College of Pharmaceutical Sciences and Drug Manufacturing
A college accredited by "NAQAAE"

Journal of Pharmaceutical Sciences and Drug Manufacturing
ISSN: 3009-6553 (Print)
ISSN: 3009-6677 (Online)

JPSDM

Section D: Pharmacology, Toxicology, and Biochemistry.

Review Article

Recently Identified MicroRNAs as Potential Diagnostic and Prognostic Biomarkers in Acute coronary syndrome

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Received: 4 June 2025
Accepted: 19 June 2025
Published: 27 June 2025

Editors
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Keywords
MicroRNAs
Biomarkers
Acute coronary syndrome
Acute myocardial infarction
Unstable angina pectoris.

Abstract

Background: Cardiovascular diseases (CVDs) remain the most prevalent cause of mortality globally. Acute coronary syndrome (ACS) is a category of CVDS with a high fatality rate. Thus, early diagnosis and effective management of ACS are crucial to improve patient outcomes. Biomarkers, which are measurable biological indicators, have emerged as essential tools for the diagnosis, prognosis, and risk stratification of ACS. Recently, small non-coding RNAs (miRs) have been found to affect messenger RNA (mRNA) stability by either suppressing their translation or promoting their degradation through complementary base pairing, thereby acting as negative regulators of protein translation. Moreover, miRs play a key role in regulating various signaling pathways and cellular functions, including intercellular communication.

Aim and concept of review: Since miRs expression has been identified in the blood of patients with various cardiovascular conditions, they are regarded as promising noninvasive biomarkers. This study provides an overview of the existing literature on the role of miRs in ACS.

Conclusion: The findings suggest that miRs could serve as potential diagnostic and prognostic biomarkers in ACS, and hence, miR regulation may offer new perspectives for therapeutic interventions in ACS.

1. Introduction

Acute coronary syndrome (ACS) encompasses a range of conditions, including angina and myocardial infarction, resulting from decreased coronary blood flow due to atherosclerosis and/or thrombosis. ACS is characterized by clinical symptoms such as chest pain, dyspnea, and arrhythmia, which arise from myocardial tissue ischemia [1]. Acute myocardial infarction (AMI) is characterized by irreversible myocardial necrosis caused by severe or persistent ischemia. It is further classified into ST-segment elevation myocardial infarction (STEMI) and non-ST- segment elevation myocardial infarction (NSTEMI). Unstable angina (UA) is mainly caused by coronary stenosis caused by plaque ruptures, dilated blood vessels, or from collateral circulation. AMI and UP, termed ACS, share the same pathogenic mechanisms, and their treatments have important similarities [2].

AMI is often associated with intense inflammation, oxidative stress, cell apoptosis, fibrosis, reactive hypertrophy, and other pathological changes that affect the myocardium following the restoration of coronary blood flow [3]. The occurrence of ACS is mainly associated with the vulnerable plaques in the coronary arteries. Vulnerable plaque refers to atherosclerotic plaque that is more susceptible to breakage in response to internal or external factors, leading to the formation of a thrombus and vascular occlusion and hence acute clinical events such as myocardial infarction or sudden death [4]. The determinant of plaque vulnerability is plaque structure. The fibrous cap, fibrous thickness, rich lipid content, cap collapse, surface irregularity, calcification, and infiltration of macrophages are all markers of vulnerable plaques. There are current methods used to detect plaque vulnerability, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT). OCT is the highest resolution imaging technique in current clinical medical images, with the axial resolution of 4-20μm. This technique is effective in identifying the rich lipid content, fibrous cap, and macrophages in the plaque, which are the main characteristics of vulnerable plaques in the coronary artery in vivo [5]. Without timely intervention, these events can cause ischemic injury and cardiomyocyte necrosis, posing a significant risk to patient survival [6]. Despite advances in management, ACS remains a leading cause of global cardiovascular mortality, accounting for over 15% of cardiovascular deaths in regions like in Egypt and other Middle East countries [7]. This highlights the need for improved early, accurate, and effective diagnostic and prognostic approaches for ACS management [8].

MicroRNAs (miRs) are a class of endogenous and highly conserved small RNA molecules that are 18-22 nucleotides long and negatively influence gene expression at the post-transcriptional level. miRs bind to the 3′ untranslated region (3′UTR) of the target messenger RNA (mRNA) for degradation and translational repression. miRs play an important role in cell proliferation, differentiation, development, apoptosis, angiogenesis, and invasion [9,10]. MiRs have been extensively studied in various physiological and pathological processes, and their expression profiles in specific diseases suggest distinct roles in development and progression. Emerging evidence has highlighted the role of miRs as potential key biomarkers in ACS [11–13].

In recent years, miRs have gained significant attention across diverse research fields. To date, over 2000 distinct miRs have been identified, many of which are implicated in either promoting or inhibiting the progression of ACS [14]. Recent studies have found that miR-21 is widely

expressed in cardiovascular diseases, particularly AMI. MiRs have been detected in intracardiac blood, in which they can circulate stably and are used as new diagnostic markers for cardiovascular diseases [15].

2. Overview of MicroRNAs (miRs)

MicroRNAs (miRs) are important and highly conserved regulators of gene expression. In animals, they are ~22-nucleotide-long, single-stranded, non-coding RNAs that bind to target mRNAs, resulting in mRNA degradation or translational repression. miRs regulate over 60% of eukaryotic genes and modulate multiple biological processes, including organ development, metabolism, and cellular processes [16]. MiRs play key roles in human diseases, including cancer and cardiovascular disorders [11,13].

MiRs are detectable in the blood and are released into the blood by various cells under physiological and pathological conditions. Both intracellular and extracellular miRs in blood are stable and can withstand prolonged storage at room temperature. Recent studies have suggested that circulating miRs are useful diagnostic and prognostic markers of several systemic diseases, including cardiovascular diseases [15,17]. Aberrant expression of circulating miRs has been demonstrated in patients with ACS. Studies assessing circulating miRs as biomarkers of diagnosis, prediction, prognosis, and reaction to therapy for ACS include various dysregulated circulating miRs in diseases. Some are potential blood-based biomarkers, but only a few are beyond the early validation phase [15].

MiR-1, miR-208a, and miR-499 are up-regulated minutes after a myocardial infarction (MI) and are increased in the presence of left ventricular (LV) dysfunction. miR-1, miR-21, and miR-146 increased with angina. miR-1, miR-499, and miR-208a enhance the diagnostic value of high-sensitivity troponin T. miR-126 was up-regulated at 6 h in MI patients, and in an animal model of MI. After MI, circulating levels of miR-155 were higher in acute MI patients who died within 1 year after discharge. Mechanical treatment was associated with circulating miRs [18–20]. MiR-194 and miR-34a correlated well with LV end-diastolic dimension 30 days after MI. miR-139-3p up-regulation is associated with acute coronary artery occlusion. In chronic instability, at risk of death from spontaneous coronary arterial dissection, miR-133a, miR-499-5p, and miR-208b were up-regulated but lost their independent association with the outcome after adjusting for high sensitivity (hs)-troponin T. Chronic bradycardia was identified by measuring miR-423-5p. In MI, free circulating miR-150 predicted LV function and remodeling after 3 months. Platelet miRs, including miR-223, miR-191, miR-126, and miR-150, were decreased upon platelet inhibition. This suggests the possibility of using circulating miRs as monitors of therapeutic efficiency [21–23].

3. MiR biogenesis and mechanism of action

MicroRNA biogenesis occurs in two stages: transcription in the nucleus and cytoplasmic processing. In the nucleus, transcription by RNA polymerase II (or occasionally RNA polymerase III), produces long primary transcripts (pri-miRs), which are typically over 1,000 nucleotides in length and comprise a 33–35 nucleotide stem, a terminal loop, and two flanking single-stranded RNA (ssRNA) regions [24]. Depending on their genomic context, miRs are classified as intergenic or intragenic. Intergenic miRs, originating from noncoding regions between genes, possess independent promoter regions. In contrast, intragenic miRs are embedded within exons or introns of

protein-coding genes, are transcribed by RNA polymerase II, and are generally co-expressed with their host genes [25]. MiR biogenesis proceeds via either canonical or non-canonical pathways [26].

