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Role of MicroRNAs in Diagnosis, Prognosis, and Treatment of Acute Heart Failure: Ambassadors from Intracellular Zone

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Abstract

Acute heart failure (AHF) is one of the burdensome diseases affecting a considerable proportion of the population. Recently, it has been demonstrated that micro-ribonucleic acids (miRNAs) can exert diagnostic, prognostic, and therapeutic roles in a variety of conditions including AHF. These molecules play essential roles in HF-related pathophysiology, particularly, cardiac fibrosis, and hypertrophy. Some miRNAs namely miRNA-423-5p are reported to have both diagnostic and prognostic capabilities. However, some studies suggest that combination of biomarkers is a much better way to achieve the highest accuracy such as the combination of miRNAs and N-terminal pro b-type Natriuretic Peptide (NT pro-BNP). Therefore, this review discusses different views towards various roles of miRNAs in AHF. [GMJ.2020;9:e1818] DOI: [10.31661/gmj.v9i0.1818](https://doi.org/10.31661/gmj.v9i0.1818)

Keywords: Heart Failure; MicroRNA; Diagnosis; Prognosis; Treatment

Introduction

Acute heart failure (AHF) is defined as “the new onset or recurrence of symptoms and signs of HF requiring urgent or emergent therapy and resulting in unscheduled care or hospitalization” [1]. It is characterized as the most life-threatening cardiovascular disease causing a huge social and economic burden in both developed and developing countries [2, 3]. The prevalence of HF in 2017 was over 5.7 million in the United States and it is estimated that it will rise up to more than 8 million by 2030, accounting for a 46 percent increase in prevalence [4]. The mortality rate within four years in patients with symptomat-

ic HF is 50 percent and only half of those with the end-stage condition survive until the next year, which is much worse than the majority of advanced malignancies [2]. From a clinical standpoint, it is of high importance to distinguish between acute and chronic heart failure; however, it is not always feasible through taking an accurate history, physical exam, and echocardiogram [5]. Therefore, developing objective accurate diagnostic tests has become a main concern in the recent decade. Currently, brain (B-type) natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are recommended by the established guidelines for assigning the diagnosis of AHF and determining the prognosis of patients presenting in

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the emergency department. However, serum levels of BNP and NT-proBNP are affected by a series of conditions such as obesity, age, renal function, atrial fibrillation, thromboembolic events, etc. [6, 7]. Also, a multicenter trial investigating a considerable number of patients - approximately 1,100 high-risk HF patients - failed to establish any beneficial effect of using NT-proBNP-guided strategy in the routine outpatient management of these patients [8]. Therefore, investigations are still continued to find other biomarkers with higher accuracy and clinical applicability. Recently, many research studies have demonstrated that micro-ribonucleic acids (miRNAs) can exert diagnostic roles in a variety of conditions including AHF. There is also some evidence advocating the prognostic and therapeutic role of these biologic agents. As Figure-1 demonstrates, the related publication on the association between miRNA and HF has grown considerably since 2007. Therefore, different roles of miRNAs in AHF will be discussed in the following sections.

Structure of MicroRNAs

Generally, miRNAs are some small non-coding RNAs with 21-25-nucleotide length [9]. Since their discovery in 1993 in nematode *Caenorhabditis elegans* and seven years later in humans, their role in different physiological and pathological conditions has been widely studied [10-14]. The role of miRNAs in cardiac development was first described in 2005 by Kwon *et al.* [15]. As completely elucidated by Ali Sheikh *et al.*, miRNAs take

several modifications from inside the nucleus until they enter the bloodstream [16]. After the mature miRNAs enter the bloodstream as circulating miRNAs, they can be detected in a variety of body fluids (Figure-2) [19, 20]. Although the secretion mechanism of miRNAs into extracellular space and bloodstream is not completely understood, there are some theories trying to explain the cellular process such as secretion through membrane-bounded vesicles or by means of protein-miRNA complexes (AGO2, NPM1, and HDL) [16].

