinical and Procedural Determinants

The development of no-reflow in acute coronary syndromes is strongly influenced by a combination of patient-related, clinical, angiographic, and procedural factors. Identification of these

determinants is essential for risk stratification and for tailoring preventive strategies during PCI.

Among patient-related factors, advanced age has consistently been associated with an increased risk of no-reflow, likely reflecting age-related microvascular dysfunction and reduced ischemic tolerance (Resnic, et al., 2003). Diabetes mellitus is another well-established determinant, owing to chronic endothelial dysfunction, capillary basement membrane thickening, and impaired vasodilatory reserve. Similarly, chronic kidney disease is linked to heightened oxidative stress, inflammation, and microvascular remodeling, all of which predispose to impaired reperfusion at the tissue level (Ndrepepa, & Kastrati, 2023).

Clinical presentation plays a pivotal role. STEMI patients experience higher rates of no-reflow compared with NSTEMI, primarily due to prolonged and complete coronary occlusion, larger infarct size, and higher thrombus burden. Longer symptom-to-balloon time is one of the strongest predictors of no-reflow, emphasizing the time-dependent nature of irreversible microvascular injury (De Luca et al., 2004). Hemodynamic instability, cardiogenic shock, and anterior infarct location further increase susceptibility to microvascular obstruction.

Angiographic and lesion-related characteristics are also critical. High thrombus burden, long lesion length, complex or lipid-rich plaques, and multivessel coronary artery disease have all been associated with an elevated risk of distal embolization and subsequent no-reflow (Ahn et al., 2015). Intravascular imaging studies have demonstrated that plaques with large necrotic cores are particularly prone to embolization during PCI. Patient-related, clinical, angiographic, and procedural determinants associated with the development of no-reflow in acute coronary syndromes are outlined in Table 2.

Table 2. Clinical, Angiographic, and Procedural Determinants of No-Reflow

Category	Determinant	Proposed Mechanism
Patient-related	Advanced age	Reduced microvascular reserve, endothelial dysfunction
	Diabetes mellitus	Capillary basement membrane thickening, impaired vasodilation
	Chronic kidney disease	Oxidative stress, inflammation, microvascular remodeling
Clinical	STEMI presentation	Prolonged ischemia, large infarct size
	Longer symptom-to-balloon time	Irreversible microvascular injury
	Cardiogenic shock	Severe microcirculatory hypoperfusion
Angiographic	High thrombus burden	Increased distal embolization
	Long or complex lesions	Plaque fragmentation during PCI
	Anterior infarct location	Larger jeopardized myocardium
Procedural	Balloon predilatation	Thrombus and plaque embolization
	High-pressure stent deployment	Microvascular injury and embolization
	Repeated device manipulation	Endothelial trauma, distal debris

Abbreviations: ACS: acute coronary syndromes, PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non–ST-segment elevation myocardial infarction, CKD: chronic kidney disease

Procedural factors significantly modulate no-reflow risk. Aggressive balloon predilatation, high-pressure stent deployment, and repeated device manipulation may increase distal embolization of thrombotic and plaque material. Conversely, direct stenting strategies and careful lesion preparation have been associated with lower rates of no-reflow in selected patients. Pharmacological pretreatment and intraprocedural antithrombotic strategies also influence microvascular outcomes, highlighting the interplay between procedural technique and biological vulnerability (Maekawa et al., 2005).

Taken together, no-reflow emerges as the result of cumulative risk rather than a single trigger. The convergence of adverse clinical profile, ischemic burden, lesion complexity, and procedural factors determines the likelihood and severity of microvascular reperfusion failure in ACS.

Diagnostic Assessment of No-Reflow

Accurate diagnosis of the no-reflow phenomenon is essential for both immediate clinical decision-making and prognostic stratification in patients with acute coronary syndromes. However, assessment of no-reflow remains challenging, as conventional angiographic evaluation of epicardial coronary flow does not reliably reflect myocardial tissue perfusion.

Invasive coronary angiography is the most commonly used diagnostic tool in the acute setting. Reduced TIMI flow grade after PCI represents the classic angiographic manifestation of no-reflow. Nevertheless, a substantial proportion of patients demonstrate normal TIMI 3 flow despite significant impairment of microvascular perfusion. To address this limitation, myocardial blush grade has been introduced as a surrogate marker of myocardial reperfusion. Impaired or absent myocardial blush is strongly associated with larger infarct size and worse clinical

outcomes, even when epicardial flow appears normal (Gibson et al., 2000). Despite its utility, angiographic assessment remains operator-dependent and lacks sensitivity for detecting subclinical microvascular obstruction.

Cardiac magnetic resonance imaging has emerged as the reference standard for non-invasive assessment of myocardial no-reflow. Late gadolinium enhancement sequences allow direct visualization of microvascular obstruction as hypoenhanced regions within the infarct core. The extent of microvascular obstruction detected by cardiac magnetic resonance closely correlates with infarct size, adverse ventricular remodeling, and long-term mortality, independent of traditional clinical and angiographic variables (Wu et al., 1998). Importantly, cardiac magnetic resonance can identify no-reflow that is not apparent during angiography, underscoring the concept of subclinical no-reflow.

Echocardiographic techniques, particularly myocardial contrast echocardiography, provide bedside assessment of myocardial perfusion by evaluating microbubble replenishment within the microcirculation. Reduced or absent contrast enhancement reflects impaired capillary flow and has been shown to predict poor functional recovery and adverse outcomes after myocardial infarction (Galiuto, & Iliceto, 1998). However, limited availability and operator dependency restrict its widespread use.

Nuclear imaging modalities, including single-photon emission computed tomography, can detect persistent perfusion defects after reperfusion therapy. Although these techniques offer quantitative assessment of myocardial perfusion, their role in acute decision-making is limited by low spatial resolution and delayed acquisition (Itti et al., 2004). The main invasive and non-invasive modalities used for the assessment of no-reflow, along with their pathophysiological targets and prognostic implications, are summarized in Table 3.

