Review Article

Non-coding RNA in cardiovascular disease: a general overview on microRNAs, long non-coding RNAs and circular RNAs

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Abstract: Non-coding ribonucleic acids (ncRNAs) are ubiquitous RNA molecules not translated into proteins and involved in different steps of gene regulation and transcription. Their dysregulation has been widely demonstrated in different forms of cardiovascular disorders. The present review discusses how ncRNAs [including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs)] are involved in cardiovascular biology and diseases, highlighting their potential role as circulating diagnostic and prognostic biomarkers, and therapeutic targets. The review also addresses future directions in research, covering issues still unresolved and the relevant factors limiting their widespread use in the clinical practice.

Keywords: MicroRNAs (miRNAs); long non-coding RNAs (lncRNAs); circular RNAs (circRNAs); cardiovascular disorders

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Introduction

Cardiovascular diseases (CVDs) remain the main cause of morbidity and mortality in the Western world, and there is need for basic science research to provide insights into disease mechanisms. Indeed, obtaining a better understanding of the molecular and cellular mechanisms driving CVD development and progression is essential to identify new biomarkers and novel therapeutic targets in order to improve care and prevent the development of life-threatening complications.

Over the last decade, the advances in high-throughput sequencing technology have allowed the opportunity to expand our knowledge on the complexity of the human transcriptome, showing that the non-coding portion of the genome plays a more significant role in human biology than previously thought (1). Currently, we know that the most of the human genome is not translated into proteins, but transcribed into various classes of functional non-coding RNAs (ncRNAs) that are powerful regulators of a plethora of cellular and disease processes (2).

Based on their size, these molecules are classified into small ncRNAs (<200 nucleotides long), including microRNAs (miRNAs), and long ncRNAs (lncRNAs), exceeding a length >200 nucleotides. lncRNAs can also present circular form, called circular RNAs (circRNAs).

Recently, several review articles have been published discussing the involvement of three major types of ncRNAs (miRNAs, lncRNAs and circRNAs) in cardiovascular system, outlining their biogenesis, physiologic actions and pathogenic role (3-6). The present review discusses how ncRNAs (including miRNAs, lncRNAs and circRNAs) are involved in cardiovascular biology and diseases, highlighting their potential role as circulating diagnostic, and prognostic biomarkers and therapeutic targets. The review also addresses future directions in research, covering issues still unresolved and the relevant factors limiting their widespread use in the clinical practice.

miRNAs in the cardiovascular system

miRNAs are endogenous RNAs of ~22 nucleotides that negatively regulate expression of target genes by usually binding to the 3' untranslated region (UTR) of mRNA and inhibiting their translation (7,8). They are synthesized as