The Role of MiRNAs in the Pathophysiology of Cardiovascular Disease

Rooij *et al.* in 2006 revealed that miR-195 was significantly increased in the failing human heart. They also demonstrated that miR-195 has an essential role in cardiac remodeling in transgenic mice [21]. Thereafter, a variety of biologic effects of miRNAs in the cardiovascular system have been introduced by further studies. Table-1 summarizes some of the most cited miRNAs having a significant role in the cardiovascular system. Some miRNAs are reported to play roles in cardiac development including miRNAs -1, -27, -130a, -133, and -199a [22-26]; however, their role is not limited to development of heart muscle and they have essential effects on both physiological and pathologic mechanisms in the cardiovascular system. Ten miRNAs are revealed to be mainly involved in cardiac hypertrophy (Table-1). Some of them are related to the pathophysiology of multiple disorders such as miRNA -1 and -133. Both miRNA-1 and -133

NUMBER OF PUBLISHED ARTICLES

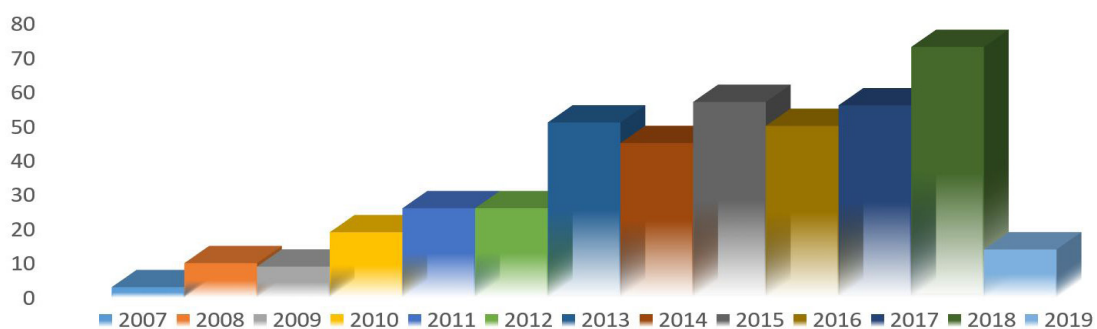


Figure 1. Number of medline-indexed publications per year obtained from www.Pubmed.com at 12/8/2019 using the keywords of ("Heart Failure"[Mesh]) and "MicroRNAs"[Mesh]