3.1. The canonical pathway

The canonical miR biogenesis pathway is the primary route through which microRNAs are produced [27]. It begins with the transcription of primary miRs (pri-miRs) from miR genes [28]. These pri-miRs are then processed in the nucleus by a protein complex known as the microprocessor, which includes the RNA-binding protein DGCR8 (DiGeorge Syndrome Critical Region 8) and the RNase III enzyme Drosha. DGCR8 identifies specific sequence motifs within the pri-miR, such as N6-methyladenylated GGAC, where Drosha cleaves the base of the hairpin structure, producing a pre-miR with a two-nucleotide overhang at the 3′ end [29]. The pre-miR is then transported from the nucleus to the cytoplasm by the exportin 5 (XPO5)/RanGTP complex [30]. In the cytoplasm, Dicer, another RNase III endonuclease, removes the loop region of the pre-miR to form a short double-stranded miR duplex [31].

This duplex consisted of two strands: the 5p strand, originating from the 5′ end of the pre-miR, and the 3p strand, derived from the 3′ end. Both strands have the potential to be incorporated into Argonaute (AGO) proteins; specifically, AGO1 through AGO4 in humans; in an ATP-dependent process. The proportion of 5p versus 3p strand incorporation can vary significantly between cell types and conditions, ranging from nearly equal amounts to a clear preference for a single strand [32]. Strand selection is influenced by the stability of the 5′ ends and the presence of uracil (U) at the first nucleotide. Generally, strands with less stable 5′ end pairing or 5′ U are more likely to be loaded into the AGO as the guide strand, which then directs gene silencing. The other strand, known as the passenger strand, is typically unwound and degraded. If the strands are fully complementary, the passenger strand is cleaved by AGO2, leading to efficient degradation and a strong strand bias. In contrast, duplexes with central mismatches or those not loaded into AGO2 were unwound through other mechanisms and were degraded more passively [33], **(Fig .1)**.

3.2. Non-canonical pathways

Non-canonical miR biogenesis pathways also utilize components of the canonical pathway and are generally classified as either Drosha/DGCR8-independent or Dicer-independent [34]. In Drosha/DGCR8-independent pathways, miRs known as miRtrons are derived from introns of protein-coding genes via splicing machinery, bypassing Drosha processing. These miRtrons correlate with the expression of their host genes and are subsequently exported to the cytoplasm, where they are processed by Dicer [24]. In contrast, Dicer-independent pathways involve Drosha-mediated processing of endogenous short hairpin RNAs (shRNAs) into pre-miRs that are too short for Dicer. Instead, these pre-miRs are directly loaded into AGO2, which cleaves the 3p strand. Final maturation involves 3′–5′ trimming of the 5p strand within the AGO2 [35].

4. Mechanistic Overview of miRs in ACS

In heart disease, peripheral vascular disease, subacute myocardial infarction, or sudden cardiac death, atherosclerosis (AS) is closely related to one or several ruptured plaques have grown for decades [1]. The structural integrity of atherosclerotic plaques depends heavily on the fibrous cap, a protective layer composed

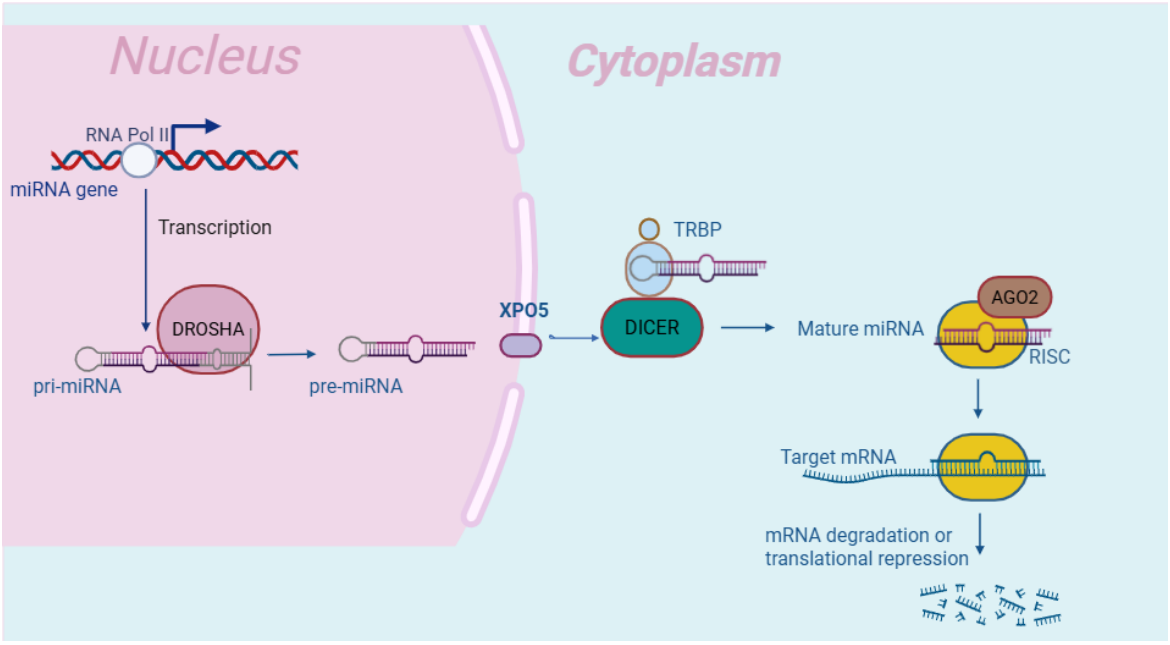

Fig.1. MiR Biogenesis; Simple Illustration for Canonical Pathway.

MiRs are initially transcribed by RNA polymerase II into primary miR transcripts (pri-miR). These pri-miRs are then processed into precursor miRs (pre-miRs) by the Drosha-containing microprocessor complex. The pre-miRs are transported from the nucleus to the cytoplasm via exportin-5 (XP05), where Dicer cleaves them into double-stranded miR molecules. Once incorporated into the RNA-induced silencing complex (RISC), the Argonaute protein (AGO) separates the strands. The guide (mature) strand remains bound to RISC to interact with target mRNAs for gene regulation, while the passenger strand is degraded.

primarily of vascular smooth muscle cells (VSMCs). These cells play a critical role in maintaining plaque stability by effectively containing an underlying lipid core. However, when VSMCs undergo programmed cell death triggered by inflammatory mediators or reactive oxygen species, this protective barrier becomes compromised. The resulting structural weakness significantly increased the vulnerability of the plaque to rupture [36]. Among the various molecular regulators of this process, miR-21 has emerged as a particularly noteworthy one. Although initially characterized by its oncogenic properties in certain malignancies, this small non-coding RNA demonstrates remarkable cardioprotective capabilities. Its most prominent function appears to be enhancing cellular resistance to oxidative damage, a characteristic that warrants further deeper investigation into its potential influence on plaque destabilization mechanisms [36–38].

Genetic studies of premature atherosclerosis cases have revealed multiple pathogenic variants affecting the low-density lipoprotein receptor (LDLR) structure. These mutations impair the receptor's binding capacity for ApoB-associated lipoproteins and disrupt the normal cellular uptake mechanisms. Consequently, defective LDLR function results in the abnormal accumulation of cholesterol-rich remnants in the circulation [39]. Persistent elevation of remnant lipoproteins creates a pro-inflammatory state that promotes vascular dysfunction. Phagocytic cells engulf these lipid particles, transforming them into foam cells that release pro-inflammatory cytokines including interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1. This cytokine milieu stimulates vascular smooth muscle cell activation and enhances monocyte recruitment, which drives the formation of characteristic lipid-laden lesions. Interestingly, animal models on a high-fat diet typically

develop only early-stage atherosclerotic changes rather than complex plaques. The transition to vulnerable plaques appears to require additional factors, particularly oxidative damage, which weakens the protective fibrous cap. Ultimately, plaque destabilization triggers acute thrombotic complications through amplified inflammatory pathways and coagulation activation [40,41].

4.1. Regulation of endothelial function

The vascular endothelium forms a dynamic interface between the blood and tissues, actively regulating vascular homeostasis rather than serving as a passive barrier [42]. Endothelial dysfunction, marked by reduced nitric oxide (NO) bioavailability, is a key initiating factor in vascular pathologies [43]. Hemodynamic shear stress, particularly laminar flow, critically influences endothelial behavior and protects against atherosclerosis [44]. MiRs mediate the endothelial response to shear stress. The miR-143/145 cluster and miR-20 family attenuate inflammation and atherosclerosis by suppressing proinflammatory pathways [45]. Recent studies have identified novel flow-sensitive miRs that modulate plaque development [46]. Genetic and pharmacological studies have confirmed that miRs are central regulators of shear-stress responses and vascular disease progression [47].