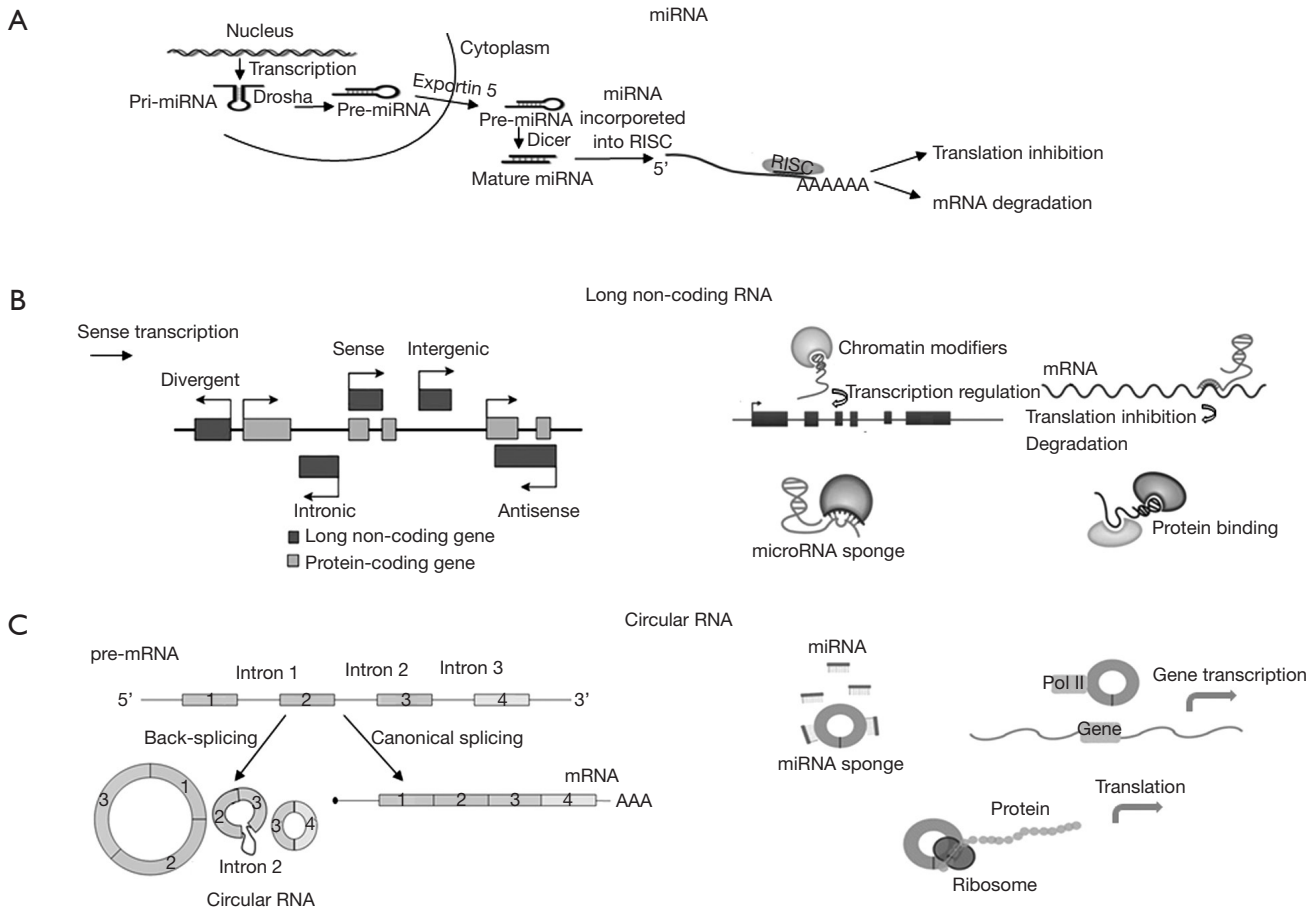

Figure 1 Schematic representation of the biogenesis and function of miRNA (A), lncRNA (B) and circRNA (C). (A) MiRNA is transcribed from longer precursors (pre-miRNAs) in the nucleus and further processed via specific nucleases to form the RISC complex in the cytoplasm. Within this complex, miRNAs regulate mRNA target transcript expression by degradation or translational repression. (B) Upon transcription of a lncRNA from its gene location, it can regulate proximal events (cis-acting) or distal events (trans-acting) regulating the expression of genes by interacting directly with DNA recruiting chromatin or regulating mRNA degradation and translation. lncRNAs act as sponges for other RNA species (miRna sponge) or proteins. (C) Circular RNAs is produced via back splicing and can be formed from a single exon or more or contain introns that have been retained between one or more circularized exon. Functions of circRNAs include miRNA sponges, gene transcription regulation, and translation.

precursors in the nucleus (*Figure 1*), where they undergo maturation with several enzymatic reactions and are translocated to the cytoplasm where they exert their biological function recruiting specific silencing proteins that form the RNA induced silencing complex (RISC) (9,10). It has been predicted that, in humans, about 60% of mRNAs are targets for miRNAs and one miRNA may target more than 100 mRNAs (8).

Specific miRNAs are differently expressed in cardiac tissue and vascular cells, playing a crucial role as regulators of cardiovascular biological functions, including cardiovascular cell differentiation, growth, proliferation, apoptosis, angiogenesis and cell contractility (11).

Consequently, aberrant expression of miRNAs has been reported in heart suffering of several CVD, such as myocardial infarction (12) and end-stage cardiomyopathy (13).

Several miRNAs (*miRNA-1*, *miRNA-133a*, *miRNA-208a/b*, *and miRNA-499*) are believed to be cardiac-specific molecules and abundantly expressed in the myocardium (14).

