

Invited Review Article

MicroRNA and Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVD) are one of the most common causes of death in both developing and developed countries in the world. Even though improvement in primary prevention, the prevalence of CVD is increasing in recent years. Hence, it is very crucial in both to investigate a molecular pathophysiology of CVD in depth and to find novel biomarkers in terms of early and proper prevention and diagnosis of these diseases. miRNAs are an endogenous, conserved, single-stranded and 21-25 nucleotide in length non-coding RNAs. miRNAs have an important role in various cellular events such as embryogenesis, proliferation, vasculogenesis, apoptosis, cell growth and differentiation and tumorigenesis. They also have potential roles in cardiovascular system like angiogenesis, cardiac cell contractility, control of lipid metabolism, plaque formation, arrangement of cardiac rhythm and cardiac cell growth. Circulating miRNAs are promising novel biomarkers for purposes of diagnosis and prognosis of CVD. Cell or tissue specificity, stability in serum or plasma, resistance to degradative factors such as freeze-thaw cycles or enzymes in blood, fast release kinetics, provide potential for miRNAs to be a surrogate marker for early and accurate diagnosis of the disease and for prediction of middle or long term prognosis. Moreover, it can be a logical approach combining miRNAs with traditional biomarkers to improve risk stratification and long term prognosis. In addition to efficacy for diagnosis and prognosis, miRNA-based therapeutics may be more beneficial to treat CVD by using novel platforms and computational tools and combining with traditional analysis methods. microRNAs are promising novel therapeutic agents, which can affect multiple genes by using different signalling pathways. miRNAs therapeutic modulation techniques were used in the settings of atherosclerosis, acute myocardial infarction, restenosis, vascular remodelling, arrhythmias, hypertrophy and fibrosis, angiogenesis, aortic aneurysm, pulmonary hypertension and ischemic injury. This review will present detailed information about miRNAs in terms of structure and biogenesis, stages of synthesis and functions, expression profiles in serum/plasma of living organisms, diagnostic and prognostic potential as a novel biomarker and therapeutic applications in various different diseases.

Keywords: Cardiovascular disease, Gene expression, MicroRNAs

Introduction

Cardiovascular diseases (CVD) are one of the most common causes of death in both developing and developed countries in the world (1). Even though improvement in primary prevention, the prevalence of CVD is increasing in recent years. Hence, it is very crucial in both to investigate a molecular pathophysiology of CVD in depth and to find novel biomarkers in terms of early and proper prevention and diagnosis of these diseases. While nearly 80% of genes in human body undergo transcription, just 1-2% of them respectively translated into protein, which lead to constructing many non-coding RNA transcripts (ncRNA)(2,3). Non-coding RNA, which is composed of small nuclear and nucleolar RNAs, Piwi interacting RNAs, Y-RNAs, microRNAs(miRNA) and long ncRNAs, is very important to regulate gene expression and to use in epigenetic applications. Furthermore, they are supposed to be one of the important etiologic factors for developing of CVD. To this date, miRNAs are the most studied and characterized ncRNA in the literature(4).

miRNAs are an endogenous, conserved, single-stranded and 21-25 nucleotide in length non-coding RNAs(5). Lin-4, which is the first miRNA, was discovered in *Caenorhabditis elegans* in 1993. Moreover, the primary miRNA database was released in 2002 with only 218 entries and they were continually rising in the following years. The

latest miRBase Sequence Database includes 28,645 entries stands for hairpin precursor miRNAs, which includes 35,828 mature miRNAs in 223 species. After that, approximately 20,4196 novel hairpin sequences and 5441 novice mature products have been accompanied (6). As a member of huge family of posttranscriptional modulators, miRNAs regulate various different gene expression at the post-transcriptional level by binding to 3' untranslated regions (UTR) of target messenger RNAs (mRNAs). miRNAs arrange diverse gene functions by mRNA digestion, inhibition of translation or miRNA-mediated mRNA decay due to several factors including complementary degree, the number and function of binding sites of target mRNA, which are positively correlated with each others (7,8). On the other hand, miRNAs can interact with the 5' UTR of target mRNA causing stimulation and activation of targeted proteins or inhibition of translation (9,10). Moreover, various miRNAs can interact with promoter protein structures like argonaute-2 and fragile X mental-retardation-related protein 1, which results in an indirect up-regulation of translation of the targeted genes (11). To this date, over 2500 miRNAs have been discovered and presented in human body (12). Also, many different novel computational programmes have been found to predict target mRNAs of each specific miRNAs such as TargetScan (<http://www.targetscan.org>), miRanda ([http:// www.microRNA.org](http://www.microRNA.org)) and TarBase (<http://www.microna.gr/tarbase>). miRNAs have very complex regulatory mechanisms based on complementary base-pairing between miRNA and target mRNA, which individual miRNA is able to arrange the expression and functions of multiple genes, conversely, single genes can be regulated by many different miRNAs (13). A diverse role of dysregulated miRNAs in several different diseases in human body was reported in previous study (1,13,14). This review will present a detailed informations about miRNAs in terms of structure and biogenesis, stages of synthesis and functions, expression profiles in serum/plasma of living organisms, diagnostic and prognostic potential as a novel biomarker and therapeutic applications in various different diseases.