Laminar shear stress promotes endothelial health through, a) homeostasis maintenance that sustains NO production, b) anti-inflammatory effects resulting in suppression of adhesion molecules, and c) plaque stability leading to modulation of the extracellular matrix (ECM) [48]. Endothelial miRs act as mechanosensitive regulators, that transduce shear stress into changes in gene expression. Dysregulation of these miRs contributes to hypertension and atherosclerosis [49], thereby highlighting their therapeutic potential.

4.2. Platelet activation

Circulating platelets, with their characteristic 10-day lifespan, originate from bone marrow megakaryocytes before entering the bloodstream as anucleate cell fragments [50]. Despite their lack of nuclei, these dynamic cells maintain significant biosynthetic capacity, enabling the production of proteins, eicosanoids, and regulatory miRs [51]. This unexpected complexity allows platelets to actively participate in both physiological hemostasis and pathological thrombosis [52]. Among their regulatory molecules, miRs have emerged as particularly important modulators of platelet function, with growing evidence implicating them in the pathogenesis of cardiovascular disease. MiRs influence multiple aspects of platelet biology, including activation thresholds [53], aggregation responses [54], and thrombus stability [55]. In the context of ACS, dysregulation of platelet-specific miRs appears particularly significant. For instance, miR-223-3p, one of the most abundant platelet miRs, regulates critical processes ranging from megakaryocyte maturation [56] to P2Y12 receptor expression [57] and platelet reactivity [58]. These regulatory functions become clinically relevant when considering that ACS patients demonstrate altered platelet miR profiles compared to healthy controls, with specific upregulated species showing excellent diagnostic discrimination [59].

The pathophysiological significance of platelet miRs extends to their modulation of thromboxane A2 (TXA2) signaling pathways, which are known to be hyperactive in ACS [60]. This hyperactivity manifests as enhanced platelet aggregation responses to TXA2 receptor agonists, a characteristic feature of ACS pathophysiology. While

current research has identified several candidate miRs associated with these processes, including six consistently upregulated species in ACS patients, the complete mechanistic picture remains incomplete [61]. This knowledge gap presents both a challenge and an opportunity that understanding these regulatory networks could lead to novel diagnostic approaches, improved risk stratification tools, and potentially new therapeutic targets for ACS management. The continued investigation of platelet miRs promises to provide valuable insights into the molecular basis of acute thrombotic events and may yield clinically useful biomarkers for monitoring antiplatelet therapy efficacy.

4.3. Cardiac apoptosis, fibrosis and hypertrophy

The pathophysiology of AMI involves a complex interplay of ischemic cardiomyocyte injury, inflammatory activation, and subsequent tissue remodeling processes. Following coronary occlusion, the initial ischemic insult triggers cardiomyocyte apoptosis and necrosis through oxygen deprivation and metabolic dysfunction [62]. Cellular damage initiates a robust inflammatory cascade characterized by neutrophil infiltration and cytokine release that mediates both tissue clearance and reparative fibrosis [63]. While essential for wound healing, this inflammatory-fibrotic response can progress maladaptively, leading to excessive ECM deposition and ventricular wall stiffening that impairs cardiac function [64]. Emerging research has identified miRs as critical regulators of post-AMI remodeling processes, with specific miR families demonstrating distinct roles in modulating cardiomyocyte survival, inflammatory responses, and fibrotic pathways [65].

Recent studies have elucidated several key miR-mediated regulatory mechanisms involved in cardiac remodeling. The miR-30 family, particularly miR-30d, has shown cardioprotective effects by attenuating cardiomyocyte apoptosis during ischemia, though its precise molecular targets remain controversial [66]. Inflammatory modulation appears to be differentially regulated by various miRs, with miR-29 and miR-21 suppressing macrophage activation, where miR-155 promotes pro-inflammatory cytokine production [67]. Particularly noteworthy is miR-30b-5p, which exerts potent anti-fibrotic effects by directly targeting the platelet-activating factor receptor (PTAFR) and carboxypeptidase M in cardiac fibroblasts, thereby inhibiting transforming growth factor (TGF)-β1-induced phenotypic transition and extracellular matrix production [68]. Experimental models have demonstrated that miR-30b-5p overexpression reduces fibrotic gene expression by over 40% in vitro and significantly attenuate ventricular remodeling in vivo [69].

Technological advancements in miR profiling have enabled the development of novel approaches to studying these regulatory networks. Innovative techniques, such as endogenous miR-based gene trapping systems have revealed unexpected connections between cardiac remodeling and systemic metabolic regulation [70]. For instance, GATA4-mediated miR signaling has been shown to coordinately regulate both cardiac fibroblast proliferation and hypothalamic metabolic control, suggesting an integrated cross-talk between cardiac repair mechanisms and whole-body energy homeostasis [71]. These findings highlight the therapeutic potential of miR modulation, though significant challenges remain in developing clinically viable delivery systems that ensure tissue specificity and minimize off-target effects [72]. Current research efforts focus on nanoparticle-based delivery platforms and targeted modification of

endogenous miR expressions to harness these regulatory molecules to prevent adverse post-AMI remodeling while preserving essential cardiac repair mechanisms.

5. MiRs and endothelial dysfunction

The development of ACS stems from progressive atherosclerotic changes in the coronary arteries, which are characterized by endothelial dysfunction, vascular inflammation, and plaque destabilization [73]. Atherosclerosis represents a chronic inflammatory condition involving complex interactions between vascular cells, lipids, and immune components that ultimately lead to fibroatheroma formation and plaque progression [74]. Despite advances in preventive therapies including statins, many patients experience residual cardiovascular risk, highlighting the need for better biomarkers and targeted treatments [75]. Recent research has identified miRs as crucial regulators of endothelial function through the modulation of key vascular signaling pathways [76]. The NO-cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) signaling axis, which maintains endothelial integrity and regulates vascular tone, is central to vascular homeostasis [77]. NO-stimulated cGMP production activates PKG, leading to phosphorylation of downstream targets that promote vasodilation and endothelial protection [78]. Several miRs have been shown to critically influence this pathway: miR-24 and miR-103 directly target PKGI, reducing cGMP availability and impairing vasorelaxation [79], whereas members of the miR-20 family (miR-20a/b) attenuate PKG phosphorylation, thereby enhancing angiotensin II-induced vasoconstriction [80]. Additionally, miR-218 isoforms regulate endothelin-1 and tumor necrosis factor-α (TNF-α) production, thereby significantly impacting endothelial function in diabetic conditions [81].

These miR-mediated effects substantially contribute to endothelial dysfunction in ACS through multiple mechanisms. Elevated expressions of miR-24 and miR-103 in atherosclerotic plaques promote pro-inflammatory M1 macrophage polarization while suppressing anti-inflammatory M2 phenotypes [82]. Experimental inhibition of these miRs has been shown to restore endothelial function and reduce plaque formation in animal models [83]. Similarly, the miR-327-sirtuin-1 axis plays an important role in endothelial homeostasis, and miR-327 overexpression impairs NO bioavailability [84]. Plaque erosion, which is responsible for approximately 30% of ACS cases, demonstrates distinct miR profiles compared with rupture-prone plaques [85]. Erosion-prone lesions exhibit several characteristic features, including enhanced endothelial apoptosis (showing a 2.8-fold increase compared to stable plaques), reduced collagen content (42% decrease versus ruptured plaques), and unique miR signatures including upregulated miR-145 and downregulated miR-92a [81]. These molecular differences indicate the potential for miR-based diagnostic and therapeutic approaches.

Preclinical studies have shown promising results for miR-targeted therapy. Administration of locked nucleic acid (LNA)-modified anti-miRs against miR-103 improves endothelial-dependent vasodilation by 65% in hypercholesterolemic mice [86]. Similarly, miR-20b inhibition restores flow-mediated dilation by 40% in hyperhomocysteinemic models [80]. These findings highlight the translational potential of miR-based interventions for ACS prevention and treatment, although

challenges remain in terms of delivery specificity and long-term safety.

6. Inflammatory pathways modulated by miRs

ACS arises from multiple pathogenic mechanisms, including vascular dysfunction, inflammatory processes, and metabolic disturbances, and ultimately results in plaque destabilization, thrombus formation, and impaired cardiac blood flow [87]. Emerging research highlights the involvement of miRs in modulating these pathways through epigenetic regulation, with particular relevance to metabolic disorders and cardiovascular pathologies[88,89]. Despite growing evidence of their association with ACS, the clinical applications of miRs remain an area of ongoing investigation [90]. This interaction suppresses protein translation and triggers mRNA degradation. Through protein translation suppression or triggering mRNA degradation, miRs influence diverse cellular processes such as growth, programmed cell death, energy metabolism, and inflammatory responses, contributing to the pathogenesis of various conditions, including malignancies and heart disease [91,92].