In animal models, aberrant expression of cardiac-specific miRNAs has been associated with the onset and

progression of cardiac conditions, such as arrhythmias, cardiac hypertrophy and fibrosis (15,16). The dysregulation of cardiac-specific miRNAs has been also reported in cardiac tissue of patients with heart failure and myocardial infarction (17,18).

However, other miRNAs (e.g., *miRNA-21-5p*, *miRNA-126-3p*) that are not cardiac-specific or muscle-enriched molecules are important players in several cardiovascular processes, contributing the onset and progression of CVDs (19).

Overall, expression profiling studies in experimental and human heart disease have shown that the expression of a large number of miRNAs is altered in several cardiovascular disorders (3-6), including myocardial infarction (*miRNA-1*, *miRNA-20a*, *miRNA-21*, *miRNA-126*, *miRNA-155*, *miRNA-210*, *miRNA-214*), cardiac arrhythmia (*miRNA-1*, *miRNA-17-92*, *miRNA-106b-25*, *miRNA-133*, *miRNA-133a*, *miRNA-212*), cardiac fibrosis (*miRNA-21*, *miRNA-29*, *miRNA133*), cardiac hypertrophy (*miRNA-21*, *miRNA-23a*, *miRNA-24*, *miRNA-199*, *miRNA-208a*) and heart failure (*miRNA-1*, *miRNA-21*, *miRNA-29*, *miRNA-30*, *miRNA-195*, *miRNA-210*, *miRNA-499*).

miRNAs are also critical in many key processes linked to vascular biology and atherosclerotic development, regulating endothelial dysfunction (*miRNA-27b*, *miRNA-130a*, *miRNA-126*, *miRNA-221* and *miRNA-222*) and vascular smooth muscle cell proliferation and contractile function (*miRNA-143* and *miRNA-145*) as well as inflammatory macrophage responses (*miRNA-33*, *miRNA-155*, *miRNA-146a*, *miRNA-let7a*, *miRNA-21*, *miRNA-223* and *miRNA-125a*) (20-23).

Furthermore, a number of other specific miRNAs have been implicated in lipid metabolism and cholesterol homeostasis including *miRNA-33* that is one of the most extensively studied miRNAs and it represses multiple genes involved in cellular cholesterol trafficking (24,25).

Recently, profiling analyses also reported differential expression of miRNAs (*miRNA-21*, *miRNA-26a*, *miRNA-30b*, *miRNA-141*, *miRNA-125b*, *miRNA-148a*, *miRNA-204*, *miRNA-214*) in cardiac valve disease, regulating key processes underlying disease progression, such as fibrosis, calcification, matrix degradation remodeling, and inflammation (26-28).

lncRNAs in cardiovascular physiopathology

lncRNAs are a heterogeneous group of RNA transcripts with lengths >200 nucleotides that can be classified as sense, antisense, intronic, intergenic and divergent lncRNAs according to their relative genome position (*Figure 1*). lncRNAs can be broadly classified into those that act in *cis*, influencing proximal events, and those that influence distal biological functions throughout the cell in *trans* (29,30).

Indeed, lncRNAs are involved in numerous and different biological events, such as chromatin structure changes, transcription and post-transcriptional processing, intracellular trafficking, and regulation of enzymatic activity (29,30). lncRNAs can also regulate the activity of other ncRNAs, specifically miRNAs, by acting as competing endogenous RNAs (31).

LncRNAs are less conserved than miRNAs, suggesting a species-specific role of these RNA molecules (32). Although the dysregulation of lncRNAs has been implicated in various human diseases (33), the functional roles and mechanisms of most lncRNAs remain, however, elusive (34).

LncRNAs have been reported to predominantly function as key regulators of cell fate commitments in embryonic and organism development (35). In 2013, a novel lncRNA, named Braveheart, was identified in mouse heart and demonstrated to be a key regulator of cardiovascular lineage and cardiac gene expression during heart development (36). Subsequently, an elegant study identified a human-specific lncRNA, named Heart Brake LncRNA 1 (*HBL LncRNA 1*), which negatively regulates human cardiomyocyte development from pluripotent stem cells (hiPSCs) by silencing miRNA-1 activity (37).