MicroRNA Biogenesis and Functions

MicroRNAs have biogenesis that consists of multisteps processes including transcription, processing, splicing and export to cytoplasm, maturation and target binding. The first step is a synthesis of pri-miRNA, which is a large structure composed of several sequences for many different miRNAs, from either an independent miRNA gene or parts of introns of protein coding RNA polymerase II transcripts via RNA polymerase II enzyme in nucleus. Second step is a cleavage of pri-miRNA Droscha (RNA-specific RNase-III-type endonuclease) and its cofactor DGCR8 to produce pre-miRNA, that consists of nearly 70 nucleotides. Then, pre-miRNA are transported to cytoplasm passing through nuclear pores in membrane via exportin-5 and RanGTPbinding protein (15). After that, pre-miRNA is undergone to further cleavage by Dicer (the cytoplasmic RNase-III endonuclease) into a double stranded miRNA duplex (22 nucleotides) consisting of active and functional mature guide strand and inactive passenger strand in cytoplasm. Subsequently binding of this duplex to target, it is unwinded and mature strand is loaded into RNA-induced silencing complex (RISC), which is composed of Argonaute proteins and another modulatory effectors organizing the suppressor effect of this complex. Last, RISC guides the active strand for binding to its target mRNA through complementary interaction between miRNA and target mRNA seeding sequences. Ultimately, miRNA show their effects in human genome (16,17).

After synthesis and processing, extracellular miRNAs are secreted into blood circulation by packaging them in different carriers such as exosomes, microparticles, lipid vesicles and bound with argonaute-2 or nucleophosmin-1 proteins or with high or low density lipoproteins for protecting them from digestion (18-20). Hence, miRNAs can maintain their stability in blood in harsh conditions like extreme environmental basic pH, high temperature, multiple repeated freeze-thaw cycles, prolonged storage, degradation by ribonuclease enzyme activity. However, exogenous free synthetic miRNAs are degraded easily by ribonucleases in blood stream(18-20). The most of the miRNAs are also produced from blood cells and tissues such as liver, heart, kidney, lung (21).

miRNAs have an important roles in various cellular events such as embryogenesis, proliferation, vasculogenesis, apoptosis, cell growth and differentiation and tumorigenesis. They also have potential roles in cardiovascular system like as angiogenesis, cardiac cell contractility, control of lipid metabolism, plaque formation, arrangement of cardiac rhythm and cardiac cell growth(22).

miRNA and cardiovascular system development

A crucial role of many different miRNAs in development and function of heart and blood vessel in human body was demonstrated in previous sequence, microarray and other array based profiling studies. miR-1 and miR-133, which have highest expression levels in the heart, have controversial tasks on cardiac cells; which promote and inhibit cardiac cells proliferation and differentiation respectively (23). Moreover, several different miRNAs such as miR-1, miR-195, miR-133, miR-126, miR-16, miR-590, miR-199, miR-143, miR-208a, miR-499, miR-27-b, miR-497, miR-126, miR-30-d, miR-208b, miR-15a/b, miR-16-1/2 take part in regulation of cardiovascular sytem development, cardiogenesis, cardiac cell proliferation and differentiation, cell growth and integrity, cardiac cell communication, premature cardiac cell cycle arrest and cardiac cell injury due to ischemia and/or hypoxia (24). Some miRNAs like miR-130, miR-145/miR-143 cluster, miR-210 and let-7f play an important role for vascular smooth muscle cell proliferation and differentiation, migration, vessel development and tubulogenesis (24,25).

miRNA and cardiac hypertrophy and remodelling

Cardiac remodeling is very important for adaptive responses of heart to stressful conditions or stressors. However, it leads to pathological hypertrophy, fibrosis, myocardial infarction, arrhythmias, tissue necrosis, cardiomyopathies and heart failure, if continues such a long time. It is divided as follows: cardiomyocyte apoptosis, hypertrophy, interstitial fibrosis and regeneration. An involvement and role of some miRNAs for developing physiological and pathological cardiac hypertrophy were reported in previous studies. While miR-26, miR-9, miR-208 a and b, miR-133 a and b, miR-1, miR-195, miR-199, miR-18b, miR124, miR223, miR-98 and miR-499 were found to be as regulator of cardiac hypertrophy in the setting of physiological or pathological, miR24, miR miR-101a and b, miR-30, miR-133, miR-21 and miR-29 were reported as players of cardiac fibrosis (26). Moreover, miR-221, miR-590, miR-33-b, miR-320, miR-34a can participate in cardiac cell regeneration (27).

miRNA and vascular disease

In human body, endothelial cells and vascular smooth muscle cells play a crucial role for providing vascular cell survival, integrity and functions. Abnormal miRNAs expression may lead to several different CVD such as atherosclerosis, vascular inflammation, diabetes with vascular complications, coronary and peripheral artery diseases. miR-200, miR-34a, miR-217 and miR-146a were reported as highly expressed in the setting of endothelial cell senescence, which is characterized as uncontrolled apoptosis, severe inflammation, reduced endothelial nitric oxide synthesis and releasing leading to endothelial dysfunction, atherosclerosis and its complications (26).