A key advantage of miRs is their detectability in bodily fluids, such as serum and plasma, where they show distinct expression patterns in different diseases, including cardiovascular disorders [93]. Certain miRs have demonstrated potential as diagnostic and prognostic indicators in oncology [25], and similar applications are being explored in cardiology [94]. For instance, miR-3646 has been implicated in ACS, where it appears to drive vascular inflammation and enhance the motility of vascular smooth muscle cells, and processes linked to coronary artery disease progression [95]. However, the precise role of miR-3646 in ACS pathogenesis, however, requires further elucidation. Elevated plasma concentrations of miR-3646 are strongly correlated with total cholesterol, low-density lipoprotein, and glucose levels [96]**.** Experimental studies have revealed that miR-3646 upregulation stimulates TNF-α production, which in turn elevates interleukin (IL)-1β, IL-6, and additional TNF-α, creating a pro-inflammatory cascade. This effect is mediated through the activation of the NF-κB signaling pathway in VSMCs [97].

Bioinformatic and experimental analyses, including dual-luciferase reporter assays, identified Ras Homolog Family Member H (RHOH) as a direct target of miR-3646 [95]. An inverse relationship exists between miR-3646 and RHOH expression in both ACS patients and TNF-α-stimulated VSMCs [98]. Functional studies have demonstrated that RHOH overexpression counteracts the effects of miR-3646, by suppressing cellular proliferation, migration, and the release of pro-inflammatory cytokines [95]. These findings position RHOH as a promising therapeutic target for the ACS management **(Fig.2).**

6.1. MicroRNA-mediated cytokine regulation in acute coronary syndrome

The inflammatory response plays a pivotal role in ACS pathogenesis, with miRs emerging as critical regulators of this process. Recent studies have identified miR-146 as being particularly significant, demonstrating its strong correlation with inflammatory cytokine levels in ACS patients. This relationship suggests miR-146's potential as both a diagnostic biomarker and therapeutic target, as evidenced by murine models showing reduced myocardial injury following miR-146 inhibition [99,100]. However, key mechanistic questions remain, particularly regarding miR-146's interaction between ADAM10, a protease essential for TNF-α processing, which requires further

investigation to fully understand its role in ACS pathophysiology [101].

Emerging evidence has demonstrated the critical role of specific miR signatures in ACS risk stratification and outcome prediction. For early diagnosis, elevated miR-1, miR-21, and miR-499 significantly enhance the diagnostic accuracy of troponin testing, with detectable elevations within just one hour of symptom onset [18,19]. In the acute phase, miR-155 serves as powerful predictor of adverse outcomes, indicating an increased risk of cardiogenic shock and higher mortality rate [20], whereas miR-126 is likely associated with progressive AMI [102]. For long-term prognosis, the miR-192/194/34a triad demonstrates high sensitivity for predicting six-month heart failure development and left ventricular ejection fraction decline [103,104], whereas miR-150 shows exceptional negative predictive value for favorable remodeling and strongly correlates with one-year survival [105,106]. Dynamic monitoring of these miRNA signatures improves predictive accuracy by 31-45% compared to single measurements, making it a powerful tool for personalized risk assessment. Current clinical trials are actively investigating miR-guided therapeutic protocols, which may soon revolutionize ACS management by enabling more precise, biomarker-directed interventions [107], **(Fig.2).**

6.2. Effect on immune cell recruitment

Circulating miRs, present in both free form and within extracellular vesicles in plasma, have emerged as promising mediators of immune cell recruitment in atherosclerosis. Exosome miRs demonstrate enhanced stability and tissue-specific signatures that may serve as valuable clinical biomarkers[108,109]. Current detection methodologies, including next-generation sequencing and microarray platforms, enable the comprehensive profiling of both high- and low-abundance miR species, providing critical insights into their immunoregulatory functions during plaque development [110]. Despite significant advances in the understanding of miR biology, therapeutic applications face substantial translational challenges, with no FDA-approved miR-targeting therapies currently available for cardiovascular disease [111]. Experimental antisense oligonucleotide approaches show variable duration of biological activity depending on formulation characteristics and administration routes, whereas optimized delivery systems incorporating PEGylation or viral vector strategies demonstrate improved tissue specificity and reduced off-target effects in preclinical models. Critical considerations for therapeutic development include precise control of miR processing enzymes during manufacturing [112], prevention of unintended immune activation through Toll-like receptor pathways [113], and strict adherence to current Good Manufacturing Practice standards [114]. Ongoing translational research continues to address these challenges, with a particular focus on developing targeted delivery mechanisms that balance therapeutic efficacy with acceptable long-term safety profiles for chronic cardiovascular conditions [115]**, (Fig.2).**

7. Cardiac remodeling and miRs

Cardiac remodeling following myocardial injury involves complex genetic reprogramming that significantly alters the myocardial structure and function [116]. The transition from α-myosin heavy chain (α-MHC) to β-myosin heavy chain (β-MHC) expression represents a fundamental molecular switch in this process, with α-MHC predominating in healthy adult cardiomyocytes and β-MHC upregulated under pathological stress conditions,

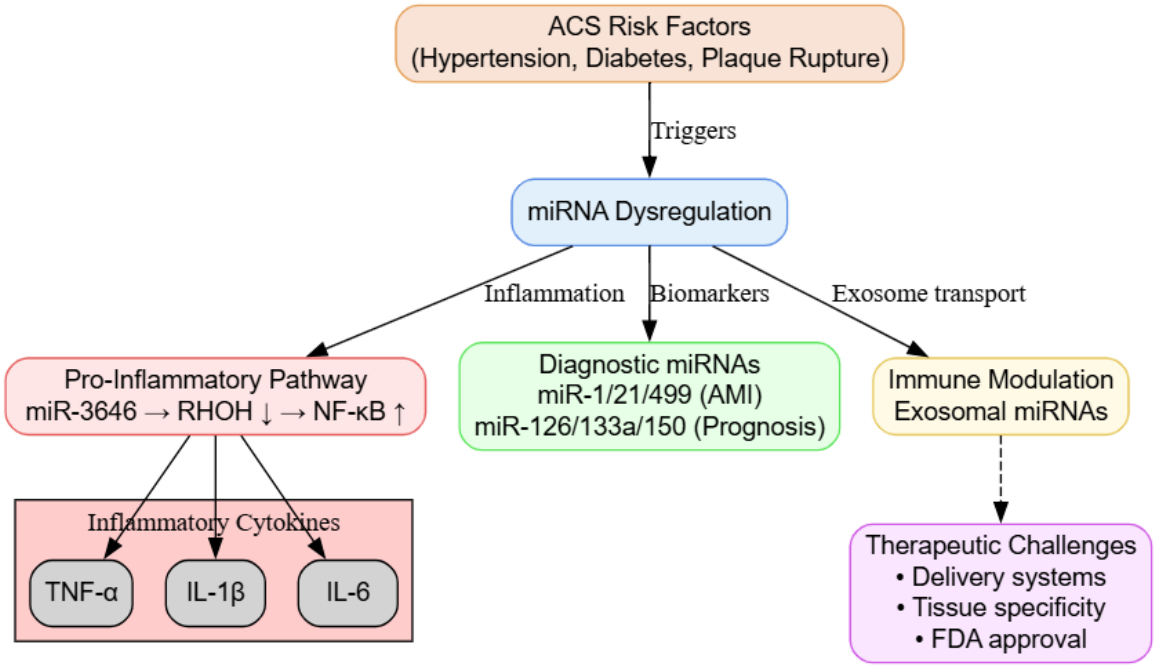

Figure.2. Schematic overview of miRNA-mediated pathways in ACS.