To date, the deregulation of lncRNAs has been reported in some cardiovascular conditions such as myocardium infarction, myocardial fibrosis, cardiac hypertrophy and heart failure (38-45).

For instance, lncRNA-Wisp2 super-enhancer-associated RNA (*lncRNA-wisper*) has been found to be a cardiac fibroblast-enriched lncRNA that regulates cardiac following myocardial infarction in a murine mode (46). Moreover, the expression of lncRNA-wisper was also correlated with the cardiac fibrosis in heart tissue from human patients suffering from aortic stenosis (46).

Myocardial infarction associated transcript (*MIAT*) was originally identified as a non-coding functional RNA able to confer risk of myocardial infarction (47). Subsequently, through a mouse model of myocardial infarction, it has been demonstrated the critical involvement in cardiac fibrosis and dysfunction (48), probably by sponging miRNA-150 (49) and miRNA-93 (50) expression in cardiomyocytes.

The lncRNAs cardiac hypertrophy-associated transcript (*CHAST*) is increased upon pressure overload-induced

HF in mice and is preserved in humans. Interestingly, *CHAST* homolog in humans is significantly up-regulated in human embryonic stem cell-derived cardiomyocytes upon hypertrophic stimuli and in hypertrophic heart tissue from aortic stenosis patients (51). On the contrary, *Myheart* or *Mhrt* is a cardiac lncRNA, located in the locus of the cardiac-specific gene myosin heavy chain 7, which prevents cardiomyocyte hypertrophy by sequestering Brg1, a stress-activated, ATP-dependent chromatin-remodeling factor, and, therefore, avoiding the transcription of hypertrophy related genes that are induced during stress through a Brg1-mediated chromatin remodeling mechanism (52).

circRNAs in CVD

circRNAs are a peculiar group of lncRNAs, consisting of at least a few hundred nucleotides (53). As schematized in *Figure 1*, circRNAs are generated via back-splicing, a form of alternative splicing, and characterized by covalently closed loop structures through joining the 3' and 5' end together by exon or intron circularization (53,54). In the past, circRNAs were considered to have no biological function (55), but it has been recently demonstrated that they are abundant and preserved in mammalian cells and have biological functions by regulating gene expression at the transcriptional or post-transcriptional level (53,56,57).

circRNAs have the ability to bind to miRNAs and consequently regulate miRNA function, acting as sponge (58). Moreover, circRNAs have a relatively higher biological stability than linear RNA due to their circular structure that cannot be recognized or hydrolysed by RNA exonuclease (59).

Although several RNA-sequencing analyses have revealed that there is a high-abundance of specific cardiac-expressed circRNAs in human heart (60,61), much less is known about their role in diseased cardiac tissue. Recently, experimental studies have begun to delineate the role of circRNAs as crucial modulators of miRNA levels in cardiac conditions, such as myocardial infarction (62), cardiac fibrosis (63,64) and hypertrophy (65).

A circRNA profiling in left ventricle RNA samples with hypertrophic and dilated cardiomyopathy and unaffected heart tissues found 80 circRNAs expressed from the titin (*TTN*) gene (66). In particular, the authors showed that the RNA-binding motif protein 20 (RBM20), an important pathogenic gene of dilated cardiomyopathy, regulated the biosynthesis of circRNAs from the *TTN* gene (66).

Recently, a very interesting study identified an abundant expression of cardiac circRNAs (*circSLC8A1*, *circCACNA1D*, *circSPHKAP* and *circALPK2*) in heart tissues as well as in human induced pluripotent stem cells-derived cardiomyocytes, which might be used as biomarkers (67). Furthermore, the expression level of *circSLC8A1* significantly increased in specimens from patients with dilated cardiomyopathy when compared to the healthy controls (67).

Altogether, these findings encourage future investigation to identify the differential expression circRNAs in different disease phenotypes in patients.

Circulating ncRNAs as biomarkers

In addition to the relevance of ncRNAs as regulators in the molecular mechanisms of disease, numerous evidence suggests their potential use as novel biomarkers for the diagnosis and clinical decision making (19,68,69). The best-studied circulating ncRNAs group is represented by circulating miRNAs, that are released into circulation usually packaged in different micro-particles (exosomes, micro-vesicles and apoptotic bodies) or associated with lipoprotein complexes or RNA-binding proteins, which provide stability and resistance to plasma RNase digestion and enable miRNA transfer from one cell to another (70).