Angiogenesis is affected by distorted endothelial cell dysfunction. It may cause increased inflammation, which ultimately results in vascular disease, ischemic cardiac events, atherosclerosis. miR-126, miR-132, miR-16, miR-130, miR-101, miR-424, miR-221-222, miR-17-92, miR-200-b, miR-23-24 were presented to be specifically expressed in vascular cells/tissues that participate in angiogenesis (26). Furthermore, vascular inflammation is defined as leukocytic activation and infiltration, production and secretion of inflammatory cytokines, growth factors and adhesive molecules, which may lead to changes in several different miRNAs expressions, functions in endothelial cells. miR-31, miR-21, miR-10a, miR-17, miR-424, miR-181b, miR-106a, miR-17-92, miR-146, miR-17-5b, miR-150, miR-155 were found to be play a role in the setting of vascular inflammation in previous studies (26).

miRNA and atherosclerosis

Atherosclerosis is a complex disease that has many steps for emerging such as endothelial cell dysfunction, inflammatory cells infiltration and migration, impaired vascular cell integrity, vulnerable plaque formation, formation of oxidize foam cells, lipid metabolism abnormalities and vascular smooth muscle cell differentiation, which may lead to ischemic heart diseases, hypertension, aortic aneurysms, heart valve diseases, peripheral artery diseases and stroke. An important role of miRNAs both in humans and animals in the development of atherosclerosis was reported in some studies. In endothelial dysfunction; miR-31, miR-181-b, miR-10a/b, miR-126, miR-17-3p were demonstrated to be participate in this process (28). Moreover, miR-122 and miR-33a/b were found to be an important regulator of cholesterol homeostasis(28). Plaque development is one of the key step in developing atherosclerosis and miR-26a, miR-221, miR-155, miR-21 and miR-125a-5p expressions were altered in this setting(28). Moreover, miR-145, miR-127, miR-100 and miR-133a/b were reported as dysregulated miRNAs in plaque instability and rupture, which may result in acute coronary syndromes (28). In atherosclerosis, activated oxidized low density lipoprotein containing foam cells can secrete different inflammatory cytokines including those participate in neoangiogenesis. Several various miRNAs such as miR-210, miR-222, miR-155, miR-27a/b and miR-221 may accompany in developing of neoangiogenesis (28).

miRNA and hypertension

Hypertension is one of the most important risk factor for developing of atherosclerotic heart diseases, heart failure, stroke and peripheral artery disease. Arterial stiffness, aging, inflammation, renin-angiotensin-aldosterone sytem, endothelial dysfunction accompany to pathogenesis of hypertension. In recent years, altered expressions of some miRNAs such as miR132, miR-155, miR-212, miR-143/145, miR-145 have been reported as regulators of blood pressure in humans by using renin-angiotensin-aldosterone sytem (29). Furthermore, miR-145 was presented to be a mediator of hypertension induced vascular impairment in previous study (30). A relation of single nucleotide polymorphisms in miRNAs binding site and essential hypertension was also demonstrated in the literature. Also, these SNPs located in miRNAs binding site can frequently lead to changes of blood pressure level (31). In serum or plasma of humans; some miRNAs like as miR-130a, miR-210, miR-150, miR-191, miR-23b, miR-1246 and miR-451 detected as highly expressed and defined as biomarkers for early and precise diagnosis of hypertension (26). Furthermore, miRNAs were found to be strong potential non-invasive biomarkers for early and correct detection of stroke related to hypertension (32). In recent study, miR-30a, let-7b and miR-126 have been reported as beneficial biomarkers for hypertension-related ischemic stroke (33).

miRNA and congenital heart disease

Congenital heart diseases (CHD) consist of the big part of congenital malformations, which have a prevalence rate of 8 in every 1,000 childs (34). CHD is also related with both raised maternal and child mortality and

morbidity in the world (34). The most common subtypes of CHD are atrial (ASD) and ventricular septal defects (VSD), patent ductus arteriosus (PDA), tetralogy of Fallot (TOF), coarctation of the aorta, pulmonary valve atresia (PA) and transposition of the great arteries (TGA). An association between altered expressions of the miRNAs and VSD was reported in some studies (35). miR-1-1, miR-181c, miR-19-b, miR-29-c, miR-195, miR-498, miR-133a, miR-92, miR-1-2, miR-133a-1/miR-1-2, miR-133a-2/miR-1-1, miR-1-1/miR-181c, miR-155-5p, miR-379-5p, miR-222-3p, miR-433, miR-409-3p, miR-487b, miR-17-92 member were found to be dysregulated in the setting of VSD. Moreover, NOTCH1, GATA3, ZFP281 and HAND1 were presented as target of miRNAs in development of VSD (34,35). For ASD; hsa-let-7a, hsa-let-7b, miR-486 were found to be up-regulated in human body (36).