Table 3. Diagnostic Modalities for Assessment of No-Reflow and Their Clinical Implications

Modality	Parameter	What It Assesses	Prognostic Value
Coronary angiography	TIMI flow grade	Epicardial coronary flow	Limited when TIMI 3 is present
	Myocardial blush grade	Tissue-level perfusion	Strong predictor of infarct size and mortality
Cardiac magnetic resonance	Microvascular obstruction (LGE)	Direct visualization of no-reflow	Strongest predictor of adverse remodeling and mortality
Myocardial contrast echocardiography	Contrast replenishment	Microvascular perfusion	Predicts functional recovery
Nuclear imaging (SPECT)	Persistent perfusion defects	Regional myocardial perfusion	Limited acute applicability
Biomarkers	Inflammatory and endothelial markers	Indirect microvascular injury	Investigational

Abbreviations: TIMI: Thrombolysis In Myocardial Infarction, MBG: myocardial blush grade, CMR: cardiac magnetic resonance, LGE: late gadolinium enhancement, SPECT: single-photon emission computed tomography

Beyond imaging, circulating biomarkers have been investigated as indirect indicators of no-reflow. Elevated inflammatory markers, markers of endothelial dysfunction, and indices reflecting microvascular injury have been associated with impaired myocardial reperfusion. While promising, biomarker-based diagnosis of no-reflow remains investigational and lacks standardized thresholds for routine clinical application (Kaul, 2014).

Therapeutic Strategies

Therapeutic approaches to the no-reflow phenomenon in acute coronary syndromes can be broadly divided into preventive strategies and treatments applied once no-reflow has occurred. Given the multifactorial pathophysiology of no-reflow, no single therapy has proven uniformly effective, and management generally requires a combined pharmacological and procedural approach.

Preventive strategies begin before and during PCI. Adequate antithrombotic and antiplatelet therapy is fundamental to reduce thrombus burden and distal embolization. Potent P2Y12 inhibitors and appropriate anticoagulation have been associated with improved microvascular perfusion, particularly in high-risk STEMI patients. In addition, early and high-dose statin therapy has been shown to exert pleiotropic effects, including anti-inflammatory and endothelial-stabilizing actions, which may reduce the incidence of no-reflow when administered before PCI (Patti et al., 2007).

Once no-reflow is identified during the procedure, intracoronary pharmacological therapy represents the mainstay of acute management. Adenosine is among the most extensively studied agents and acts through vasodilation, inhibition of neutrophil activation, and attenuation of reperfusion injury. Several clinical studies have demonstrated improvements in microvascular flow parameters following intracoronary adenosine administration,

although consistent effects on hard clinical endpoints remain unproven (Marzilli et al., 2000). Calcium channel blockers such as verapamil and nicardipine are also commonly used, particularly when microvascular spasm is suspected, and have shown favorable effects on angiographic and myocardial perfusion indices.

Other vasodilators, including sodium nitroprusside, have been employed to directly reduce microvascular resistance. Intracoronary nitroprusside has been shown to rapidly improve coronary flow and myocardial blush in patients with established no-reflow, suggesting a role for targeted microvascular vasodilation (Amit et al., 2006). Glycoprotein IIb/IIIa inhibitors have also been investigated, based on their ability to reduce platelet aggregation and microthrombus formation, with some studies indicating improved microvascular reperfusion when administered intracoronarily (Harrison et al., 2013).

Mechanical and interventional strategies aim primarily at preventing distal embolization. Routine manual thrombus aspiration has not demonstrated consistent clinical benefit in large randomized trials and is no longer recommended as a standard strategy; however, selective use in patients with large thrombus burden remains controversial. Deferred stenting, allowing thrombus resolution before definitive stent implantation, has been proposed as a means to reduce microvascular obstruction, though evidence remains limited and conflicting (Carrick et al., 2014).

Overall, current therapeutic strategies for no-reflow focus on prevention, early recognition, and prompt intracoronary treatment. Despite advances in pharmacological and interventional techniques, no-reflow remains a challenging complication, highlighting the need for individualized management and further research into targeted therapies.

Prognostic Implications

The presence of the no-reflow phenomenon has profound prognostic implications in patients with acute coronary syndromes. Numerous studies have demonstrated that impaired myocardial reperfusion, irrespective of epicardial coronary patency, is a strong and independent predictor of adverse short- and long-term clinical outcomes.

In the acute phase, no-reflow is associated with larger infarct size and reduced myocardial salvage. Inadequate microvascular perfusion limits oxygen and nutrient delivery to viable myocardium, thereby promoting irreversible myocyte necrosis. Imaging-based studies have consistently shown a close relationship between the extent of microvascular obstruction and infarct size, as well as early impairment of left ventricular systolic function (de Waha et al., 2012). These effects translate into higher rates of acute heart failure and malignant ventricular arrhythmias during hospitalization.

Beyond the early phase, no-reflow has a sustained impact on ventricular remodeling. Persistent microvascular obstruction promotes chronic inflammation, interstitial fibrosis, and adverse geometric changes of the left ventricle. Patients with no-reflow exhibit reduced recovery of left ventricular ejection fraction and a higher likelihood of progressive ventricular dilation compared with those achieving effective myocardial reperfusion (Lombardo et al., 2012). These structural changes form the substrate for chronic heart failure and arrhythmogenesis.

Long-term outcome data indicate that no-reflow is independently associated with increased mortality after myocardial infarction. This association remains significant after adjustment for traditional risk factors, infarct size, and baseline ventricular function, underscoring the unique prognostic value of microvascular integrity (Ndrepepa et al., 2010b). Importantly, both angiographic and imaging-defined no-reflow carry adverse

prognostic significance, although cardiac magnetic resonance–detected microvascular obstruction appears to provide the strongest risk stratification.

Prognostic implications may differ according to ACS subtype. While the impact of no-reflow has been most extensively studied in STEMI, emerging evidence suggests that impaired microvascular perfusion in NSTEMI is also associated with worse functional recovery and higher rates of adverse cardiovascular events (Guerra et al., 2014). Moreover, persistent no-reflow confers a substantially worse prognosis than transient no-reflow, highlighting the importance of early reversal of microvascular dysfunction when possible.

Overall, no-reflow represents a final common pathway linking acute ischemic injury to chronic adverse outcomes. Its detection identifies a high-risk patient population that may benefit from closer follow-up and intensified secondary prevention strategies (Ito, 2006).

Future Directions and Research Gaps

Despite substantial advances in the understanding of the no-reflow phenomenon, important gaps remain in its diagnosis, prevention, and treatment. One of the major unresolved issues is the lack of a universally accepted definition and standardized diagnostic criteria. Heterogeneity in the use of angiographic indices, imaging modalities, and timing of assessment complicates comparison across studies and limits translation of research findings into routine clinical practice (Niccoli et al., 2010).

Another critical gap concerns early risk stratification. Current clinical and angiographic predictors identify high-risk patients only with moderate accuracy. There is growing interest in integrating clinical variables with advanced imaging and circulating biomarkers to enable earlier identification of patients

prone to microvascular injury. Biomarkers reflecting endothelial dysfunction, inflammation, and microvascular damage show promise, but none have yet achieved sufficient validation for routine use (Bekkers et al., 2010).