Numerous studies have explored the potential of miRNAs as clinical biomarkers in CVD in the diagnosis and prognosis of CVDs (19,68-71).

For instance, a recurrent group of cardiomyocyte-enriched miRNAs (*miRNA-1*, *miRNA-133*, *miRNA-208a/b* and *miRNA-499*) and non-cardiac miRNAs (*miRNA-21*, *miRNA-26a*, *miRNA-27a*, *miRNA-30c/d*, *miRNA-106a-5p*, *miRNA-122*, *miRNA-126*, *miRNA-134*, *miRNA-145*, *miRNA-146*, *miRNA-150*, *miRNA-197*, *miRNA-199*, *miRNA-223*, *miRNA-328*, *miRNA-423-5p*, *miRNA-486*) in plasma or serum have been suggested as biomarkers of coronary artery disease and myocardial infarction as well as correlated with the diagnosis and the prognosis of heart failure (19,68-71).

Other circulating miRNAs (*miRNA-1*, *miRNA-21*, *miRNA-133a/b*, *miRNA-146a*, *miRNA-150*, *miRNA-328)* have been associated with cardiac arrhythmia and atrial fibrillation (19,69).

Other studies identified several circulating (*miRNA-1*, *miRNA-21*, *miRNA-22*, *miRNA-133*, *miRNA-210*, *miRNA-382*) as potential biomarkers for valvular heart disease, especially aortic stenosis, in combination with clinical and imaging parameters (26,72,73).

Despite these promising findings on circulating miRNAs as novel CVD biomarkers, great uncertainty remains on their diagnostic feasibility and clinical use due to inconsistent results among studies, attributable, at least in part; to a number of technical limitations for their measure in biological fluids (71).

In addition to miRNAs, lncRNAs can be released into the extracellular space and subsequently be detected in body fluids, such as serum and plasma (19,69).

Accordingly, some circulating lncRNAs were recently described as potential biomarkers for coronary artery disease/acute myocardial infarction (*ZFAS1*, *UCA1*, *HOTAIR*, *LIPCAR*, *ANRIL*, *KCNQ1OT1*, *LncPPARδ**, *CoroMarker)* and heart failure (*SENCR*, *NRON*, *LIPCAR*, *MHRT*), encouraging future studies to determine the value of lncRNAs as novel cardiac biomarkers (38,69,74-79).

Moreover, circRNAs have a great potential as they are extraordinarily more stable in body fluids than other noncoding RNAs because their circularization protects them from endonuclease activities (80).

Several studies have also reported circRNAs as diagnostic and prognostic biomarkers of CVD (4,19). For instance, a clinical study identified a circRNA, *MICRA*, whose expression levels measured at reperfusion in peripheral blood samples of 642 patients with acute myocardial infarction from two independent cohorts, predicted left ventricular dysfunction after 3 to 4 months (81).

Furthermore, a circRNA, designated *circRNA_081881*, may be correlated with myocardial infarction since it was down - regulated more than 10 - fold in blood samples of patients (82).

An increased risk of atherosclerosis has been associated with the circular isoform of ANRIL (*cANRIL*) that is associated with the *INK4/ARF* locus on human chromosome 9p21 (83).

A very recent study investigated the circRNA profile in the peripheral blood of patients with coronary artery disease, reporting a circRNA (*hsa_circ_0124644*) as a biomarker with a great diagnostic value for the disease (84).

The main circulating ncRNAs involved in the CVDs are summarized in *Figure 2*.

Concluding remarks and future perspectives

In conclusion, ncRNAs are ubiquitous RNA molecules that play a key role in modulating the molecular mechanisms underlying the pathogenesis of the CVD. Accordingly, there are attractive and promising applications of ncRNAs in the diagnosis and treatment of these diseases (3-6).

From a therapeutic perspective, the use of molecules to inhibit or overexpress small and long ncRNAs could be used as novel therapeutic strategy to combat various cardiac disorders.