Down syndrome, which is one of the most important syndrome including congenital heart defects, is characterized by trisomy of chromosome 21. It has variety of symptoms and clinical findings and is diagnosed by using specific techniques such as fluorescence in situ hybridisation. The rate of CHD in the setting of Down syndrome nearly of 40–60% (36). An increased expressions of the specific miRNAs like let-7c, miR-155, miR-802, miR-99a and miR-125b-2 in Down syndrome were demonstrated in previous study (37).

TOF, which is composed of large and non-restrictive VSD, right ventricular outflow tract obstruction, an overriding aorta and right ventricular hypertrophy, is the most commonly seen of cyanotic CHD. It comprises approximately 5–7% of CHD (38). An important link between miRNAs and TOF was reported by O'Brien et al. They detected 61 miRNAs for having important expression level changes in children with TOF as compared to those without disease. Furthermore, 33 miRNAs were reported significantly downregulated in myocardial tissue samples in patients with TOF as compared to the healthy myocardium (39). While miR-22, miR-138, miR-222, miR-375, miR-421, miR-424/424* were demonstrated to be up-regulated, miR-1, miR-206 and miR-940 were down-regulated in this condition (39,40).

Bicuspid aortic valve (BAV) is another commonly seen CHD with a prevalence of 1–2% in general population. The main complications of this disease are aortic valve diseases such as calcific stenosis or insufficiency and thoracic aortic aneurysms (41). A novel dysregulated miRNAs, 8 miRNAs upregulated and 27 miRNAs downregulated (miR-141 was the most one), were detected in BAV leaflets of aortic valve in recent study (42). An association between miRNAs and BAV was assessed in Nigam et al. study. In this study, miR-26a, miR-30b and miR-195 levels were importantly decreased in the aortic valve leaflet of these patients (43). A potential use of miRNAs as biomarkers to identify foetal CHD in prenatal period in maternal serum was reported by Zhu et al. study (44). They found that miR-19b, miR-22, miR-29c, miR-375 were importantly upregulated in mothers carrying foetuses with CHD. This study was significant in terms of promising a possibility of use of miRNAs in clinical practice to identify CHD in prenatal period (44). Finally, altered miRNA expressions (up or down or co-expression) have common and specific impact on cell communicating pathways via signals in development of CHD.

miRNA and pulmonary hypertension

Pulmonary arterial hypertension (PAH) is one of the most leading cause of death all over the world. It is divided in several subtypes such as idiopathic PAH (IPAH), heritable PAH (HPAH), and PAH associated with other diseases (45). Although genetic, environmental and epigenetic factors were supposed to be etiopathologic causes of this disease, certain factors were not found precisely (46). Inflammation, endothelial cell proliferation of the pulmonary artery, proliferation, severe constriction, contraction and migration of pulmonary vascular smooth muscle cells and fibroblast activation, migration and proliferation are well known pathogenetic mechanisms of the PAH (46). A potential pathogenetic role of miRNAs has been investigated and reported in previous studies. miR-21, miR-204, miR-17-92, miR-145, miR-124 and miR-210 were shown as dysregulated miRNAs in proliferation, migration and contraction pulmonary artery smooth muscle cells (46). Moreover, miR-503, miR-27a, miR-424, miR-17-92 and miR-21 were expressed in endothelial cells and participated in proliferation and resistance to apoptosis (46). In recent studies; early diagnostic and prognostic value of miRNAs as novel biomarkers in PAH was reported (47). An important correlation between decreased expression level of miR-150 and poor prognosis in patients with PAH was demonstrated by the study of Rhodes et al (47). In addition, Schlosser et al. reported a positive relation of miR-26a with raised right ventricular systolic pressure, right ventricular hypertrophy and exercise capacity by using six minute walk distance (48). miRNAs can play a key role not only in correct and early diagnosis and risk stratification, but also in treatment of PAH. They can be novel therapeutic drugs by used as mimics and antagonists in humans based on their capability of affecting several different genes within a genome, which makes them more beneficial.