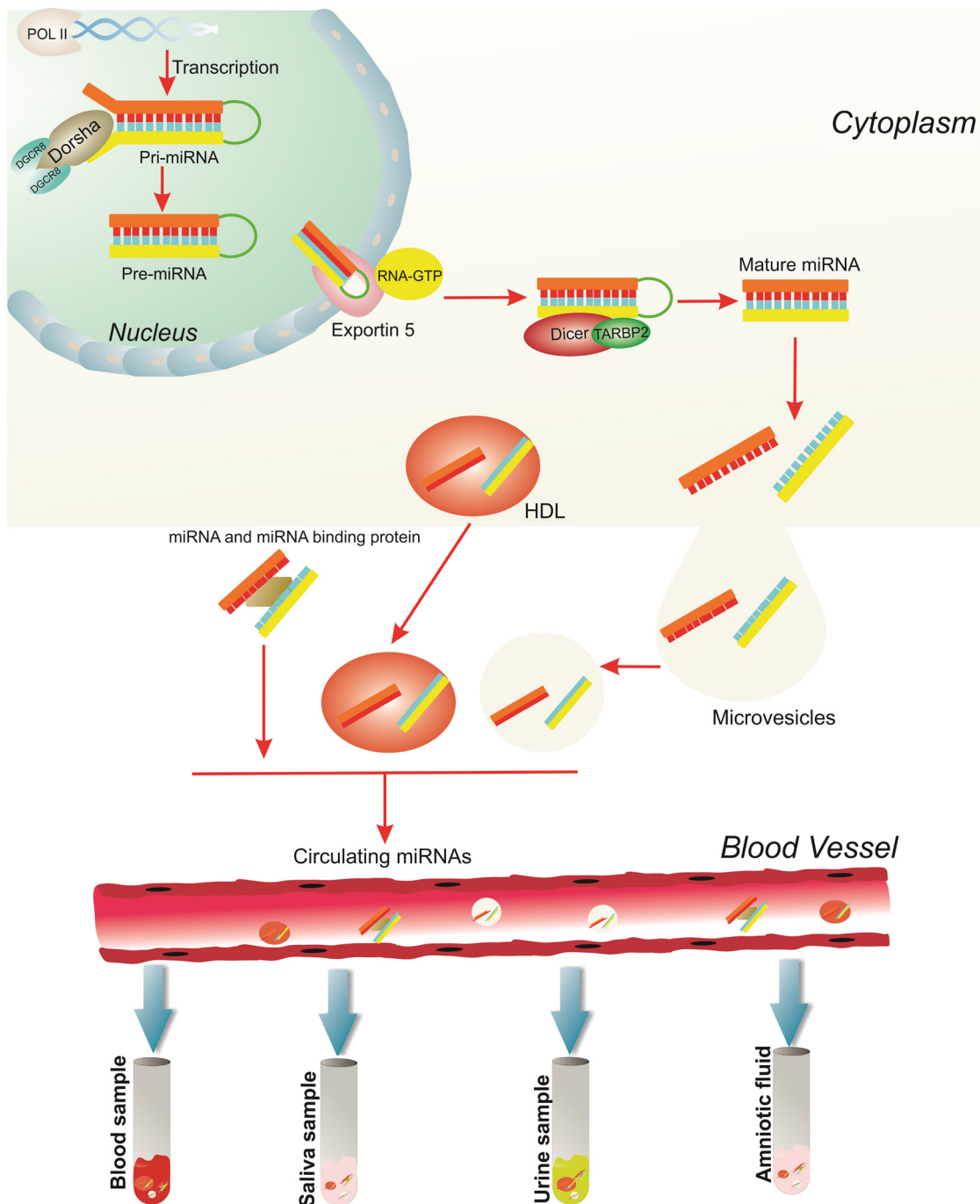


Figure 2. Biogenesis and pathways of circulating miRNAs. After transcription from source DNA into pri-miRNAs (with the length of hundreds or thousands of nucleotides), pri-miRNAs are cleaved by Drosha (RNase III enzyme) into preliminary miRNAs with 70- to 100- nucleotide-long (pre-miRNAs) to be able to be transported by exportin-5 to the cytoplasm. In the cytoplasm, the Dicer enzyme cleaves the pre-miRNAs and generates double-stranded immature miRNA duplexes. These 21 to 25-nucleotide length immature miRNA duplexes then become unwound and by associating with Argonaute proteins generate the RNA-induced silencing complex (RISC). The RISC can regulate the fundamental functions of cells through the degradation of complementary messenger-RNAs (mRNA) of cells' functional proteins and repression of translation [17, 18].

have been identified to target key molecules in the signaling pathways relating to cardiac hypertrophy, cardiac fibrosis, and arrhythmia [24, 27-29]. In vitro and in vivo studies suggest that the possible mechanism that miR-

NA-1 may contribute to cardiac hypertrophy is through its role in cell mass and reduced level of miRNA-1 expression is necessary for cell mass increase [23, 24]. Overexpression of miRNA-1 can bring about arrhythmia.

Table 1. Discovered Functions of Some Prominent MiRNAs in the Cardiovascular System

Role in the Cardiovascular System	Related miRNA	Reference
Cardiac development	1, 27, 130a, 133, 199a	[22-26, 37, 94-100]
Vascular inflammation	10a,b, 221, 222	[71, 101, 102]
Apoptosis induction	15, 16, 21	[21, 28, 103]
Apoptosis inhibition	451	[104]
Endothelial function modulation	21, 125a,b, 150, 126	[71, 103, 105-107]
Cardiac hypertrophy	1, 21, 23 a,b, 27a,b, 124, 133, 195, 208, 223, 499	[12, 21,24, 34, 98, 108, 109]
Angiogenesis inhibition	17, 21, 34a,b, 92, 132, 221, 222, 214, 195, 499-5p,	[21, 72, 102, 110-117]
Angiogenesis promotion	27, 101a,b, 126	[105, 107, 117-119]
Regulation of beta-adrenergic receptors	100, 133	[72]
Ischemic injury	1, 22, 320, 374	[25, 120-123]
Differentiation of vascular smooth muscle	143, 145	[124]
Cardiac fibrosis	1, 15, 21, 22, 24, 26, 29, 30, 34, 101, 122, 132, 133, 155, 199, 203, 208, 214, 433, 489, 503	[28, 36, 45, 84, 125, 126-128]
Arrhythmia	1, 26, 30, 130, 133, 208	[27, 29, 34, 129, 130]