For instance, pharmacological inhibition of *miRNA-33a* and *miRNA-33b* (miRNAs involved in the regulation of cholesterol transport) led to an increased levels of plasma HDL cholesterol and a coincident reduction of VLDL triglycerides without any adverse side effects in non-human primates, supporting the development of antagonists (also called antagomiRs or blockmiRs) of *miRNA-33* as potential therapeutics for dyslipidemia and related atherosclerotic diseases (85).

Furthermore, inhibition of *miRNA-29 in vivo* abrogates aortic dilation in mice, suggesting that blocking *miRNA-29* may represent a potential molecular target to treat aortic aneurysms (86).

On the other hand, the administration of systemic miRNAs through miRNA mimics or introducing genes coding for miRNAs into viral constructs could be an attractive therapeutic approach for many diseases (87).

In the cardiovascular field, it has been recently shown that the overexpression with mimic (88) or adeno-associated virus-mediated cardiomyocyte-targeted expression of miR-378 (89) produced significant anti-apoptotic and anti-hypertrophic activities in cardiac cells, representing a potential treatment for ischemic heart disease. Additionally, a recent study demonstrated the feasibility of using viral-based delivery of DNA code for non-native miRNA *in vivo* to significantly limit target RNA translation in the whole heart (90).

The miRNA-based therapy to inhibit an overexpressed miRNA during diseased condition or to mimic a disease–down-regulated miRNA is schematized in *Figure 3*.

In spite of these encouraging premises, there is still much to learn and several concerns need to be addressed before ncRNAs can be deployed as a therapeutic option in cardiovascular conditions. Indeed, the fact that miRNA or long ncRNAs exert broad effects on multiple pathological pathways can be viewed as a major limitation with regard to both therapeutic efficacy and "off-targets" systemic effects (4-6). Therefore, further research on the enhancement of target affinity, stability and specificity are required to overcome the off-target effects and potential toxicity before ncRNA therapeutics can be used safely and effectively in the clinical setting.