miRNA and acute myocardial infarction

Acute myocardial infarction (AMI), which is one of the results of atherosclerosis, is a life threatening disease with a high mortality and morbidity. Vulnerable atherosclerotic plaque rupture, acute coronary artery occlusion due to formation of thrombus, severe coronary vasoconstriction, supply and demand imbalance are important pathological mechanisms of the AMI. Cardiac remodelling including heart chamber dilatations and ventricular wall thinning due to severe necrosis and fibrosis following AMI can lead to systolic heart failure. Early and precise diagnosis and timely and appropriate treatment is very crucial to prevent complications of AMI including

death. In recent years, many different biomarkers have been using for predicting mortality and morbidity rates in the world. As novel biomarkers, miRNAs have been investigated in the setting of AMI in previous studies. Altered expressions of the miRNAs (miR-499, miR-636, miR-380, miR-133a, miR-17, miR-21, miR-29b, miR-192, miR-194, miR-499, miR-1915, miR-34a, miR-423, miR-328, miR-134, miR-1254, miR-1, miR-181c, miR-208b, miR-566, miR-7-1, miR-92a, miR-455-3p, miR-126, miR-423-5p, miR-636, miR-486, miR-1291 were up-regulated and miR-197, miR-106 and miR-223 were down-regulated) have been detected in serum/plasma of patients with AMI and they have been used as new biomarkers for predicting major adverse cardiovascular events in past studies (26). Clinical studies including miRNAs that had both diagnostic and prognostic significance in the setting of AMI were demonstrated in Table 1(49-56). Coskunpinar et al. reported an increase of miR-221-3p in AMI subjects, which were correlated with ejection fraction (inversely), troponin and risk scores (57). In addition, it was reported to be a good biomarker candidate in this setting (57). A good correlation of miR-1 and miR-133, which play a key role in cardiac muscle growth and differentiation, with myocardial infarct size was presented in Townley-Tison et al. study (58). They were also related with left ventricular ejection fraction and mortality in their study (58). Moreover, a potential role of miR-21 as a novel predictive biomarker for cardiac remodelling following AMI was shown in Liu et al. study (59). Similar to previous study, miR-21 was positively correlated with troponin and had a strong diagnostic accuracy (59). Widera et al. reported an association between increased level of miR-208 and six months major adverse cardiovascular events including mortality or heart failure (60). Furthermore, an elevated miR-499 was found to be more reliable biomarker as compared to traditional ones in AMI, which had both higher sensitivity and specificity than troponin for early diagnosis of AMI (61). It was also be presented as a new strong biomarker for detecting perioperative MI especially in cardiovascular surgery (61). To identify miRNAs expression differences between non-ST segment elevation (NSTEMI) and ST segment elevation MI (STEMI), some studies were done and miR-133a, miR-208b, miR-499, miR-451 and miR-134 levels were found to be higher in STEMI compared to NSTEMI. However, miR-145 was found to be lower in STEMI group than those in NSTEMI (62). miRNAs can play an important role not only in diagnosis but also in prognosis of AMI. miR-208b was reported to be a biomarker for predicting a mortality after other risk adjustment in past study(51). Moreover, miR-133a was significantly demonstrated to be associated with all-cause mortality following age and gender adjustment (63). However, opposite to these studies, some studies were not supported these previous studies findings about potential prognostic role of miR-133a and miR-208b (63,64). According to various different studies results, it can be said that miRNAs could be beneficial to predict short or middle term prognosis in terms of mortality in AMI.

Delivery of circulating miRNAs to recipient target cells to arrange translation of proteins, having a specific secretory pathways or passive secretion of miRNAs into blood circulation immediately after cell disruption and death are possible mechanisms of miRNAs to be used as biomarkers for AMI (25). Cyclic changes in miRNAs expressions associated with myocardial viability and growth, fibrosis and remodelling can affect ventricular performance and contraction ability of heart (65).

miRNAs and arrhythmias

Arrhythmia is an abnormal heart rhythm that may lead to several complications including sudden death. It may be classified as tachycardia or bradycardia or supraventricular or ventricular according to some electrocardiographic and/or electrophysiologic findings. A relation of dysregulated miRNAs with development of arrhythmia was reported in the literature (66). While miR-133, miR-31, miR-483, miR-208b, miR-328 were upregulated in the setting of ventricular tachycardia, postoperative atrial fibrillation (AF) and AF respectively, miR-150, miR-23a and miR-1 were downregulated in AF and supraventricular tachycardia orderly. Furthermore, miR-1, miR-27 and 28, miR-34, miR-146, miR-206, miR-590 and miR-155 were up-regulated and miR-1, miR-26, miR-30, miR-106, miR-29, miR-125 and 126, miR-133, miR-199, miR-590 and miR-409 were down-regulated in AF (66).

AF, which is a chronic and most common form of arrhythmia, has many complications such as stroke, heart failure, AMI, CAD and death. Several different factors such as anatomical and electrical remodeling, structural changes, autonomic nervous system dysfunction, calcium handling impairment, severe inflammation, and variations at the level of nucleotides in miRNA and its targeted genes are related with the initiation and progression of AF (66). miRNAs have significant role both in development and progression of disease. miR-29 was demonstrated to be a stimulator of AF by arranging apoptotic and fibrotic cardiac genes (67). In addition to miR-483, miR-23a and miR-26a can be modulators of postoperative AF (68). miRNAs were supposed to be regulators of atrial remodelling by affecting Ca^{+2} channel protein expression. miR-328, miR-30d, and miR-499 play a crucial role in this pathway (46). Moreover, miR-21, which was reported an elevated levels in both human and animal studies, may contribute a structural remodelling including fibroblast activation and proliferation, interstitial fibrosis, and cardiac hypertrophy of atrial myocardium by using extracellular signal-regulated or mitogen activated protein kinase pathways resulting the AF (69). A decreased level of miR-150 in platelets of AF patients was also shown in previous study, which it was thought to be associated with inflammation, fibrosis and increased platelet function(70).