(Top) Established ACS risk factors (hypertension, diabetes, plaque rupture) trigger dysregulation of circulating miRs. **(Center)** Key dysregulated miRs segregate into three functional categories: a) miR-3646 inflammatory pathway (↓RHOH, ↑NF-κB, pro-cytokine release), b) Diagnostic/prognostic miRs: acute MI markers (↑miR-1/21/499) and outcome predictors (↑miR-126/133a/150) and c) Immune modulation via exosomal transport**. (Bottom)** Therapeutic development faces challenges in delivery systems and regulatory approval. **Arrows indicate directional relationships between components.** ACS: acute coronary syndrome, AMI: acute myocardial infarction, IL: interleukin, NF-κB: nuclear factor kappa-B, RHOH: Ras Homolog Family Member H, TNF-α: tumor necrosis factor-alpha.

indicating heart failure progression [117]. This isoform shift, along with other molecular changes, contributes to the progression from adaptive cardiac hypertrophy to maladaptive remodeling and eventual heart failure [118]. Recent advances have identified miRs as crucial epigenetic regulators of these remodeling processes, offering new insights into potential therapeutic targets [119]. The essential role of miR processing in cardiac homeostasis was first demonstrated through studies using cardiac-specific Dicer knockout models. Dicer, an RNase III endonuclease required for miRNA maturation, processes key cardiac miRs including miR-133a, and miR-206 clusters [120]. Genetic deletion of Dicer results in decreased levels of these miRNAs and consequent dysregulation of their ion channel targets, including Scn5a (sodium channel) and potassium channels Kcnq1 and Kcnd2, resulting in severe cardiac arrhythmias and contractile dysfunction [121]. These findings establish the fundamental importance of intact miR processing for normal cardiac electrophysiology function.

Further investigations revealed that the loss of Dicer in adult hearts triggered pathological remodeling characterized by mitochondrial dysfunction, inflammation, and fibrosis. Computational analyses predicted that downregulated miRs collectively regulate hundreds of genes involved in ion channel function,

sarcomeric integrity, mitochondrial metabolism, and protein import pathways. Phenotypically, Dicer-deficient hearts exhibit arrhythmias, slow conduction velocity, hypertrophic growth, and extensive fibrosis. These compelling results have spurred comprehensive studies focusing on specific miRs orchestrating cardiac remodeling processes, underscoring their therapeutic potential [122] **(Fig.3).**

7.1. MiRs in cardiac hypertrophy

Cardiac hypertrophy is a compensatory response triggered by various cardiovascular conditions such as MI, hypertension, aortic stenosis, and cardiomyopathies. Although initially adaptive, pathological hypertrophy often progresses to heart failure, arrhythmias, ischemia, and sudden cardiac death. A hallmark of this condition is the enlargement of cardiomyocytes, which makes it essential to understand the molecular mechanisms to develop effective therapeutic strategies [123]. Several miRs exhibit cardiac-specific expression patterns and have been implicated in heart development and disease. These miRs influence fundamental cardiomyocyte functions such as proliferation and apoptosis and are increasingly recognized as potential biomarkers and therapeutic targets in cardiac pathologies. Notably, certain miRs accumulate during cardiac hypertrophy and modulate the key signaling pathways involved in this process [119,124].

The thyroid hormone signaling pathway also plays a significant role in cardiac hypertrophy. Elevated thyroid hormone levels induce physiological hypertrophy characterized by increased expression of genes such as sarcoplasmic reticulum calcium ATPase (SERCA2a), α-myosin α-MHC, and atrial natriuretic peptide (ANP) in healthy hearts. Conversely, a diminished thyroid hormone signaling response is associated with concentric hypertrophy and heart failure [125]. A cluster of miRs encoded within the MHC genes, miR-208a, miR-208b, and miR-499, has been identified as a critical regulator of cardiac hypertrophy. Experimental studies in neonatal rat cardiomyocytes demonstrated that treatment with triiodothyronine **(**T3) increased α-MHC and miR-208a expression while decreasing β-MHC and miR-208b levels over time. Loss of miR-208a function disrupts this regulation, leading to decreased α-MHC and increased β-MHC, underscoring miR-208a's essential role in T3-mediated modulation of MHC isoforms. Mechanistically, T3 enhanced miR-208a expression by activating the binding of transcription factor myocyte enhancer factor 2 (Mef2) to its promoter region [126,127] **(Fig.3).**

7.2. Cardiac Fibrosis and the role of miRs

Cardiac fibrosis has been recognized as a critical factor contributing to adverse clinical outcomes in cardiovascular diseases, including arrhythmias, heart failure, and remodeling following ACS [64,128]. This pathological condition is characterized by the excessive accumulation of ECM proteins within the myocardium. Cardiac fibroblasts (CFs) are the primary cells responsible for ECM production and can differentiate into myofibroblasts, which exhibit enhanced synthetic and contractile properties, exacerbating fibrotic remodeling [129]. In recent years, miRs have been identified as key modulators in the complex regulatory networks controlling cardiac fibrosis. Because of their ability to simultaneously target multiple mRNAs, miRs influence a broad spectrum of cellular pathways involved in fibrosis and other pathological processes, making them promising targets in both preclinical and clinical research [130].

miR-21 is one of the most conserved and extensively studied miRNAs implicated in cardiac fibrosis. It plays crucial roles in cardiac development, hypertrophic growth, and fibrotic remodeling [131]. Elevated levels of miR-21 have been detected in human cardiac tissues subjected to stress, suggesting its potential utility as a biomarker for cardiac remodeling and heart failure following ACS [132]. Functional analyses have demonstrated that miR-21 actively promotes fibrotic processes in post-infarction heart. Mechanistically, TGF-β1, a central driver of fibrosis, induces miR-21 expression, establishing a positive feedback loop mediated by TGF-β receptor III signaling [133]. Conditioned media from activated cardiac fibroblasts enhance miR-21 expression in cardiomyocytes, which in turn stimulates fibroblast proliferation and migration via paracrine signaling involving platelet-derived growth factor (PDGF). Pharmacological inhibition of PDGF receptors significantly decreased miR-21 levels, highlighting the critical role of miR-21 in fibroblast-cardiomyocyte crosstalk that contributes to fibrotic remodeling [134], **(Fig.3).**

8. Diagnostic and prognostic potential of miRs

Coronary artery disease (CAD) continues to be a leading global health burden, responsible for approximately 17.9 million deaths annually according to recent epidemiological data [135]. The progressive nature of atherosclerosis, the underlying pathology of CAD, creates a critical need for improved diagnostic tools that can detect early disease stages and accurately stratify patient risk [136]. While advanced imaging modalities, such as coronary CT angiography provide detailed anatomical assessment [137], their clinical utility is limited by substantial costs, radiation exposure, and restricted availability in resource-limited settings [138]. These limitations have driven significant interest in developing circulating biomarkers that could complement existing diagnostic approaches, with miRs emerging as particularly promising candidates owing to their remarkable stability in biological fluids and disease-specific expression patterns [139].

The development of high-throughput sequencing technologies has enabled comprehensive characterization of miR profiles in cardiovascular diseases, revealing their potential as sensitive biomarkers for CAD detection and risk assessment [140]. Multiple studies have demonstrated that specific miR signatures can distinguish patients with ACS from healthy controls with diagnostic accuracies exceeding 85% in some cases [141]. For instance, the combination of miR-133a and miR-208b has shown particular promise for the early detection of myocardial injury, with elevation detectable within 3 h of symptom onset [142]. In stable CAD populations, circulating levels of miR-145 exhibit strong correlation with coronary plaque burden, suggesting their potential utility for monitoring disease progression [143]. These findings parallel the successful applications of miRNA biomarkers in oncology, where they are increasingly being incorporated into clinical decision-making.