This is possibly due to its regulatory effect on intracellular calcium level balance and consequently altering the automaticity and cardiac conductance [30]. The miRNA-133 has a protective role against cardiac hypertrophy by some mechanisms such as intracellular calcium concentrations regulation and reduction of ANP and myosin heavy chain beta MHC- β by suppression of their mRNAs' translation. Changes in MHC- β can lead to cardiac hypertrophy, fibrosis, and contractile function impairment [31, 32]. The miRNA-208a is reported to be associated with the increase of MHC- β in cardiomyocytes [33, 34]. Silencing miRNA-208 in neonatal mice model of myocardial infarction inhibited apoptosis, hypertrophy, and fibrosis; and it improved cardiac function [35]. The miR-21 plays an important role in the pathophysiology of cardiac fibrosis, hypertrophy, and apoptosis [36-39]. It is

preferentially expressed in cardiac fibroblasts and its role in cardiac hypertrophy is reported to be due to stimulation of mitogen-activated protein (MAP) kinases in fibroblasts. The miRNA-195 is claimed to be sufficient for inducing pathological cardiac hypertrophy and heart failure in mice model [21]. There is evidence that miRNA-223 attenuates cardiac hypertrophy by reducing intracellular calcium concentration, inhibiting cardiomyocyte contractility, and phosphorylating cardiac troponin I (cTNI) [40]. Also, other miRNAs such as miRNA-124 and -499 have significant influence in cardiac hypertrophy by inducing angiotensin II-induced hypertrophy and altered expression of contractile proteins, respectively [41, 42]. More than twenty different miRNAs are reported to be involved in cardiac fibrosis. These miRNAs exert their pro- or anti-fibrotic effects by means of a vari-

Table 2. The MiRNAs in Diagnosis, Prognosis, and Treatment of Patients with Acute and Chronic Heart Failure Measured in Whole Blood, Plasma, or Serum Samples

MIRNA	Diagnosis		Severity		Prognosis	Therapeutic Target	Underlying Condition	References
	AHF	CHF	HFpEF	HFREF vs HFpEF				
1	-/+			-			Hypertensive or DCM	[50, 61, 68, 131, 132]
7							DCM	[131]
let-7i-5p	+			+++				[60, 78, 133]
9							Hypertensive	[134]
16	+			+			Hypertensive	[54, 60]
17							ICM	[135, 136]
18a-5p	++			++				[60, 66]
19							Congenital	[62]
20							Hypertensive or ICM	[54, 134]
21		++		+			Hypertensive or ICM	[61, 68, 76, 135, 132, 137, 138]
22			+	+				[53]
23a	+							[61]
24						+++	Diabetic	[89, 90, 139]
26	++		+	++			Hypertensive	[60, 66, 134, 140]
27	+++			++			congenital	[60- 62, 66, 78, 119]
29			++				DCM or congenital	[131, 140, 141]
30	+++	++	+	+++			Diabetic or CAD	[60, 63, 66, 77, 140, 142]
34		+						[143, 144]
65				+			ICM	[78]
92		++		+			Hypertensive	[53, 136, 140]
93							DCM	[54]
99							Congenital	[145]
103	+							[61, 146]

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Continue of Table 2. The MiRNAs in Diagnosis, Prognosis, and Treatment of Patients with Acute and Chronic Heart Failure Measured in Whole Blood, Plasma, or Serum Samples

MiRNA	Diagnosis			Severity	Prognosis	Therapeutic Target	Underlying Condition	References
	AHF	CHF	HFpEF vs HFrEF					
106	++				++		Hypertensive or ICM	[54, 60, 66, 135]
122	+	+		+				[50, 52, 137]
125a		+				+	ICM or DCM	[135, 147]
126	+	+		++	-/+		Hypertensive or ICM	[68, 76, 134, 136, 148-150]
130							Congenital	[62]
133	-			+			Hypertensive or Diabetic	[17, 73, 134, 107, 151]
142-3p	+		+					[61, 152]
143								[134]
145		+					Hypertensive	[131, 134, 140]
146		+				+		[63]
147							DCM	[145]
155		+					ICM, DCM, or Congenital	[136, 137, 145, 146, 153]
181							DCM	[131]
182		+			+		CAD	[137, 154]
183-3p		+						[147]
190a		+	+			+		[147]
192		+						[144]
193		+						[147]
194		+					DCM	[144, 145]
198							Congenital	[62]
199	+++				+++		Diabetic	[60, 61, 66, 143]

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Continue of Table 2. The MiRNAs in Diagnosis, Prognosis, and Treatment of Patients with Acute and Chronic Heart Failure Measured in Whole Blood, Plasma, or Serum Samples