miRNAs and aortic aneurysm

Aneurysms of artery are organized segmental or diffuse symmetrical dilatation of arterial wall. It is most commonly seen in the infra-renal part of the abdominal aorta. Precise pathological mechanism of this disease is severe intraluminal pressure exceeding the expandable capacity of arterial wall, which results in weakness of vessel structure. Abdominal aortic aneurysms (AAA) are one of the most common cause of death especially over 65 years men. Although it can be asymptomatic over long time, its acute clinical manifestations such as acute aortic rupture or dissection may lead to death without acute treatment. Thoracic aortic aneurysm (TAA) is also silent, commonly seen and curative aortic disease. It can be subdivided into portions due to affected segment of thoracic aorta (71). Aneurysms are seen more common in the abdominal aorta compared to thoracic portion and atherosclerosis is the main pathogenetic mechanism in both development and progression of the AAA. Traditional common risk factors of aortic aneurysms are similar to coronary artery disease such as age, gender, genetics, hypertension, hyperlipidemia, smoking and diabetes except ascending thoracic aorta, which is affected by genetic factors, connective tissue disease, hypertension and bicuspid structure of aortic valve. Beneficial contribution of the miRNAs for early diagnosis and middle to long term prognosis and preventive potential of the aortic aneurysms were demonstrated in recent studies (71). While miR-205, miR-195, miR-221-222, miR-21 and miR-29 were found to be upregulated, miR-26a and miR143/145 were downregulated in aortic aneurysms (71). miRNAs can participate in this process by affecting proliferation, apoptosis, differentiation and functions of vascular smooth muscle cells. In addition, in TAA, miR-491-3p, miR-338-5p, miR-433, miR-183, miR-553, miR-30c had an increased expressions. On the other hand, miR-24, miR-143, miR-22, miR-93, miR-145 were downregulated in this setting (72).

microRNA and valvular heart disease

Valvular heart disease (VHD) is one of the most leading cause of cardiovascular mortality. Aortic and mitral valve disorders are seen more frequently than right sided valves. Calcific aortic valve stenosis (AVS) is one of the most commonly seen valvular disease in developed countries. It has risk factors similar to coronary artery disease and its treatment is possible as replacement of valve by using interventional and surgical techniques. AVS is defined as chronic, progressive narrowing of valve orifice. Endothelial dysfunction, atherosclerosis, inflammation, oxidized lipid deposits and impairment of calcium metabolism are main pathophysiologic mechanisms of the disease (73). Moreover, excessive collagen synthesis, severe calcification due to apoptosis, osteogenic transdifferentiation of the valvular interstitial cells lead to valve remodelling including extracellular matrix rearrangement and fibrosis (73). Finally, due to chronic constant inflammation and calcification, mobility of leaflets decreases, valve stenosis occurs and blood flow through orifice decreases. Several different dysregulated miRNAs such as miR-22, miR-486, miR-210, miR-125, and miR-21 were presented in recent studies (74). Moreover, miR-210, miR-21 and miR-133a, which play a key role in left ventricular remodelling and fibrosis, were reported as strong prognostic biomarkers in patients with aortic stenosis in the literature (73-75,76).

Mitral valve disease, which is classified as stenosis and insufficiency, is the other commonly seen valvular pathology. It can lead to moderate-advanced heart failure, arrhythmias and sudden cardiac death. In mitral insufficiency, valve leaflet structure impairment or secondary pathologies due to left ventricle dilatation can be etiological factors for development. Systolic and diastolic heart failure, electrical abnormalities and arrhythmias are main clinical outcomes of mitral insufficiency. Mitral stenosis is other mitral valve disease, which has similar risk factors and pathophysiologic mechanisms to aortic stenosis. Changes in miRNAs expression levels in mitral valve leaflets in the setting of rheumatic mitral stenosis and mitral valve prolapsus were reported in some studies (74). While, miR-26a-5p, miR-133b, miR-145-5p, miR-30c-5p, miR-1, miR-23b-3p, miR-125-5 were down-regulated, miR-4484, miR-3613-3p and miR-466 were up-regulated in both left and right atrial appendage tissue of patients with rheumatic mitral valve disease indicating surgery in previous studies (74,77). Furthermore, some miRNAs such as miR-34c-3p, miR-656, miR-500, miR-3174, miR-379-3p and miR-664a-3p were found to be highly expressed in patients with myxomatous mitral valve leaflet prolapsus (78). In contrary, miR-1193, miR-646, miR-203, miR-939, miR-4298, miR-17, miR-505 and miR-1273e were down-regulated in the setting of mitral valve prolapsus (79).