From a therapeutic perspective, most available treatments target downstream consequences rather than upstream mechanisms of no-reflow. Pharmacological agents such as adenosine and vasodilators improve surrogate markers of microvascular perfusion but have not consistently translated into improved hard clinical outcomes. This highlights the need for therapies that directly modulate reperfusion injury, inflammation, and microvascular integrity (Heusch, 2020). Novel approaches targeting mitochondrial dysfunction, oxidative stress, and endothelial repair are currently under investigation.

Advances in interventional techniques may also influence future management. Improved intracoronary drug delivery systems, embolic protection strategies tailored to lesion morphology, and physiology-guided PCI may reduce distal embolization and microvascular damage. In parallel, cardiac magnetic resonance is increasingly used as a surrogate endpoint in clinical trials, providing a sensitive tool to evaluate the efficacy of emerging therapies (Ibanez et al., 2019).

Finally, precision medicine approaches integrating genetic, metabolic, and inflammatory profiles may help explain interindividual variability in susceptibility to no-reflow. Large, well-designed prospective studies are needed to clarify whether personalized preventive and therapeutic strategies can meaningfully reduce the burden of no-reflow and improve long-term outcomes in ACS (Camici, d'Amati, & Rimoldi, 2015).

Conclusions

The no-reflow phenomenon represents a central determinant of clinical outcomes in acute coronary syndromes, reflecting the failure of myocardial tissue reperfusion despite successful epicardial coronary artery reopening. Accumulating evidence indicates that no-reflow is a multifactorial process driven by structural and functional microvascular injury, distal embolization, ischemia–reperfusion damage, and inflammatory activation.

Clinically, no-reflow identifies a high-risk population characterized by larger infarct size, impaired ventricular recovery, adverse remodeling, and increased mortality. Although most extensively studied in STEMI, no-reflow is increasingly recognized as a relevant pathophysiological entity in NSTEMI, underscoring the broad relevance of microvascular dysfunction across the ACS spectrum.

Current management strategies emphasize prevention, early recognition, and prompt intracoronary treatment, yet no single therapy has proven universally effective. Future progress will depend on standardized definitions, improved risk stratification, and the development of targeted therapies addressing the underlying mechanisms of microvascular injury. A deeper integration of pathophysiology, advanced imaging, and personalized approaches may ultimately improve myocardial reperfusion and long-term outcomes in patients with acute coronary syndromes.

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CHAPTER 2

PRECISION MEDICINE–BASED CARDIAC REHABILITATION: CLINICAL RATIONALE, CURRENT EVIDENCE, AND FUTURE DIRECTIONS

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, accounting for an estimated 17–18 million deaths annually and representing a substantial burden on health systems despite advances in pharmacological and interventional therapies (Roth et al., 2020). Improvements in acute care have increased survival after myocardial infarction and other major cardiovascular events; however, this success has been accompanied by a growing population of patients living with chronic coronary syndromes, heart failure, and multiple cardiometabolic comorbidities. In this context, secondary prevention strategies aimed at long-term risk reduction and functional recovery have become increasingly important.

Cardiac rehabilitation (CR) is a comprehensive, multidisciplinary intervention that includes supervised exercise training, risk factor modification, patient education, and psychosocial support. Over several decades, CR has consistently demonstrated beneficial effects on cardiovascular outcomes. Meta-analyses of randomized controlled trials and large observational cohorts have shown that participation in CR is associated with significant reductions in all-cause and cardiovascular mortality, fewer recurrent cardiovascular events, and meaningful improvements in functional capacity and health-related quality of life (Anderson et al., 2016; Taylor et al., 2004). These benefits extend across different clinical settings, including post-myocardial infarction patients, individuals after coronary revascularization, and selected populations with chronic heart failure.

Despite this strong evidence base, the real-world implementation of CR remains suboptimal. Referral, enrollment, and long-term adherence rates are persistently low in many regions, with participation estimates often below 30% of eligible patients (Ades et al., 2017). Moreover, conventional CR programs are

largely built on standardized protocols that apply similar exercise prescriptions and lifestyle recommendations to heterogeneous patient populations. Such an approach insufficiently accounts for interindividual differences in age, sex, genetic background, comorbidity burden, baseline fitness, autonomic function, and psychosocial profile. As a result, responses to exercise training and behavioral interventions vary widely, and a substantial proportion of patients fail to achieve optimal benefit (Joyner & Green, 2009).

In parallel with these challenges, cardiovascular medicine has entered an era increasingly shaped by precision medicine. Advances in genomics, biomarker research, digital health technologies, and data analytics have enabled a more refined characterization of disease phenotypes and treatment responses. This paradigm shift has begun to influence multiple areas of cardiology, yet its integration into CR has been relatively slow. Given the inherently individualized nature of exercise adaptation and lifestyle change, CR represents a particularly suitable platform for precision-based approaches.

The objective of this narrative review is to examine how the principles of precision medicine can be applied to contemporary cardiac rehabilitation. By synthesizing current evidence on biological, phenotypic, and behavioral heterogeneity among cardiac patients, this review aims to highlight limitations of traditional CR models and to provide a conceptual framework for more individualized, data-driven rehabilitation strategies.

Concept of Precision Medicine in Cardiovascular Care

Precision medicine refers to a medical model that aims to optimize prevention and treatment strategies by accounting for individual variability in biological, environmental, and lifestyle factors. Unlike traditional approaches that apply uniform diagnostic and therapeutic pathways to broad patient groups, precision

medicine seeks to identify which interventions are most effective for specific subgroups or even individual patients, based on measurable characteristics. This concept gained formal recognition with advances in genomics and high-throughput molecular technologies, but its scope has since expanded well beyond genetic information alone (Bouchard et al., 2012).

It is important to distinguish precision medicine from the earlier and often loosely used concept of “personalized medicine.” While personalized medicine generally implies tailoring care to the individual, precision medicine emphasizes a systematic, data-driven stratification of patients using quantifiable parameters. These include genetic variants, molecular and biochemical markers, imaging features, physiological measurements, and digital health data. The goal is not to create a unique treatment for every single patient, but rather to define biologically and clinically meaningful subgroups in which targeted interventions can be applied with greater efficacy and safety (Collins & Varmus, 2015).

Cardiovascular medicine has been an early adopter of precision-based concepts, largely due to the heterogeneity of cardiovascular diseases and their underlying mechanisms. In coronary artery disease, for example, it has become increasingly clear that patients with similar angiographic findings may have markedly different plaque characteristics, inflammatory activity, and clinical trajectories. Biomarker profiling and advanced imaging have enabled more refined risk stratification and have informed individualized decisions regarding antithrombotic therapy, lipid lowering intensity, and preventive strategies (Libby & Pasterkamp, 2015; Keteyian et al., 2016).