MiRNA	Diagnosis				Severity		Prognosis	Therapeutic Target	Underlying Condition	References
	AHF	CHF	HFpEF	HFREF	HFpEF	HFREF				
205									DCM	[78, 145]
208	-	+						+	Hypertensive or CAD	[50, 82, 132, 155]
210		+							Diabetic	[142, 143]
211-5p		+	+							[147]
214									DCM	[131]
218									DCM	[145]
221		+								[63]
223		+					+		Hypertensive or Diabetic	[54, 60, 143]
301							+			[78]
302	+					+			ICM and DCM	[65, 135, 145]
320a							+			[53]
324-5p	+									[61]
328		+							DCM	[63]
342	+								DCM	[61, 131]
361		+							ICM	[156]
375		+								[63]
378									DCM	[131]
423-5p	+++	+	++		+		+++		Hypertensive or Atherosclerotic or DCM	[53-58, 60, 68, 76, 78]
454								+	DCM	[145, 152]
486									Congenital	[146]

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Continue of Table 2. The MiRNAs in Diagnosis, Prognosis, and Treatment of Patients with Acute and Chronic Heart Failure Measured in Whole Blood, Plasma, or Serum Samples

MIRNA	AHF	CHF	Diagnosis		Severity		Prognosis	Therapeutic Target	Underlying Condition	References
			HFrEF	HFpEF	HFrEF vs HFpEF	HFpEF				
494		+								[147]
499	++	+							Hypertensive or CAD	[50, 64, 132, 155]
500				+						[152]
518		+							DCM	[137, 145]
520d-5p						+				[52]
544									DCM	[145]
548										[64]
550-5p						+				[147]
558										[52]
618									DCM	[145]
636									DCM	[153]
638										[147]
639									DCM	[153]
646									DCM	[153]
652	++						+++			[60, 66, 78]
671		+								[147]
875									DCM	[145]
1187		+							ICM	[156]
1233		+								[147]
1246						+				[152]
1260									Congenital	[146]
1306										[157]

Reported to have significant role in + : one study, ++ : two studies, +++ : three or more studies. - : reported having no significant role. +/- : some studies confirm and some reject its role. miRNA: micro RNA, AHF: Acute heart failure, CHF: Chronic heart failure, HFpEF: Heart failure with preserved ejection fraction, HFpEF: Heart failure with reduced ejection fraction, ICM: Dilated cardiomyopathy, DCM: Dilated cardiomyopathy, ICM: Ischemic cardiomyopathy, CAD: Coronary artery disease

ety of mechanisms. The miRNA-133 and -30 modulate the expression of connective tissue growth factor (CTGF), which is a known as an essential mediator in the fibrotic process and the extracellular matrix synthesis [30, 43]. The effect of miRNA-133 and -30 by reduction of CTGF significantly reduces collagen deposition [43]. The miRNA-98 inhibits TGF- β 1-induced fibrosis in human cardiac fibroblasts [44]. The miRNA-24 prevents fibrosis by inhibiting differentiation and migration of cardiac fibroblasts [45]. In infarcted and failing heart tissue, miRNA-29 is expressed in fibroblasts, resulting in a reduction of collagen expression and inhibiting fibrosis [46]. However, miRNA-203 and -21 have a pro-fibrogenic role. He *et al.*, in an in vitro study, demonstrated that miR-203 increases the synthesis of CTGF, transforming growth factor-beta 1 (TGF- β 1), and fibronectin [47]. The contribution of miRNAs in different pathologic and physiologic cellular processes relating to HF makes them interesting targets for efficiently regulating gene expression, signaling pathways, cellular functions, and consequently heart muscle function. The changes in the level of miRNAs in body fluids reflect the intracellular events relating to the role of miRNAs in cardiomyocytes or other types of heart-related cells such as cardiac fibroblasts. Accordingly, a diagnostic role of miRNAs is also conceivable which will be investigated in the following section.

MicroRNAs and Diagnosis of AHF

Considering some favorable characteristics of miRNAs, they have become a new hope in the diagnosis of heart failure. From a laboratory aspect, appropriate stability of miRNA against severe conditions such as boiling, freezing, extreme pH levels has been well-established suggesting the feasibility of laboratory evaluation in the obtained samples from patients [48, 49]. Also, from a clinical aspect, it is postulated that unlike NT-proBNP and BNP, circulating miRNA levels are not affected by clinical confounders including age, sex, body mass index, kidney function, and blood pressure [50]. Besides, they are easily detectable from a variety of body fluids such as blood, urine, saliva, etc. Moreover, due to their special structure made up of a sequence