miRNA and restenosis

Vascular remodeling and restenosis are pathophysiologic results of the atherosclerosis. Although using a drug eluting coronary stents during percutaneous coronary intervention can decrease its probability, complication rate of restenosis remains high. Severe neointimal proliferation and hyperplasia, vascular remodeling, increased vascular smooth muscle cell (VSMC) proliferation and migration and chronic inflammation after coronary stent implantation procedure are main causes of the restenosis. Clinical results of it may as follows: recurrent ischemia and angina, the need to repeat revascularization and acute coronary syndrome. A predictive role of circulating miR-143 level for in-stent restenosis in coronary or peripheral artery diseases was reported in previous study (80). Moreover, an important role of miR-145, miR-221, miR-663, miR-599, miR-143, miR-15b, miR-9, miR-206, miR-181b, miR-16, miR-31, miR-146a, miR-222 and miR-22 in differentiation of VSMC was demonstrated in previous study (80). In addition, miR-133 was found to be a dysregulated miRNA in the setting of restenosis

(80). In the light of this study, it can be said that an elevated transc coronary miR-133 level was a good predictor of need for target lesion revascularization due to in-stent restenosis. Moreover, miR-23b, miR-125a-5p, miR-195, miR-663 were shown to be dysregulated in the setting of restenosis (80). miR-126, miR-17/92a, miR-221 and 222, miR-16, miR-21 were dysregulated miRNAs expressed in endothelial cells (80). A stimulator role of miR-21 on VSMC proliferation by using specific pathways was reported in experimental studies (81). Use of antisense oligonucleotides against miR-21 to the targeted damaged area was found to be beneficial for inhibiting vascular remodeling, VSMC proliferation and neointimal hyperplasia in-stent restenosis animal models (81). In addition, Wang et al. reported a beneficial inhibitor effects of local delivered anti-miR-21 as a coated stent on stenotic artery, which decreases in-stent restenosis with re-endothelialization (82). Also, increased level of miR-21 was shown in patients with in-stent restenosis by the study of He et al (83). Endothelial recovery is one of the protective mechanisms for preventing restenosis. Diagnostic potential of miR-21 for in-stent restenosis was also reported in previous study (81). An elevated peripheral miR-92 and miR-195 levels were found to be good independent predictors for 2 years target vessel revascularization (TVR) (84). Similar to this finding, increased transc coronary expression of miR-133a had both diagnostic and prognostic significance for TVR (85). A decreased levels of miR-145 and miR-143 in coronary artery were also concordant with previous findings in terms of both diagnosis and prognosis (83). Some miRNAs such as miR-16, miR-21, miR-92a and miR-221 and 222 were found to play a key role in this process. Moreover, miR-21, miR-92a, miR-16 and miR-126 can participate in angiogenesis, which is an important part of restenosis (80).

miRNA and heart failure

Heart failure (HF) is defined as a clinical syndrome, which heart does not provide adequate blood, oxygen and nutrient supply to meet metabolic requirements of the human body. It is divided into three as follows: systolic, diastolic and mid-range ejection fraction HF. Heart failure is one of the most common causes of death in the world. Coronary artery disease, hypertension, valvular heart disease, arrhythmias, viral infections such as myocarditis, cardiomyopathies and some cardiotoxic drugs or matters are well known etiologic factors of HF (86). An independent significant role of circulating miRNAs for both diagnosis and prognosis of HF was reported in recent studies (87-99). The results of these studies also provided strong data about a key role of miRNAs in development and progression of disease. In addition, a relation between miRNAs and clinical, imaging and laboratory findings was demonstrated in previous studies (87-99). While miR-18a, miR-26b, miR-106a, miR-30e, miR-27a, miR-199a and miR-652 were found to be decreased, miR-30d, miR-126, miR-1254, miR-37, miR-30c, miR-223-3p, miR-301a-3p, miR-210, miR-145-5p, miR-29a-3p, miR-1306-5p, miR-26b-5p, miR-199a-3p, miR-92a-3p, miR-146a, miR-221 were upregulated in patient with HF (87-99). A summary of clinical studies that showed miRNAs having both diagnostic and prognostic significance in patients with heart failure were reported in Table 2 (87-99). After 48 hours from admission for HF, declining in miR-18a, miR-652, miR-18b, miR-301a, let-7i, miR-223 and miR-423 levels were found to be significant independent biomarkers of six months mortality (92). miR-650, miR-1228, miR-662, miR-518, miR-3148, miR-21 and miR-299-3p were reported to be correlated with N-terminal pro-brain natriuretic peptide (NT-pro-BNP) in the study of Cakmak et al (98). Also, miR-182 was found to be an important prognostic marker for six months cardiovascular mortality in the same study (98). In addition to diagnostic and prognostic feature of miRNAs in HF, a relation between miRNAs and echocardiographic left ventricular anatomic structural change in systolic HF was investigated (100). miR-182, miR-568 and miR-200a were negatively correlated with left ventricular mass index (LVMI), while miR-155 and miR-595 were found to be positively correlated with LVMI (100). In another studies, altered expression levels of (up or down regulated) miR-423, miR-1254 and miR-1306 were reported as prognostic markers in HF subjects (1,99).