In heart failure, precision medicine has highlighted the limitations of treating all patients as a single entity. Distinct phenotypes such as heart failure with reduced ejection fraction and heart failure with preserved ejection fraction differ not only in

cardiac structure and function but also in comorbidity patterns, systemic inflammation, and response to therapy. These differences have direct implications for exercise tolerance, training adaptations, and non-pharmacological interventions, underscoring the relevance of precision approaches beyond drug therapy (Shah et al., 2015; Supervia et al., 2019).

Similarly, in hypertension and arrhythmias, interindividual variability in pathophysiology and treatment response has been increasingly recognized. Genetic predisposition, autonomic nervous system activity, vascular stiffness, and environmental exposures all contribute to disease expression and influence therapeutic outcomes. Collectively, these developments illustrate that precision medicine is no longer a theoretical framework but an emerging reality in cardiovascular care. Integrating this paradigm into cardiac rehabilitation represents a logical and potentially transformative next step.

Rationale for Precision Medicine–Based Cardiac Rehabilitation

The rationale for integrating precision medicine into cardiac rehabilitation arises directly from the growing recognition that cardiovascular patients differ substantially in their biological characteristics, clinical trajectories, and responses to non-pharmacological interventions. Exercise training, which represents the cornerstone of CR, is a complex physiological stimulus that interacts with multiple organ systems, including the cardiovascular, musculoskeletal, metabolic, and autonomic nervous systems. As such, its effects are inherently modulated by individual factors that extend beyond conventional clinical classifications.

One of the strongest arguments for a precision-based approach to CR is the consistent observation of large interindividual variability in training-induced adaptations. Improvements in cardiorespiratory fitness, endothelial function,

insulin sensitivity, and inflammatory profiles show wide dispersion even among patients undergoing identical exercise protocols under supervised conditions. This variability has been repeatedly confirmed in both healthy individuals and patients with cardiovascular disease, suggesting that standardized exercise prescriptions are unlikely to be optimal for a substantial proportion of participants (Ross et al., 2019). From a clinical perspective, this implies that some patients may require higher intensities, alternative training modalities, or longer program durations to achieve meaningful benefit, whereas others may respond adequately to lower workloads.

The multidimensional structure of CR further strengthens its suitability as a platform for precision medicine. Unlike isolated therapeutic interventions, CR already integrates exercise, lifestyle modification, education, and psychosocial support within a multidisciplinary framework. This structure allows for the incorporation of diverse data sources, including physiological measurements, biomarkers, imaging findings, and patient-reported outcomes, into a coherent and adaptive rehabilitation strategy. Precision medicine does not necessitate the abandonment of established CR principles; rather, it provides a framework for refining them by aligning specific interventions with patient-specific characteristics (Table 1).

Table 1. Conventional Cardiac Rehabilitation vs Precision Medicine–Based Cardiac Rehabilitation

Domain	Conventional Cardiac Rehabilitation	Precision Medicine–Based Cardiac Rehabilitation
Patient stratification	Broad diagnostic categories (e.g., post-MI, HF)	Multidimensional phenotyping (clinical, biological, behavioral)
Exercise prescription	Standardized intensity and modality	Individualized intensity, modality, and progression
Biological variability	Largely ignored	Explicitly considered (genetics, biomarkers, autonomic function)
Monitoring	Periodic, center-based assessments	Continuous or longitudinal monitoring (wearables, digital tools)
Behavioral approach	Uniform education and counseling	Tailored behavioral and psychosocial interventions
Program flexibility	Fixed schedules and structure	Adaptive, flexible, hybrid or remote models
Expected response	Assumed homogeneous benefit	Acknowledges responders and non-responders

Abbreviations: CR: cardiac rehabilitation; MI: myocardial infarction; HF: heart failure.

From a mechanistic standpoint, tailoring CR according to individual pathophysiology may enhance both efficacy and safety. For example, patients with chronotropic incompetence, autonomic dysfunction, or increased arterial stiffness may exhibit attenuated heart rate responses and abnormal blood pressure dynamics during exercise. In such cases, reliance on heart rate–based intensity prescriptions alone may be misleading, potentially resulting in undertraining or excessive physiological stress. Incorporating alternative markers of exercise intensity and recovery could allow more accurate titration of training loads and reduce adverse responses (Mezzani et al., 2013).

In addition to physiological considerations, precision-based CR has the potential to address behavioral and adherence-related challenges. Exercise preferences, motivational profiles, and psychosocial barriers differ markedly among patients and strongly influence long-term engagement. Evidence suggests that individualized exercise modalities and flexible delivery models are associated with higher adherence and sustained lifestyle change compared with rigid, uniform programs (Van Iterson et al., 2022). By aligning rehabilitation strategies with patient-specific needs and constraints, precision CR may improve participation rates and amplify population-level benefits.

Finally, the shift toward precision medicine in CR is consistent with broader trends in cardiovascular care and preventive cardiology. Contemporary guidelines increasingly emphasize risk stratification, patient-centered decision-making, and the use of objective data to guide therapy intensity. Extending these principles to CR represents a logical evolution rather than a paradigm break. Conceptually, precision-based CR seeks to deliver the right type, dose, and mode of rehabilitation to the right patient

at the right time, thereby maximizing clinical benefit while preserving feasibility in routine practice (Braverman, 2011).

Genetic and Omics-Based Insights in Cardiac Rehabilitation

Interindividual variability in response to exercise training represents one of the most compelling biological justifications for integrating genetic and omics-based data into cardiac rehabilitation. Accumulating evidence indicates that a substantial proportion of the variability in exercise capacity, training-induced improvements, and cardiovascular risk modulation is heritable. Twin and family studies have estimated that baseline cardiorespiratory fitness and its response to structured exercise training are influenced by genetic factors to a significant degree, underscoring the biological heterogeneity that underlies apparently similar clinical phenotypes (Bouchard & Rankinen, 2001).

At the genetic level, multiple candidate genes and polymorphisms have been implicated in modulating exercise responsiveness. Variants affecting mitochondrial biogenesis, oxidative phosphorylation, muscle fiber composition, and angiogenic signaling pathways have been associated with differential gains in aerobic capacity and muscular endurance. Large-scale studies such as the HERITAGE Family Study have demonstrated that individuals exposed to identical aerobic training regimens may exhibit changes in peak oxygen uptake ranging from negligible to substantial, a phenomenon partially explained by genetic predisposition (Timmons, 2010). Although routine genotyping is not currently part of standard CR practice, these findings highlight why uniform exercise prescriptions may fail to produce consistent benefits across patients.