of nucleotides and tissue or pathology specific feature, they can be followed to find the exact source [51]. Therefore, they potentially can serve as excellent noninvasive diagnostic biomarkers in cardiovascular diseases including HF (19, 20). The diagnostic role of over 80 different miRNAs has been evaluated in patients with HF (Table-2). Some of them are evaluated in only one single subtype of HF including HF with reduced ejection fraction (HFrEF) or with preserved ejection fraction (HFpEF). Moreover, HF has been assessed in relationship with different specific miRNAs due to its different etiologies. Additionally, there are pros and cons of association between the level of miRNAs and some of the HF severity-related characteristics including ejection fraction (EF) or laboratory prognostic tests [52]. One of the well-known miRNAs in the diagnosis of HF is miRNA-423-5p which has been suggested by several studies as an excellent biomarker [53-58]. However, Tutarel *et al.* claimed that the level of miRNA-423-5p was not useful to diagnose HFrEF patients [59]. A recent systematic review and meta-analysis of 10 different studies revealed that although miR423-5p had the potential of being a biomarker of HF, BNP was the most convinced biomarker of HF [55]. Several miRNAs are specifically investigated in patients with AHF, the most prominent of which include miRNA- 27, -30, -199, and -423-5p (Table-2) [54, 60-63]. Tijssen *et al.* investigated the utility of miRNA-423-5p to discriminate AHF from both healthy controls and non-HF forms of dyspnea. Their results showed miRNA-423-5p can have significant diagnostic value in AHF (area under the curve [AUC] of 0.91). Corsten *et al.* studied the plasma level of a series of miRNAs in patients with AHF comparing them with healthy controls. The results showed all the selected cardiac-related miRNAs including miRNA-208b, -1, -499, and -223 were elevated in AHF patients but only miRNA-499 reached the significance level. Also, a liver-specific miRNA (miRNA-122) was significantly elevated in AHF patients possibly suggesting hepatic venous congestion in this patient group [50]. The diagnostic accuracy of miRNA-499 was reported to be even higher in patients with AHF due to myocardial infarction [64]. Li *et*

al. studied plasma levels of circulating miR-302 family members in patients with AHF comparing them to the level of those in AHF-free patients and healthy controls. The results demonstrated that the level of plasma miRNA-302s (except miRNA-302f) was significantly higher in AHF patients with the highest AUC of 0.87 for miRNA-302b-3p. Moreover, they revealed a strong positive correlation between miRNA-302s and NT-proBNP levels [65]. Ovchinnikova *et al.* revealed diagnostic potential of 12 miRNAs for AHF, which only seven of them passed the Bonferroni correction threshold (including miRNA-652-3p, -199a-3p, -106a-5p, -30e-5p, -27a-3p, -26b-5p, and -18a-5p) [66]. The diagnostic capability of these miRNAs was lately confirmed by further analysis yielding the AUC within a range of 0.82–0.97. The highest AUC belonged to miRNA-199a-3p and miRNA-18a-5p [60]. Recently, Wu *et al.* investigated three different miRNAs (including exo-miRNA-92b-5p, -192-5p, and -320a) in patients with AHF due to dilated cardiomyopathy (DCM) as compared to healthy volunteers. The analysis showed that serum exo-miRNA-92b-5p expression was significantly increased in AHF patients. They also demonstrated a diagnostic potential of miRNA-92b-5 for AHF with AUC of 0.808 and sensitivity and specificity of 62.8% and 85.3 %, respectively [67]. However, Seronde *et al.* analyzed the level of selected miRNAs (including miRNA -1, -21, -23, -126, and -423-5p) at the admission of a cohort study and reported that although miRNA-1, -126, and -423-5p were significantly low in AHF compared to non-AHF, none of the selected miRNAs (AUCs<0.70) or their combinations (AUCs<0.75) had considerable diagnostic value for AHF [68]. Apparently, there is little consensus on the capacity of miRNA for being considered as the sole biomarker of AHF. Therefore, some studies suggest the combination of miRNAs and BNP or NT-proBNP as the best strategy of using current biomarkers [55, 61]. In a study by Ellis *et al.*, a combined assessment of miRNAs and NT-proBNP significantly improved the AUC of NT-proBNP in the diagnosis of AHF by 4.6% [61]. This idea has also been established for non-acute HF [69]. Apparently, miRNAs have more to offer rather than only to diag-