Despite these advances, several challenges must be addressed before miR biomarkers can achieve widespread clinical implementation in CAD management. The current literature reveals substantial heterogeneity in reported miR signatures, with limited consensus regarding which species have true pathological significance versus those that may simply reflect secondary responses to myocardial

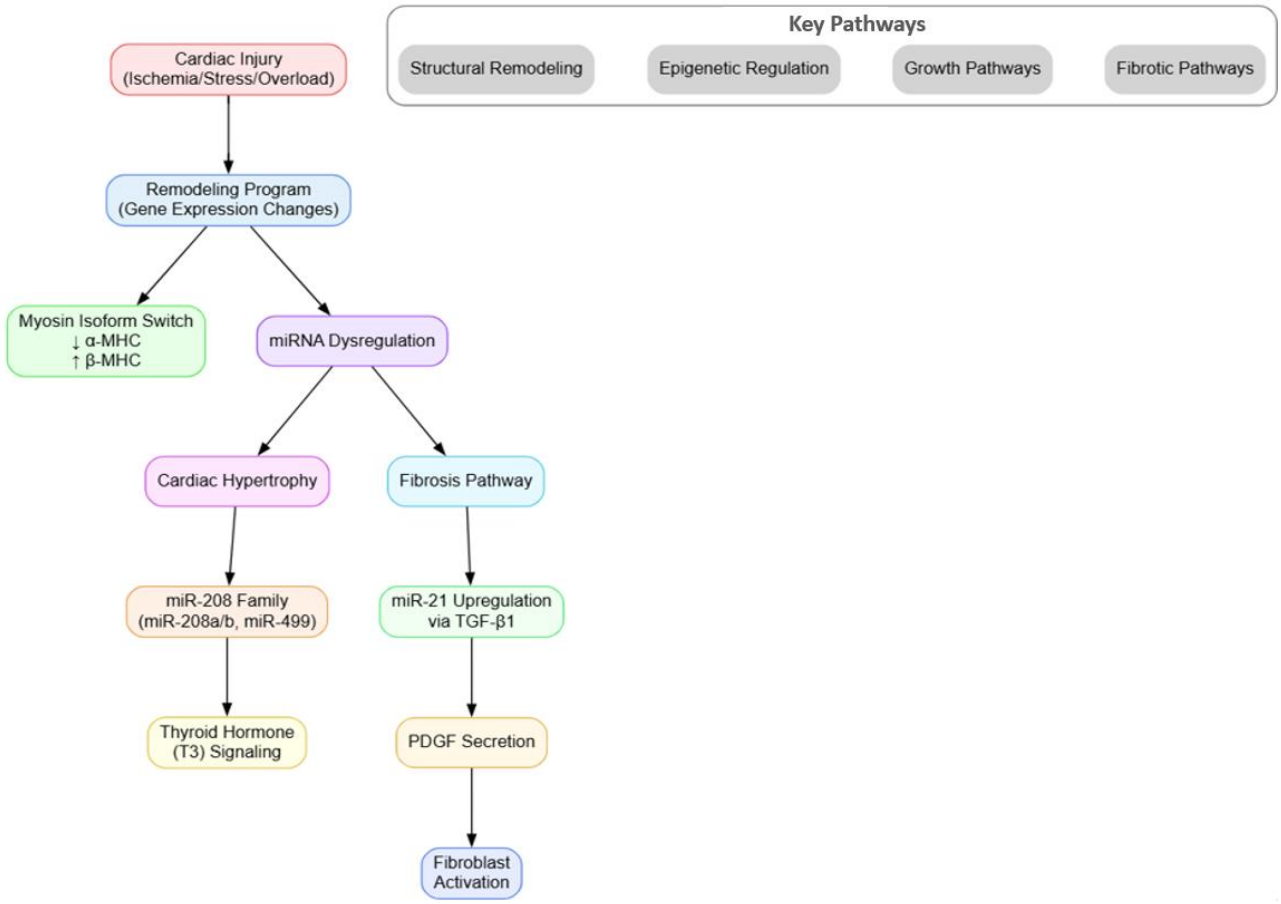

Fig.3. Schematic representation of molecular pathways driving cardiac remodeling following injury

Cardiac injury triggers a remodeling program characterized by **(1)** myosin isoform switching (↓α-MHC/↑β-MHC) and **(2)** miR dysregulation. Key miR-mediated pathways include a) hypertrophy: miR-208 family (miR-208a/b, miR-499) regulated by thyroid hormone (T3) signaling and b) fibrosis: TGF-β1-induced miR-21 upregulation promotes PDGF secretion and fibroblast activation. TGF-β1: transforming growth factor-β1, PDGF: platelet derived growth factor, MHC: myosin heavy chain.

injury [144]. Technical factors including variations in sample collection methods, RNA isolation protocols, and normalization strategies contribute significantly to this variability across studies [145]. Additionally, the dynamic nature of miR expression during different stages of ACS, from the acute phase through recovery, necessitates careful temporal profiling to distinguish transient changes from persistent alterations that may have greater prognostic value [146].

Emerging technologies have provided new opportunities to overcome these limitations and advance the field of miR-based diagnostics in CAD. Single-cell sequencing approaches have revealed previously unappreciated heterogeneity in miR expression patterns among different vascular cell types, offering insights into cell-specific contributions to atherogenesis [147]. The study of extracellular vesicle (EV)-associated miRs reveals new pathways of intercellular signaling within the vascular wall, offering promising avenues for biomarker discovery and therapeutic intervention in cardiovascular diseases [148]. Recent applications of machine learning techniques to large-scale miR expression datasets have demonstrated enhanced predictive performance over single biomarker approaches, especially when integrated with traditional

clinical risk factors [149]. These advancements, along with efforts to harmonize pre-analytical and analytical methodologies, are accelerating the translation of miR-based diagnostics and therapeutics into clinical practice for CAD management [150].

Key research priorities include the development of standardized multiplex assays that combine panels of 3-5 validated miRs with established biomarkers, prospective validation in diverse patient populations to demonstrate generalizability, and mechanistic studies to elucidate causal relationships between specific miRs and atherosclerotic progression [151]. Successful translation of these efforts could enable more precise risk stratification, earlier disease detection, and personalized therapeutic approaches tailored to the molecular profiles of individual patients. As the evidence base continues to grow, miRs are poised to become increasingly important tools in the ongoing effort to reduce the global burden of CAD.

8.1. Biomarkers for ACS

Recent advances in molecular cardiology have highlighted the critical involvement of miRs in pathogenesis of ACS [152]. Comprehensive profiling studies have revealed distinct miR expression patterns in peripheral mononuclear blood cells (PBMCs) that effectively discriminate between AMI, UP and chronic CAD [142]. These molecular signatures not only reflect disease subtypes but also correlate with specific pathophysiological processes, AMI profiles are predominantly associated with immune activation pathways, while UA patterns show stronger links to lipid metabolism dysregulation [143]. The diagnostic potential of PBMC-derived miRs is particularly promising, with multiple candidates demonstrating robust performance in plasma validation studies [149]. Among these, miR-29 has emerged as a key regulator of cellular adaptation to hypoxic stress, showing a significant elevation during ACS events [144]. This miR operates within an intricate network of inflammatory mediators, including IL-6, IL-10, and IL-18, which collectively influence infarct severity and clinical outcome [146]. Mechanistic studies have demonstrated that the targeted modulation of IL-18 activity can attenuate post-infarction remodeling and reduce scar formation by approximately 40% in experimental models [153]. Pathway analysis of AMI-associated molecular changes revealed enrichment of 35 distinct biological processes, with the majority (80%) involving immune system activation and inflammatory cascades [145].

The clinical utility of these findings is enhanced by the stability of miR in the circulation and their rapid release kinetics following plaque rupture [90]**.** Current research efforts are focused on translating these discoveries into practical diagnostic applications, with particular emphasis on developing standardized measurement protocols and establishing clinically relevant cutoff values [149]. The deepening understanding of miR biology in ACS highlights the potential of these molecular signatures to transform current risk stratification methods and pave the way for more personalized therapeutic strategies [136].

8.2. MiRs in risk stratification

The clinical presentation of ACS varies significantly, from STEMI to UA, and is influenced by factors such as plaque composition, vascular remodeling, and collateral circulation development [73]. Even within STEMI, patient outcomes can differ widely, underscoring the need for reliable risk stratification tools. While traditional biomarkers like cardiac troponins, CK-MB, and

myoglobin are valuable for diagnosing ACS, they are less effective in predicting its onset [154,155]. Other markers, including C-reactive protein (CRP), fibrinogen, and homocysteine, contribute to risk assessment but are limited in acute settings due to delayed detectable changes [155,156]. Consequently, research has focused on the identification of novel biomarkers that can enhance early risk prediction.

Among the potential candidates, circulating micromolecules, such as lipids, HDL, lipoprotein(a), and miRs, show promise. In particular, lipids are rapidly released into the bloodstream following plaque rupture, making them useful for immediate risk assessment in patients presenting with ACS symptoms. miRs stand out due to their exceptional stability under extreme conditions, including pH fluctuations, temperature variations, and repeated freeze-thaw cycles, positioning them as ideal biomarkers [157,158]. MiR-122, miR-150, miR-195, and miR-16 were identified as robust miRsignatures that enhanced risk prediction beyond conventional markers across different ACS patient groups. Notably, this miR profile outperformed traditional biomarkers in forecasting non-focal ACS in at-risk populations [159]. Continuous monitoring in both ACS patients and asymptomatic high-risk individuals could determine its utility as a predictive companion biomarker. Additionally, the therapeutic inhibition of miR-150 and miR-195 has been proposed as a potential strategy for managing atherosclerosis, highlighting the dual diagnostic and therapeutic potential of miRNAs in cardiovascular disease [160,161].