Beyond genomics, omics technologies have expanded the understanding of systemic responses to exercise and rehabilitation. Metabolomic profiling has revealed that exercise induces complex

and dynamic changes in lipid metabolism, amino acid turnover, and insulin sensitivity, with distinct signatures observed among responders and non-responders. In patients with cardiovascular disease, these metabolic adaptations are further influenced by comorbid conditions such as diabetes, obesity, and chronic kidney disease, suggesting that metabolic phenotyping could inform more targeted rehabilitation strategies (Lewis, 2010).

Proteomic and transcriptomic approaches have provided additional insights into the molecular mechanisms underlying exercise adaptation. Exercise training modulates the expression of proteins involved in inflammation, oxidative stress, endothelial function, and extracellular matrix remodeling. Importantly, baseline inflammatory status appears to influence the magnitude of training-induced benefit, with chronic low-grade inflammation attenuating favorable adaptations. This observation is particularly relevant for cardiac patients, in whom systemic inflammation is common and prognostically significant (Gleeson et al., 2011).

Despite their promise, the clinical translation of genetic and omics data into routine cardiac rehabilitation remains in an early phase. Current evidence does not support the use of single genetic markers to guide exercise prescription. However, integrative, multi-omics approaches combined with clinical and physiological data may ultimately enable more accurate stratification of patients according to expected benefit, optimal training modality, and required intensity. Rather than replacing established CR principles, genetic and omics-based insights should be viewed as tools that can refine risk assessment and personalize rehabilitation within a broader precision medicine framework (Kelly & Pomp, 2013) (Table 2).

Table 2. Key Precision Medicine Domains Relevant to Cardiac Rehabilitation

Precision Domain	Examples of Measures	Potential Impact on CR Design
Genetic factors	Exercise-response–related polymorphisms	Explains interindividual variability in training response
Omics profiling	Metabolomics, proteomics, inflammatory signatures	Identifies metabolic and inflammatory phenotypes
Clinical phenotype	HFrEF vs HFpEF, frailty, comorbidity burden	Guides exercise modality and progression
Autonomic function	Heart rate variability, baroreflex sensitivity	Refines intensity prescription and safety monitoring
Vascular phenotype	Arterial stiffness, blood pressure response	Influences aerobic vs combined training strategies
Behavioral profile	Motivation, readiness to change, depression/anxiety	Improves adherence and long-term lifestyle change
Digital health data	Activity levels, heart rate trends, sleep metrics	Enables dynamic, adaptive rehabilitation

Abbreviations: CR: cardiac rehabilitation; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HRV: heart rate variability.

Phenotype-Driven Cardiac Rehabilitation Strategies

The application of precision medicine to cardiac rehabilitation naturally leads to a phenotype-driven approach, in which rehabilitation strategies are aligned with distinct clinical and physiological patient subgroups rather than broad diagnostic labels alone. Cardiovascular diseases, particularly heart failure and chronic coronary syndromes, encompass a wide spectrum of phenotypes that differ in pathophysiology, symptom burden, exercise tolerance, and prognosis. Recognizing and addressing this heterogeneity is essential for optimizing the effectiveness of rehabilitation interventions.

Heart failure represents one of the clearest examples of phenotypic diversity relevant to CR. Patients with heart failure with reduced ejection fraction and those with preserved ejection fraction exhibit fundamentally different mechanisms of exercise intolerance. In reduced ejection fraction, limitations are often driven by impaired cardiac output, abnormal chronotropic response, and peripheral muscle dysfunction, whereas in preserved ejection fraction, increased ventricular stiffness, impaired diastolic reserve, vascular dysfunction, and systemic inflammation play a more prominent role. These differences translate into variable responses to aerobic and resistance training, suggesting that identical exercise prescriptions may not be appropriate across heart failure phenotypes (Pandey et al., 2017).

Beyond ejection fraction, peripheral factors such as skeletal muscle quality, mitochondrial function, and endothelial health critically influence functional capacity and rehabilitation outcomes. Studies have demonstrated that exercise intolerance in many cardiac patients is more closely related to abnormalities in peripheral oxygen extraction and muscular metabolism than to central hemodynamic limitations alone. This observation supports

the incorporation of resistance training, interval-based exercise, and functional training modalities in selected phenotypes, particularly in older patients and those with sarcopenia or frailty (Haykowsky et al., 2011).

Age and biological sex further modulate rehabilitation needs and responses. Older adults often present with multimorbidity, reduced physiological reserve, and increased vulnerability to adverse events during exercise. Frailty, rather than chronological age, has emerged as a key determinant of functional outcomes and mortality in cardiovascular populations. Frailty-adapted CR programs that emphasize balance, strength, and gradual progression have been shown to be feasible and beneficial, yet remain underutilized in routine practice (Afilalo et al., 2014). Similarly, women are underrepresented in CR despite evidence that they derive comparable improvements in functional capacity and quality of life. Sex-specific differences in symptom perception, psychosocial stressors, and exercise preferences may influence engagement and adherence, underscoring the importance of tailored program design.

Comorbidity burden represents another critical phenotypic dimension. Patients with diabetes, chronic kidney disease, obesity, or chronic obstructive pulmonary disease exhibit distinct physiological constraints that influence exercise tolerance and risk profiles. For example, autonomic dysfunction and impaired chronotropic response are common in diabetes, while increased arterial stiffness and volume sensitivity are prevalent in chronic kidney disease. A phenotype-driven CR strategy acknowledges these differences and adapts training intensity, monitoring, and progression accordingly, rather than applying uniform protocols (Selig et al., 2010).

Overall, phenotype-driven cardiac rehabilitation aligns closely with the core principles of precision medicine by

integrating clinical, functional, and biological characteristics into individualized intervention strategies. Such an approach does not require abandoning standardized safety frameworks, but rather refining them to ensure that rehabilitation is both effective and responsive to patient-specific needs. As evidence continues to accumulate, phenotype-based stratification is likely to become a cornerstone of next-generation CR models (Forman et al., 2017).

Biomarkers and Autonomic Function–Guided Rehabilitation

Biomarkers provide objective insights into underlying pathophysiological processes and have become integral to risk stratification and prognostic assessment in cardiovascular medicine. Their potential role in guiding and individualizing cardiac rehabilitation, however, remains underexplored. Incorporating biomarker profiles into CR may help identify patients who are likely to derive greater benefit from specific training modalities, as well as those who require closer monitoring or modified exercise prescriptions.