nose AHF. It seems that the evaluation of miRNAs in patients with possible AHF can be considered not only to diagnose HF but also to evaluate the possible underlying etiology of AHF [70]. Being aware of the underlying cause of AHF can improve the management of these patients. Ikeda *et al.* studied the patterns of miRNAs expression in patients with ischemic cardiomyopathy (ICM), aortic stenosis, and idiopathic cardiomyopathy. The results showed that various types of miRNAs are regulated differentially in each underlying condition [71]. Also, Sucharov *et al.* reported similar results demonstrating that miRNAs had a distinct expression in two types of heart failure including idiopathic dilated cardiomyopathy (DCM) and ICM [72]. Another study revealed that miRNA-499-5p was significantly higher in patients having AHF due to non-ST elevation myocardial infarction than other AHF patients [64]. Some studies advocate the correlation between the severity of AHF and the level of miRNA. Danowski *et al.* reported that the level of serum miRNA-133 significantly decreased with increased severity of AHF in terms of both the New York Heart Association (NYHA) functional class and pulmonary artery occlusion pressure [73]. Wong *et al.* demonstrated that using an 8-microRNA discovery panel can distinguish HF patients with HF_rEF and HF_pEF [69]. Also, Li *et al.* demonstrated the same capacity for miRNA-302 [65]. Furthermore, Tijssen *et al.* postulated that miRNA-423-5p and miRNA-675 were higher in atherosclerotic forms of AHF as compared to non-atherosclerotic forms of AHF [56].

Prognosis

Prognosis is essential in the management of HF patients and decision making. Although a variety of miRNAs are discovered to have a diagnostic role in HF, few studies have reported clinically applicable prognostic significance of miRNAs [74, 75]. Yet, some miRNAs are demonstrated to have substantial prognostic values such as miRNA-423-5p. In a study by Seronde *et al.*, it was observed that miRNA-423-5p could properly predict one-year hospital re-admission (adjusted odds ratio [OR], 0.70) and one-year mortality

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(OR, 0.54). Patients with lower serum miRNA-423-5p had a significantly higher risk of long-term mortality [68]. Also, Schneider *et al.* evaluated AHF patients by measuring the level of selected miRNAs in several stages including within 24 h of hospital admission, at the time of hospital discharge, and a few weeks post-discharge, and following them for a period of two years. The results demonstrated that patients with higher miRNA4235p level between the time of admission and clinical compensation experienced fewer hospital readmissions in two years. Moreover, in this study, increased levels of miRNA-21 and -126 at the time of clinical compensation predicted better two-year survival and fewer readmissions [76]. Another study revealed that the prognostic value of miRNA-182 was even higher than NT-proBNP and high-sensitivity C-reactive protein (AUC were 0.695, 0.350, and 0.475, respectively). Further analysis by Cox regression yielded a significant predictive value of miRNA-182 for cardiovascular mortality [76]. Xiao *et al.* reported that miRNA-30d can independently predict one-year-all-cause mortality in AHF patients and it can be considered as a prognostic biomarker in AHF (AUC=0.806) [77]. Vegter *et al.* demonstrated that seven miRNAs were significantly negatively correlated to some previously recognized prognostic biomarkers; miRNA-16-5p was correlated to C-reactive protein, miRNA-106a-5p to creatinine, miRNA-223-3p to growth differentiation factor 15, miRNA-652-3p to soluble ST-2, miRNA-199a-3p to procalcitonin, and galectin-3 and miR-18a-5p to procalcitonin [60]. They also previously reported that lower levels of seven miRNAs (including miRNA-let-7i-5p, -18a-5p, -18b-5p, -223-3p, -301a-3p, -423-5p, and -652-3p) two days after AHF admission were in significant association with high risk of 180-day mortality, although only miRNA-18a-5p and -652-3p passed Bonferroni correction in the AHF validation cohort [66]. Other than cardiac-related prognostic characteristics, miRNAs can also predict renal functions in AHF patients. This was revealed by Bruno *et al.* investigating the association between 12 miRNAs and renal function in AHF patients from admission time until three days later. Among several miRNAs (including miRNA-199a-3p, -27a-3p,

-652-3p, -423-5p, and -let-7i-5p) which were associated with increase in creatinine during the first 3 days of hospitalization, miRNA-199a-3p was the strongest predictor of renal dysfunction (OR, 1.48 and a C-index, 0.701) [78].