Despite their promise, significant challenges remain in translating miR research into clinical practice. Technical hurdles include the standardization of detection methodologies and interpretation of results across different platforms. Biological complexities such as discrepancies between circulating and tissue miR profiles, variable extracellular vesicle packaging, and differential degradation rates in plasma must be addressed. Furthermore, the selective release mechanisms governing miR expression patterns in different ACS presentations require deeper understanding. Current research efforts are focused on overcoming these obstacles through improved detection protocols and more comprehensive studies of miR function in ACS progression, with the ultimate goal of developing reliable miR-based diagnostic tools and targeted therapies for cardiovascular disease management [162,163].

9. Recently identified miRs as diagnostic and prognostic biomarkers in ACS

A comprehensive overview of the recently identified miRs implicated in acute ACS is presented in **Table 1**. The table summarizes the expression patterns, diagnostic and prognostic roles, and key molecular targets and mechanisms for each miR.

9.1. MiR-223-5p

MiR-223-5p has been shown to modulate platelet reactivity, attenuate oxidative stress, influence cardiac remodeling, and suppress inflammatory responses, thereby contributing to cardiovascular protection [164]. Zhang et al. [165] revealed that miR-223-5p is associated with myocardial injury and extent of CAD. The authors found that miR-223-5p expression was elevated in patients with ACS and its expression was positively correlated with cardiac troponin I (cTnI) levels and the Gensini score, both of which are established clinical markers for assessing the presence and severity of ACS. Moreover, they reported that miR-223-5p could serve as a

risk factor for ACS with high diagnostic accuracy, effectively distinguishing ACS patients from healthy individuals with strong sensitivity and specificity. Additionally, they found that miR-223-5p levels were higher in ACS patients who later developed major adverse cardiovascular events (MACE), indicating an increased risk of such outcomes. These findings highlight miR-223-5p as a valuable biomarker for diagnosing ACS and predicting post-percutaneous coronary intervention (PCI) cardiovascular complications, potentially aiding the development of personalized treatment strategies.

9.2. MiR-133b and miR-21

Kumar et al. [166] highlighted a significant association between the plasma levels of miR-133b and miR-21 and the severity of atherosclerotic disease. MiR-133b expression exhibited a gradual decline as the disease progressed from a pre-atherosclerotic state to more severe clinical stages like ACS, where its levels were the lowest. In contrast, miR-21 expression progressively increased from normal coronary arteries to ACS. These expression patterns suggest that both miR-133b and miR-21 can effectively distinguish ACS from other forms of CAD and healthy individuals. Therefore, they could serve as diagnostic biomarkers for detecting CAD progression and predicting complications at an earlier stage, potentially allowing timely intervention. Furthermore, by evaluating whether miR-133b and miR-21 could differentiate ACS subtypes (STEMI vs. UA/NSTEMI), it was found that miR-133b levels were markedly lower in STEMI than in UA/NSTEMI, indicating its discriminative potential. Although miR-21 expression was altered in both groups, it did not differ significantly between the groups. Importantly, receiver operating characteristic curve (ROC) analyses confirmed that both miR-133b and miR-21 more accurately predict ACS overall than stable angina, highlighting their promise as noninvasive diagnostic markers in CAD [166]. MiR-133b was predicted to target SGPP1, a gene implicated in the sphingolipid signaling pathway. Meanwhile, miR-21 was found to regulate ATG5 and LRP6, which are key components of the autophagy process and Wnt signaling pathway, respectively, indicating that these biomarkers represent promising therapeutic targets for the treatment of CAD [167].

9.3. MiR-182-5p

Agwa et al. [168] identified an miRs panel, the authors found that miR-182-5p, miR-146a-5p, miR-23a-3p, and miR-183-5p were all elevated in the serum of ACS patients compared with individuals experiencing non-cardiac chest pain and healthy controls. Among these, miR-182-5p showed the greatest ability to distinguish ACS, exhibiting a 3-to-4-fold increase compared to healthy subjects. Notably, miR-182-5p surpassed cardiac troponins in differentiating between STEMI and NSTEMI, STEMI and non-cardiac chest pain, NSTEMI and non-cardiac chest pain, as well as STEMI and unstable angina [168].

9.4. MiR-377

Zhang et al. [169] reported that miR-377 has a strong diagnostic potential for distinguishing patients with ACS from healthy individuals. MiR-377 expression demonstrated a positive correlation with cardiac troponin I (cTnI), a key biomarker of myocardial injury. Using a rat model of acute coronary syndrome (ACS), the authors further reported that miR-377 may contribute to disease progression by enhancing inflammation and vascular damage. These findings underscore the potential of miR-

377 as both a diagnostic biomarker and a therapeutic target in ACS [169].

9.5. MiR-133a

In a case-control study comparing individuals with ACS to control subjects, plasma miR-133a expression was consistently detectable in individuals with ACS but was significantly reduced compared to controls. MiR-133a demonstrated strong diagnostic accuracy in differentiating ACS patients from healthy individuals, with an area under the ROC curve (AUC) of 0.911, yielding a sensitivity of 87.1% and a specificity of 100% at a threshold of 44.035. When the control cohort was expanded to include both healthy individuals and those with non-ACS comorbidities, miR-133a retained its diagnostic significance, with an AUC of 0.874, a sensitivity of 76.9%, and a specificity of 100% at a cut-off value of 11.69, suggesting that miR-133a could be used effectively as diagnostic biomarker for ACS [170].

9.6. MiR-183-5p & let-7i-5p

A cohort study, on young male patients with ACS, including a panel of miRs [miR-183-5p, miR-134-5p, miR-15a-5p, and let-7i-5p] demonstrated that plasma miR-183-5p was significantly upregulated by approximately eightfold in patients with NSTEMI, while miR-134-5p, miR-15a-5p, and let-7i-5p were markedly downregulated by about fivefold, sevenfold, and 3.5-fold, respectively, in individuals with STEMI, compared to healthy controls. miR-183-5p exhibited strong discriminatory capacity for identifying NSTEMI patients, with an AUC of 0.917. In the context of STEMI, let-7i-5p demonstrated the highest individual diagnostic performance (AUC = 0.833), followed by miR-134-5p and miR-15a-5p. Notably, a combined panel of these three miRs further improved diagnostic accuracy, achieving an AUC of 0.935. These findings highlight the distinct expression profiles of miR-183-5p, miR-134-5p, miR-15a-5p, and let-7i-5p in STEMI and NSTEMI patients, underscoring their potential utility as circulating biomarkers for differentiating between these two forms of ACS [171].

9.7. MiR-483-5p

Elevated circulating levels of miR-483-5p have been reported in patients with ACS and were positively correlated with both the SYNTAX and Gensini scores. Notably, miR-483-5p demonstrated high diagnostic accuracy in distinguishing ACS patients from healthy controls (AUC = 0.919) and in differentiating AMI patients from non-AMI ACS patients (AUC = 0.867). Moreover, miR-483-5p emerged as a strong predictor of MACE (HR = 5.955, 95% CI = 1.928–18.389, P = 0.002). These findings suggest that serum miR-483-5p may serve as a valuable non-invasive biomarker for the diagnosis of ACS and for predicting MACE risk following PCI [172].

9.8. MiR-409-5p

Ubiquitin-specific peptidase 7 (USP7) is a key deubiquitinating enzyme that interacts with and regulates a wide range of substrate proteins. Through its enzymatic activity, USP7 modulates the stability and function of various targets, thereby influencing cellular programming across multiple cell types [173,174]. Among its targets is the proapoptotic protein p53, which is crucial for promoting cardiomyocyte apoptosis, particularly following AMI [175,176]. USP7 contributes to the regulation of p53 and its negative regulator MDM2 by removing ubiquitin chains, thereby stabilizing both proteins under physiological and stress conditions [177]. The expression of USP7 was markedly upregulated in AMI and negatively regulated by miR-409-5p. MiR-409-

5p expression was significantly downregulated in AMI and was inversely associated with cTnI expression. Thus, both USP7 and miR-409-5p are promising candidates for early diagnosis and potential therapeutic intervention in AMI [178].