Inflammatory biomarkers are of particular relevance in this context. Chronic low-grade inflammation is a hallmark of atherosclerosis, heart failure, and metabolic disease, and elevated inflammatory markers are consistently associated with worse cardiovascular outcomes. Exercise training has been shown to exert anti-inflammatory effects, yet the magnitude of this response varies substantially between individuals. Patients with persistently elevated inflammatory markers may exhibit attenuated improvements in functional capacity and vascular function, suggesting that baseline inflammatory status could influence rehabilitation responsiveness and potentially guide adjunctive strategies such as exercise intensity modulation or combined lifestyle interventions (Ridker et al., 2018).

Cardiac-specific biomarkers also offer valuable information relevant to rehabilitation planning. Natriuretic peptides reflect myocardial wall stress and are strong predictors of prognosis in heart failure and other cardiac conditions. Although elevated levels do not preclude exercise training, they may signal reduced hemodynamic reserve and increased vulnerability to volume shifts during physical activity. Serial assessment of natriuretic peptides in the context of CR has been proposed as a tool for monitoring physiological adaptation and identifying patients who may benefit from slower progression or closer supervision (Buchan et al., 2022).

Beyond biochemical markers, autonomic nervous system function represents a critical yet often overlooked determinant of exercise tolerance and cardiovascular risk. Autonomic imbalance, characterized by reduced parasympathetic activity and heightened sympathetic tone, is common in patients with coronary artery disease and heart failure and is associated with arrhythmias, sudden cardiac death, and adverse outcomes. Heart rate variability (HRV) provides a noninvasive measure of autonomic regulation and has been shown to improve with structured exercise training. Importantly, baseline HRV and its early response to training may predict long-term improvements in functional capacity and prognosis, supporting its potential role as a precision marker in CR (Sandercock, Bromley, & Brodie, 2005).

Baroreflex sensitivity offers complementary information on autonomic and vascular control of blood pressure and heart rate. Impaired baroreflex function is associated with increased mortality and reduced exercise tolerance in cardiac populations. Exercise training can partially restore baroreflex function, but responses are heterogeneous. Patients with severely blunted baroreflex sensitivity may require individualized intensity targets and alternative monitoring strategies, as traditional heart rate–based prescriptions

may not accurately reflect internal workload (La Rovere et al., 1998).

Arterial stiffness, closely linked to both autonomic dysfunction and vascular aging, further integrates biomarker and physiological domains. Increased arterial stiffness is associated with impaired exercise capacity and abnormal blood pressure responses during exertion. Evidence suggests that certain exercise modalities, particularly aerobic and combined training, can reduce arterial stiffness, although responses vary according to baseline vascular phenotype. Incorporating measures of arterial stiffness into CR assessment may therefore refine risk stratification and help tailor rehabilitation strategies within a precision medicine framework (Vlachopoulos, Aznaouridis, & Stefanadis, 2010).

Digital Health, Wearables, and Tele-Rehabilitation

Digital health technologies have emerged as key enablers of precision-oriented cardiac rehabilitation by allowing continuous data capture, remote supervision, and flexible program delivery. Traditional center-based CR models, while effective, are constrained by geographic access, scheduling rigidity, and resource availability. Tele-rehabilitation and wearable technologies offer solutions to these limitations while simultaneously generating individualized physiological and behavioral data that can inform tailored interventions.

Wearable devices capable of monitoring heart rate, physical activity, energy expenditure, and sleep patterns are now widely available and increasingly accurate. Validation studies have demonstrated that contemporary wearables can provide reliable heart rate measurements across a range of exercise intensities, making them suitable for use in cardiac populations when appropriately selected and supervised (Shcherbina et al., 2017). Continuous monitoring enables a shift from episodic assessment

during supervised sessions to longitudinal evaluation of daily activity patterns, recovery, and adherence. From a precision medicine perspective, these data allow clinicians to identify discrepancies between prescribed and actual exercise dose, detect early signs of over- or undertraining, and adapt rehabilitation plans in near real time.

Tele-cardiac rehabilitation programs build upon these technologies by delivering structured exercise training, education, and counseling remotely. Randomized trials and meta-analyses have shown that home-based and tele-rehabilitation programs can achieve improvements in functional capacity, cardiovascular risk factors, and quality of life comparable to those of conventional center-based CR, without compromising safety (Taylor, Dalal, & McDonagh, 2022). Importantly, tele-rehabilitation has been associated with higher participation and completion rates, particularly among patients who face logistical barriers to attending hospital-based programs.

Hybrid models that combine initial in-person assessment with subsequent remote supervision may offer an optimal balance between safety and flexibility. Early supervised sessions allow individualized risk assessment, education, and familiarization with exercise techniques, while subsequent tele-monitored phases support long-term adherence and lifestyle integration. Such models are particularly well suited to precision CR, as they allow progressive adjustment of training variables based on continuously collected data rather than fixed program timelines (Frederix et al., 2015).

Beyond exercise training, digital platforms facilitate personalized behavioral and educational interventions. Mobile health applications can deliver tailored feedback, goal setting, and motivational messages, reinforcing behavior change strategies aligned with individual preferences and readiness. Evidence

suggests that digitally supported CR interventions improve self-management and may enhance long-term maintenance of physical activity, a critical determinant of sustained cardiovascular benefit (Varnfield et al., 2014).

Despite these advantages, several challenges remain. Data integration across devices and platforms, data privacy concerns, and variability in digital literacy may limit widespread implementation. Moreover, the clinical interpretation of large volumes of wearable-derived data requires validated algorithms and clear thresholds for action. Nevertheless, as digital health technologies continue to evolve, their integration into CR represents a cornerstone of precision medicine–based rehabilitation, enabling more responsive, patient-centered, and scalable care models (Kraal et al., 2017).

Behavioral and Psychosocial Precision in Cardiac Rehabilitation

Behavioral and psychosocial factors are critical determinants of both short- and long-term outcomes in cardiac rehabilitation, yet they are insufficiently integrated into conventional CR models. Depression, anxiety, chronic stress, and maladaptive health behaviors are highly prevalent among patients with cardiovascular disease and are independently associated with increased morbidity, mortality, and healthcare utilization. Importantly, these factors also exert a strong influence on participation, adherence, and response to rehabilitation interventions, making them central to any precision-based CR framework.

Depression affects approximately 20–30% of patients entering CR and has been consistently linked to poorer functional improvement and reduced program completion. Mechanistically, depression is associated with autonomic dysregulation, heightened

inflammatory activity, and impaired motivation, all of which may blunt the physiological benefits of exercise training. Standardized CR programs typically offer generic psychosocial support; however, evidence suggests that patients with clinically significant depressive symptoms may require targeted interventions, such as structured cognitive-behavioral therapy or collaborative care models, to fully benefit from rehabilitation (Blumenthal et al., 2012).