Therapeutic Role of MiRNAs

As described previously in this review, miRNAs play a substantial role in the pathophysiology of HF. Therefore, the therapeutic role of miRNAs in a variety of diseases including HF has become an interesting topic of recent studies and a novel approach in target therapy. Two different techniques are mostly applied for altering the level of miRNA expression within the cells including using antagomirs and miRNA-mimics in order to decrease or increase target miRNAs expression, respectively [79, 80]. A study by Hullinger *et al.* revealed that systemic delivery of miRNA-15 antagomir in myocardial infarction models reduces the infarct size and cardiac remodeling and improves cardiac function [81]. Moreover, Montgomery *et al.* reported that systematic delivery of antagomir against miRNA-208a in hypertension-induced HF in Dahl rats could diminish pathological myosin switching, reduce cardiac remodeling, recover cardiac function, and also increase overall survival [82]. On the other hand, Suckau *et al.* used miRNA-mimics to reduce cardiomyocytes' diameter, cardiac fibrosis, dilation, and hypertrophy. In this in vivo study, RNA interference was delivered by adeno-associated virus vector, which was intravenously injected to target the heart of a rat model of pressure overload. This intervention restored systolic functional parameters to normal ranges [83]. In vitro and in vivo investigations of the effect of miRNA-29b in heart of mice demonstrated that enhancing the activity of miRNA-29b can prevent angiotensin II-mediated cardiac fibrosis and cardiac dysfunction. They also found that this positive effect is through targeting the TGF- β /Smad3 pathway by miRNA-29b [84]. Kumarswamy *et al.* demonstrated that sarcoplasmic reticulum calcium ATPase 2a gene therapy through an Akt/FoxO3A-dependent pathway can normalize the level of miRNA-1 in a chronic rat HF model resulting in rescued cardiac function [85]. Another study

using antagomir against miRNA-132 improved cardiac hypertrophy and HF in mice, suggesting a possible therapeutic approach [86]. As far as the researchers of this study investigated, no clinical trial has investigated the effect of therapeutic regulation of miRNAs in AHF patients yet. However, there are some *in vivo* and *in vitro* studies supporting the idea of such treatment. A series of studies have proposed the beneficial effect of inhibition of miRNA-24 in AHF due to ischemic events [87-90]. Inhibition of miRNA-24 limited myocardial infarct size in acute myocardial infarction and cardiac dysfunction mouse model by inhibiting the endothelial apoptosis and improvement of vascularity, which enhanced cardiac function and survival [87]. Also, adenovirus-directed overexpression of miR-24 in cardiomyocytes reduced both JP2 expression and Ca²⁺ transient amplitude and improved excitation-contraction coupling in heart cells, suggesting a novel possible strategy in the treatment of HF [91]. Some studies demonstrate different effects of regulation of a single miRNA in HF experimental models. Also, an *in vivo* study by Thum *et al.* demonstrated that inhibition of miRNA-21 in a pressure-overload-induced disease model mouse could significantly suppress interstitial fibrosis and ameliorate cardiac dysfunction by inhibition of cardiac ERK-MAPkinase activity [36]. On the other hand, Liu *et al.* showed that Trimetazidine leads to reduced right-ventricular cardiomyocytes apoptosis, improved ventricular function, and reduced fibrosis through increasing the expression of miRNA-21 [92]. Furthermore, considering a wide range of miRNA functions in multiple organs, systemic treatment with antagomirs and miRNA-mimics in HF patients may affect other organs, as well. For instance, some of

the miRNAs associated with cardiovascular diseases are involved in neoplasms as tumor suppressors [93]. Therefore, targeting miRNAs necessitate a thorough evaluation of parallel mechanisms in other cells and tissues to prevent adverse effects.

Conclusion

Generally, it has been demonstrated that miRNAs play an essential role in the pathophysiology of HF. Furthermore, many studies have postulated the great potential of miRNAs to be used as diagnostic biomarkers in AHF. Although there is not a proper consensus regarding which miRNA is the best for such implication, the diagnostic applicability of some miRNAs such as miRNA-423-5p have been verified by many studies but not completely successful in comparison with NT-proBNP as the most acknowledged HF biomarker. The prognostic efficacy of miRNA-423-5p and some other miRNAs are also suggested by a variety of studies; however, an adequate consensus is also lacking for this application. Although invaluable attempts have been accomplished regarding therapeutic regulation of miRNAs and these mediators have become future hopes for the treatment of AHF, extensive investigations are still necessary to advance them up to the clinical application.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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