Further studies are warranted to exhaustively elucidate

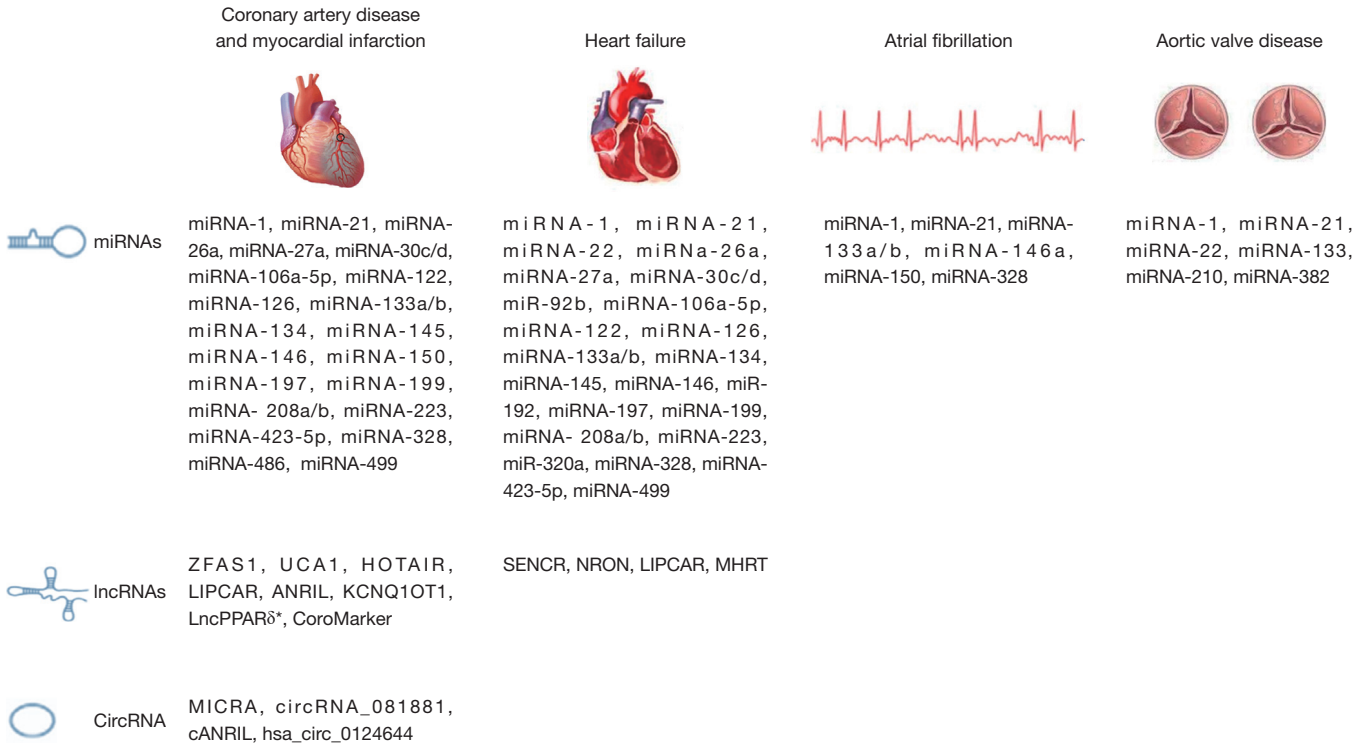

Figure 2 Overview of circulating ncRNAs as diagnostic and prognostic biomarkers from studies on different cardiovascular diseases.

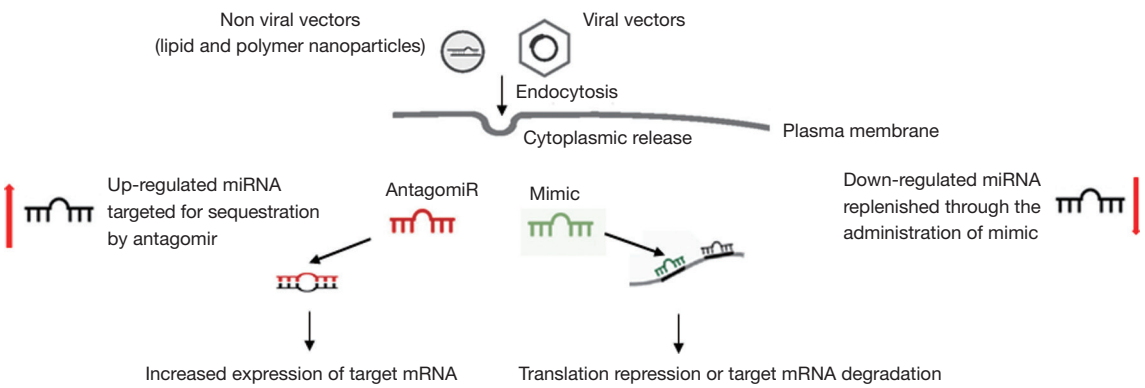

Figure 3 Schematic representation of miRNAs manipulation with miRNA mimics or antagomir developed in viral and/or nonviral vectors.

ncRNAs changes and their underlying mechanisms in various cardiovascular pathological settings, especially regarding the cardiac function of the lncRNAs and circRNAs.

From a clinical viewpoint, ncRNAs are emerging as novel biomarkers for the diagnosis and disease progression of different cardiovascular conditions.

Nevertheless, several problems still remain unresolved mainly due to the lack of reproducibility across different studies that may hamper the transition of these circulating biomarkers from promising tools to clinical practice. Several methodological aspects related to sample collection, measure methodology and normalization seem to explain the lack of reproducibility in different published studies (91,92). Thus, technological advances are necessary to ensure fast, reliable and reproducible results for the absolute quantification of circulating ncRNA. The small sample size with reduced statistical power is another relevant problem

that may have contributed to many discordant published results (91). Large-scale studies performed in a collaborative manner are also required to further validate the potential of ncRNAs as biomarkers as well as to facilitate their transfer into clinics.

In conclusion, ncRNA research is a very fascinating and challenging field that certainly will improve the knowledge of the molecular mechanisms at the basis of some cardiovascular conditions, giving the opportunity to develop new diagnostic and therapeutic approaches. However, it is a long road from a proof of concept to their widespread use as early and specific biomarkers of CVDs. It is appealing to identify specific biomarkers other than the ones conventionally used, for a precise risk stratification in patients with cardiovascular conditions. More work is needed but ncRNA are here to stay.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2018.11.03). The author has no conflicts of interest to declare.

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