Anxiety and stress-related phenotypes further contribute to heterogeneity in CR outcomes. Elevated anxiety levels may limit exercise tolerance through heightened sympathetic activation and exaggerated cardiovascular responses to physical exertion. In some patients, fear of exertion or recurrent cardiac events leads to avoidance behaviors that undermine training effectiveness. Precision-oriented CR acknowledges these differences by integrating psychological assessment into baseline evaluation and tailoring educational and behavioral strategies accordingly, rather than applying uniform reassurance and counseling approaches (Celano et al., 2016).

Behavioral change itself is not a uniform process. Patients differ markedly in readiness to change, self-efficacy, and motivational drivers. The application of behavioral science frameworks, such as the transtheoretical model of change, allows stratification of patients according to their stage of readiness and supports the delivery of stage-appropriate interventions. Studies have demonstrated that CR programs incorporating individualized goal setting and motivational interviewing achieve higher adherence and more sustained lifestyle modification than those relying on standardized educational content alone (Miller et al., 1997).

Socioeconomic and cultural contexts represent additional layers of behavioral heterogeneity. Lower socioeconomic status,

limited social support, and competing life demands are powerful predictors of non-participation and dropout from CR. Precision CR does not imply intensive intervention for all patients, but rather the identification of those at highest risk of disengagement and the allocation of targeted resources, such as flexible scheduling, tele-based support, or community-linked programs, to mitigate these barriers (Turk-Adawi et al., 2019).

Collectively, these observations underscore that psychosocial and behavioral factors are not ancillary components of cardiac rehabilitation but integral determinants of its success. Incorporating systematic psychosocial phenotyping into CR assessment aligns with precision medicine principles by enabling the delivery of the right behavioral intervention to the right patient, thereby enhancing both clinical effectiveness and real-world impact (Whooley et al., 2008).

Implementation Challenges and Ethical Considerations

While the integration of precision medicine into cardiac rehabilitation holds clear conceptual and clinical appeal, its implementation in routine practice is accompanied by substantial challenges. These challenges are not limited to technological or logistical barriers but extend to ethical, economic, and organizational domains that must be addressed to ensure equitable and sustainable adoption.

One of the principal challenges is the integration and interpretation of complex, multidimensional data. Precision-oriented CR relies on the combination of clinical variables, physiological measurements, biomarkers, and digital health data. In many healthcare systems, these data sources remain fragmented across electronic health records, wearable platforms, and laboratory databases. The lack of standardized data infrastructure complicates clinical decision-making and increases the risk of information

overload without clear actionability. For precision CR to be feasible, data must be translated into simple, clinically meaningful metrics that can guide exercise prescription and behavioral interventions without increasing clinician burden (Topol, 2019).

Cost-effectiveness represents another critical concern. Genetic testing, advanced biomarker profiling, and digital monitoring technologies may increase upfront costs, raising questions about value in comparison with conventional CR models. Although precision approaches may ultimately improve outcomes and reduce rehospitalizations, robust health economic data specific to CR are limited. Without clear evidence of cost-effectiveness, widespread implementation may be restricted to well-resourced centers, potentially widening existing disparities in access to rehabilitation services (Phillips et al., 2018).

Equity and access are closely linked ethical considerations. Cardiac rehabilitation already suffers from unequal participation across socioeconomic, geographic, and demographic groups. Precision medicine–based CR risks exacerbating these inequalities if advanced technologies and individualized interventions are preferentially available to patients with higher health literacy or financial means. Ethical implementation requires that precision strategies be designed to enhance inclusivity, for example by using tele-rehabilitation to reach underserved populations rather than reinforcing existing barriers (Castellanos et al., 2019).

Data privacy and patient autonomy also warrant careful consideration. Continuous monitoring through wearable devices and digital platforms generates large volumes of sensitive personal health data. Ensuring data security, transparent consent processes, and patient control over data use is essential to maintaining trust. Moreover, patients should be engaged as active partners in precision CR, with clear communication about how individualized data inform rehabilitation decisions, rather than perceiving such

approaches as opaque or overly technical (Rumbold, & Pierscionek, 2017).

Finally, the absence of standardized guidelines for precision-based CR limits consistent implementation. Current rehabilitation guidelines emphasize safety and efficacy but provide limited direction on incorporating biomarkers, digital data, or phenotypic stratification into program design. Bridging this gap will require prospective studies, pragmatic trials, and consensus-building efforts that translate emerging evidence into practical recommendations. Addressing these challenges is essential if precision medicine is to move from a theoretical construct to a clinically meaningful advancement in cardiac rehabilitation (Arena et al., 2012).

Future Perspectives

The future of cardiac rehabilitation in the era of precision medicine is closely linked to advances in data science, digital health, and systems-based care models. As the volume and diversity of patient-specific data continue to expand, the central challenge will shift from data acquisition to meaningful integration and clinical translation. In this context, artificial intelligence (AI) and machine learning techniques are expected to play a pivotal role by identifying complex patterns across clinical, physiological, biomarker, and behavioral domains that are not readily apparent through conventional analytic approaches.

AI-driven models have already demonstrated potential in cardiovascular risk prediction, imaging interpretation, and outcome forecasting. Extending these tools to cardiac rehabilitation could enable dynamic, adaptive exercise prescriptions that evolve in response to real-time physiological feedback and longitudinal trends rather than fixed program durations or predefined intensity thresholds. Such approaches may allow early identification of non-

responders, facilitate timely modification of training strategies, and optimize resource allocation by directing more intensive interventions to patients with the greatest potential benefit (Deo, 2015).

Another important future direction is the development of learning health systems within cardiac rehabilitation. In this model, data generated during routine clinical care are continuously analyzed and fed back into practice to refine decision-making and improve outcomes. Cardiac rehabilitation programs are particularly well suited to this approach due to their structured follow-up, repeated assessments, and emphasis on measurable functional outcomes. Over time, aggregated data from diverse patient populations could inform evidence-based personalization algorithms and support the transition from protocol-driven to data-adaptive rehabilitation pathways (Friedman, Wong, & Blumenthal, 2010).

Integration of precision-based CR into clinical guidelines represents a further step toward widespread adoption. Current guidelines emphasize eligibility, safety, and general efficacy but provide limited guidance on tailoring rehabilitation according to biological or behavioral phenotypes. As prospective studies and pragmatic trials generate stronger evidence, future guideline updates may incorporate recommendations on the use of physiological metrics, digital monitoring, and patient-reported outcomes to individualize rehabilitation intensity and modality. This evolution would align CR with broader trends in preventive cardiology and chronic disease management (Timmis et al., 2020) (Table 3).