9.9. MiR-199a-5p

Xu et al. [179] reported that serum miR-199a-5p levels were significantly upregulated in AMI patients, showing a positive association with cTnI and a negative correlation with the left ventricular ejection fraction (LVEF). ROC curve analysis demonstrated that combining miR-199a-5p with echocardiographic parameters improved the diagnostic sensitivity and specificity. Furthermore, patients with elevated miR-199a-5p levels exhibited a higher incidence of MACE, and its combination with LVEF enhanced the prediction of these outcomes. Overall, the integration of miR-199a-5p with echocardiographic assessment significantly improved the diagnostic and prognostic evaluation of AMI.

The therapeutic potential of miR-199a-5p was investigated using a non-viral, intravenous delivery platform aimed at promoting long-term cardiac repair. A mesoporous silica nanoparticle (MSN) system was developed and functionalized with a cardiac-targeting peptide (CSTSMLKAC), enabling selective accumulation in ischemic myocardial tissue. These nanoparticles were loaded with miR-199a-5p mimics, offering both protection against degradation and sustained intracellular release, with effects observable up to four weeks post-injection. The therapeutic effects of miR-199a-5p occur in two distinct phases; a) in the early phase, miR-199a-5p suppresses AGTR1 expression, attenuating oxidative stress and reducing cardiomyocyte apoptosis, b) during the recovery phase, it inhibits MARK4, a kinase that modulates microtubule detyrosination, thereby enhancing contractile function in surviving cardiomyocytes. The therapeutic outcomes in a rat MI model revealed that a single intravenous dose of the targeted nanoparticles led to significant reduction in infarct size and apoptotic cell death, enhanced cardiac contractility and function, as confirmed by echocardiography and tissue-based assays, and reduced fibrosis and attenuation of heart failure–associated gene expression, with durable effects seen up to four weeks [180].

9.10. MiR-146a

MiR-146a plays a multifaceted role in the development and progression of ACS, involving genetic polymorphisms, inflammatory responses, and potential applications as a diagnostic and prognostic biomarker. One of the most extensively studied genetic variations in miR-146a is the single nucleotide polymorphism (SNP) rs2910164, which results in a G>C substitution in its precursor sequence. This polymorphism alters miR-146a expression and function, impacting key inflammatory pathways that contribute to the pathogenesis of ACS. Carriers of this allele tend to exhibit elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α, suggesting a role in amplifying systemic inflammation. Moreover, this genotype has been linked to poorer outcomes following PCI, including a higher incidence of restenosis and adverse cardiovascular events [181,182].

Beyond genetic variation, miR-146a expression itself is dysregulated in ACS. It is notably upregulated in ACS patients, especially those with coexisting chronic periodontitis. This upregulation highlights miR-146a's critical role in modulating immune responses and inflammatory cytokine production. As a key negative regulator of the nuclear factor kappa B (NF-κB) signaling

pathway, miR-146a targets adaptor molecules such as IRAK1 and TRAF6 to suppress excessive inflammation. This immunoregulatory function suggests that miR-146a may act as a molecular bridge linking chronic inflammatory conditions like periodontitis to the onset and progression of ACS, through sustained systemic inflammation and endothelial dysfunction [183].

Recent findings have also identified serum exosomal miR-146a (exo-miR-146a) as significantly elevated in ACS patients. Notably, exo-miR-146a levels positively correlate with inflammatory markers including IL-1β, IL-6, and TNF-α, indicating its value not only as a marker of inflammation but also as a promising non-invasive diagnostic biomarker for ACS. The stability of exosomal miRNAs in circulation further supports their clinical utility in early disease detection [99].

Furthermore, the clinical significance of plasma miR-146a has been investigated in the context of unstable angina pectoris (UP), a subset of ACS. In a study by Shi et al., [184] plasma miR-146a levels were found to be elevated by approximately 1.8-fold in patients with UP compared to healthy controls. These levels were positively correlated with the severity of coronary lesions observed on angiography. A four-year follow-up revealed that patients with higher baseline miR-146a expression experienced a significantly higher incidence of MACEs. These results underscore the potential of plasma miR-146a as both a diagnostic and prognostic biomarker, particularly in identifying patients at risk of severe CAD and poor long-term cardiovascular outcomes.

Collectively, these findings emphasize the pivotal role of miR-146a, in both its genetic and circulating forms, in the pathophysiology of ACS. Its involvement in modulating inflammatory responses, linking comorbid conditions like periodontitis to cardiovascular risk, and predicting long-term clinical outcomes supports its emerging importance as a clinically relevant biomarker for diagnosis, risk stratification, and prognosis in ACS management.

9.11. MiR-3646

Emerging research highlights the significant role of miR-3646 in modulating vascular inflammation, which is a key driver in the development of ACS. Elevated levels of miR-3646 correlate with adverse metabolic markers, including higher total cholesterol, LDL, and glucose concentrations, as well as increased Gensini scores, reflecting the severity of CAD in ACS patients. Mechanistically, RHOH has been identified as a direct downstream target of miR-3646, and its suppression contributes to the attenuation of vascular inflammation. Rescue experiments in cellular and animal models confirmed this regulatory interaction, providing mechanistic insight into how miR-3646 influences atherosclerotic progression [95]. These findings enhance our understanding of miR-mediated pathways in cardiovascular disease and suggest potential therapeutic strategies targeting miR-3646 for ACS management.

Conclusion

ACS results from the rupture of a coronary artery plaque and subsequent thrombus formation, which can lead to partial or complete vessel occlusion and potentially myocardial infarction. While multiple factors such as dyslipidemia, inflammation, and oxidative stress contribute to plaque instability, the underlying mechanisms are not fully understood. Although progress has been made in identifying risk factors, identifying highly sensitive and specific molecular biomarkers for ACS remains challenging.

Table 1. Summary of recently Identified diagnostic and prognostic miRs in acute coronary syndrome.

miRNA	Expression Pattern in ACS	Diagnostic/Prognostic Role	Target(s) / Mechanism	Reference
miR-223-5p	Upregulated	Distinguishes ACS; Predicts MACE	Platelet reactivity, oxidative stress, cardiac remodeling	[165]
miR-133b & miR-21	miR-133b ↓, miR-21 ↑	ACS progression and subtype discrimination	SGPP1 (miR-133b), ATG5 & LRP6 (miR-21)	[166,167]
miR-182-5p	Upregulated	Best discriminator among ACS types	Promotes apoptosis	[168]
miR-377	Upregulated	Correlates with cTnI; Inflammation	Promotes vascular injury	[169]
miR-133a	Downregulated	High diagnostic accuracy	Cardiac remodeling and fibrosis	[170]
miR-183-5p & let-7i-5p	miR-183-5p ↑, let-7i-5p ↓	Distinguish NSTEMI/STEMI with high sensitivity	miR-183-5p promotes VSMC proliferation by inhibiting FOXO1 let-7i-5p reduces Fas and FasL expression in ACS CD4+ T cells and inhibits apoptosis	[171]
miR-483-5p	Upregulated	Predicts MACE; Correlates with Gensini/SYNTAX	Involved in endothelial dysfunction and fibrosis	[172]
miR-409-5p	Downregulated	Early AMI biomarker	USP7/p53 regulation	[178]
miR-199a-5p	Upregulated	Combined with ECHO improves diagnosis	Associated with MACE, ↓ LVEF	[179]
miR-146a	Upregulated	Associated with severe CAD and MACE	Inflammation and plaque burden	[184]
miR-3646	Upregulated	Correlation with Gensini and inflammatory markers	Targets RHOH; mediates vascular inflammation	[95]

ACS: acute coronary syndrome, AMI: acute myocardial infarction, CAD: coronary artery disease, ECHO: echocardiography, FOXO1: fork head box O1, LVEF: left ventricular ejection fraction, MACE: major adverse cardiac events, NSTEMI: non-ST- segment elevation myocardial infarction, RHOH: Ras Homolog Family Member H, STEMI: ST-segment elevation myocardial infarction, USP7: Ubiquitin-Specific Peptidase 7.

Circulating miRs are promising candidates as diagnostic and prognostic biomarkers because of their stability in the blood and ease of detection using various molecular techniques. However, only a limited subset of miRs show significant changes in ACS, and large-scale studies are needed to validate their reliability. Clinical variables and technical limitations also impact the specificity and utility of miR panels. Compared to established markers like cardiac troponins, experience with miRs in ACS is still limited, and methodological challenges persist. Thus, while circulating miRNAs hold potential as novel biomarkers for ACS, further rigorous research and standardization are required before they can be adopted in clinical practice.

Funding: There was no specific grant awarded to this study by any public or private funding organization.

Conflicts of Interest: All authors declare no competing interests.

Authors Contribution: All authors contributed to all aspects of the work.

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