Table 3. Future Directions and Challenges in Precision Medicine–Based Cardiac Rehabilitation

Area	Opportunities	Challenges
Artificial intelligence	Adaptive exercise prescriptions, response prediction	Data quality, interpretability
Digital health integration	Real-time monitoring and feedback	Data overload, interoperability
Tele-rehabilitation	Improved access and participation	Digital literacy, equity
Biomarker-guided CR	Enhanced risk stratification	Cost-effectiveness, validation
Guideline incorporation	Standardization of precision approaches	Limited prospective evidence
Ethical considerations	Patient-centered, data-driven care	Privacy, access disparities

Abbreviations: CR: cardiac rehabilitation; AI: artificial intelligence.

Patient engagement and shared decision-making are also likely to gain prominence in next-generation CR models. Precision medicine does not imply algorithm-driven care in isolation, but rather informed collaboration between clinicians and patients. Providing patients with understandable feedback derived from their own data may enhance motivation, adherence, and long-term self-management, which remain critical determinants of sustained benefit beyond the formal rehabilitation period (Hibbard, & Greene, 2013).

Ultimately, the success of precision medicine–based cardiac rehabilitation will depend on balancing innovation with pragmatism. Technologies and analytical tools must be implemented in a way that enhances, rather than complicates, clinical workflows and preserves the core principles of accessibility, safety, and equity. If these conditions are met, precision-oriented CR has the potential to transform rehabilitation from a standardized intervention into a responsive, learning system capable of delivering durable cardiovascular benefit across diverse patient populations (Khadanga et al., 2024).

Conclusion

Cardiac rehabilitation has long been recognized as a cornerstone of secondary prevention in cardiovascular disease, with robust evidence supporting its benefits on mortality, morbidity, functional capacity, and quality of life. Nevertheless, conventional rehabilitation models have largely relied on standardized protocols that insufficiently address the marked biological, clinical, and behavioral heterogeneity of contemporary cardiac populations. As cardiovascular medicine increasingly embraces precision-based paradigms, the limitations of a uniform approach to rehabilitation have become more apparent.

This narrative review highlights that precision medicine offers a coherent and scientifically grounded framework to evolve cardiac rehabilitation from protocol-driven programs toward more individualized, data-informed interventions. Variability in exercise response, influenced by genetic background, phenotypic characteristics, autonomic function, inflammatory status, and psychosocial context, provides a strong rationale for tailoring rehabilitation strategies beyond traditional risk categories. Advances in biomarkers, wearable technologies, and digital health platforms further support this transition by enabling continuous monitoring, adaptive training prescriptions, and flexible models of care delivery.

Importantly, precision-based cardiac rehabilitation should not be interpreted as a departure from established principles of safety, accessibility, and multidisciplinary care. Rather, it represents a refinement of these principles, aiming to align the type, intensity, and mode of rehabilitation with patient-specific characteristics and needs. Such an approach has the potential not only to enhance physiological effectiveness but also to improve participation, adherence, and long-term lifestyle modification, which remain critical challenges in real-world practice.

Future progress will depend on the generation of prospective evidence, the development of pragmatic implementation strategies, and the incorporation of precision concepts into clinical guidelines. Equally important will be ensuring that innovation does not exacerbate existing disparities in access to rehabilitation services. If implemented thoughtfully, precision medicine–based cardiac rehabilitation may represent a transformative step toward more responsive, equitable, and effective secondary prevention for patients with cardiovascular disease.

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CHAPTER 3

CLINICAL EXPERIENCE OF ARTERIOVENOUS FISTULAS FOR HEMODIALYSIS

EMCED KHALİL[1]

INTRODUCTION

Patients with end-stage renal disease require accurate and effective vascular access for hemodialysis. Autogenous arteriovenous fistula (AVF) remains the optimal method for dialysis access, as supported by the National Kidney Foundation Department Outcomes Quality Initiative guidelines (1). AVFs are typically created distally or proximally in the non-dominant upper limb. Distal AVFs are created at the wrist or forearm, while proximal AVFs are created at the elbow, especially in obese patients. Preoperative imaging with color Doppler ultrasound or venography aids in assessing vein suitability and accessibility (2,3). .

METHOD

A total of 49 patients presented to the cardiovascular surgery clinic at Ordu University Research and Education Hospital between January 2022 and January 2023 for AVF creation. Patients were

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randomly divided into two groups: Group A (distal AVF) and Group B (proximal AVF). All underwent clinical evaluation and preoperative duplex scanning (4,5). Patients with inadequate superficial vein flow, previous AVF at the same site, or unwillingness to participate were excluded. AVFs were created under local anesthesia by an experienced vascular surgeon using magnifying loops. Functional maturation followed Kidney Disease Outcome Quality Initiative (KDOQI) criteria (1).

RESULTS

Technical success was achieved in 47 of 49 patients (96%). Two failures occurred due to subcutaneous hematoma and irreversible thrombosis: Group A (n=27) had all patients who had distal AVF and Group B (n=22) who had AVF created proximally at the elbow. There was no statistically significant difference in the two groups (Table 1). No statistically significant differences were found between groups in age, gender, or comorbidities. Patency rates at 6 and 12 months were similar between distal and proximal AVFs (6,7).Group A (distal) had 92.6% and 70.4% patency, while Group B (proximal) had 86.4% and 72.3%, respectively.

Table 1. Baseline characteristics, risk factors, and patency rates.

Variable	Total (n = 49)	Group A (n = 27)	Group B (n = 22)	P-value
Mean Age (years)	58.9 ± 15.2	55.7 ± 16.6	62.7 ± 13.6	0.334
Gender (F/M)	22/27	10/17	12/10	0.220
BMI	27.19 ± 6.15	23.22 ± 1.52	32.05 ± 6.54	<0.001
Diabetes + HT	17 (34.7%)	9 (33.3%)	8 (36.4%)	0.209
Complications	5 (10.2%)	2 (7.4%)	3 (13.6%)	0.436
Patency (6 months)	44 (89.8%)	25 (92.6%)	19 (86.4%)	0.646
Patency (12 months)	35 (71.4%)	19 (70.4%)	16 (72.7%)	0.856

DISCUSSION

AVFs are the preferred vascular access for hemodialysis, offering superior long-term patency compared to grafts or catheters (8). However, factors such as obesity, diabetes, and vascular disease may affect fistula maturation (9). This study confirmed that proximal AVFs provide reliable outcomes in patients with multiple comorbidities or deep superficial veins(10) . Surgeons' skill and experience significantly influence AVF success, underscoring the importance of proper training and technique (2,3,5) .

CONCLUSION

Enhanced surgical experience contributes to improved AVF patency. Proximal AVF creation should be the primary choice in patients with multiple comorbidities to ensure long-term vascular access success.

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