An elevated diagnostic performance of NT-pro-BNP for HF by combining with miRNAs such as miR-146a, miR-221, miR-375, miR-423-5p, miR-30c and miR-328 was presented in past studies (1,90). Moreover, levels of circulating miRNAs can alter with some medications. Left ventricular assist device can affect miRNAs levels (miR-499, miR-208a and b, miR-133 and miR-1) either muscle specific or non-specific (101). A reverse remodelling after cardiac resynchronization treatment, which was defined as “responders”, was reported to be related with changes in miRNAs levels (102). In this study, miR-92a, miR-29a, miR-26b, miR-145 and miR-30e levels raised in responder group as compared to non-responders (102). Also, initial levels of miR-30d and miR-1306 were demonstrated to be associated with reverse left ventricular remodelling, which was defined as “responder”, in end-stage chronic HF patients. They also had a prognostic role for one year all-cause mortality in patients with acute HF (103).

miRNAs and therapeutic potential

microRNAs is a promising novel therapeutic agents, which can effect multiple genes by using different signalling pathways (104). Treatment options with miRNA drugs can be classified into two groups: miRNA depression to decrease the levels of miRNAs upregulated in cardiac diseases and replacement of missing miRNA to restore the expression of miRNAs reduced in disease condition (104). Nowadays, miRNAs have been using not only for diagnostic and prognostic purposes but also for therapeutic aims in various CVD. Many different

techniques such as viral vectors, vesicles, antagomirs or mimics, plasmids and sponges created to be used as vehicles of miRNAs to specific target tissues or organs without digestion, which increase bioavailability and bioefficacy (105). miRNAs therapeutic modulation techniques were used in the settings of atherosclerosis, acute myocardial infarction, restenosis, vascular remodelling, arrhythmias, hypertrophy and fibrosis, angio and cardiogenesis, aortic aneurysm, pulmonary hypertension and ischemic injury (105-130) (Table 3). Moreover, miRNAs can provide improved clinical outcomes. On the other hand, delivery system, off-target impact and inductive effect of immune system are big problems for miRNA based drugs for being used in clinical practice (106). While permanent impact on target tissue or organ system, easy to be regulated, ability to affect multiple pathways to show their effect, strong impact with relatively lower doses are main positive features of miRNAs, having a off-target effect, risk of toxicity with delivery agent or miRNAs themselves, difficult detection of tissue-specific pharmacodynamic effect and harsh delivery of miRNAs to target tissues are challenges of this therapeutic systems (89).

miRNAs and Future Perspectives

Circulating miRNAs are promising novel biomarkers for purposes of both diagnosis and prognosis of CVD. Cell or tissue specificity, stability in serum or plasma, resistance to degradative factors such as freeze–thaw cycles or enzymes in blood, fast release kinetics, provide potential for miRNAs to be a surrogate marker for both early and accurate diagnosis of the disease and for prediction of middle or long term prognosis. Moreover, combining miRNAs with traditional biomarkers can be logical approach to improve risk stratification and long term prognosis. miRNA-based therapeutics may be more beneficial to treat CVD by using novel platforms and computational tools and combining with traditional analysis methods.

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Table 1. Diagnostic and prognostic significance of miRNAs in acute myocardial infarction.

miRNA ID	Expression	Aim	Disease	Number of patients	Ref.
miR-499	↑	Diagnosis	CABG	30	(49)
		Diagnosis	STEMI	33	(50)
miR-133	↑	Diagnosis	STEMI	33	(50)
		Diagnosis/Mortality	ACS	444	(51)
miR-29b	↑	Diagnosis	AMI	44	(52)
miR-423	↑	Diagnosis	AMI	246	(53)
miR-328	↑	Diagnosis	AMI	51	(54)
miR-1	↑	Diagnosis	AMI	44	(52)
		Diagnosis	AMI	31	(55)
miR-208b	↑	Diagnosis/Mortality and HF	AMI	359	(56)
		Diagnosis	AMI	444	(52)
miR-221-3p	↑	Diagnosis	AMI	27	(57)
miR-21	↑	Diagnosis	AMI	198	(59)
		Diagnosis	AMI	44	(59)

AMI: acute myocardial infarction, STEMI: ST-elevation myocardial infarction, ACS: acute coronary syndrome, CABG: coronary artery bypass grafting; HF: heart failure.

Table 2. Diagnostic and prognostic significance of miRNAs in heart failure.

miRNA ID	Expression	Aim	Disease	Number of patients	Ref.
miR-30d	↓	Diagnosis/mortality	AHF	96	(87)
		Diagnosis/response to CRT	CHF	766	(88)
miR-210	↑	Diagnosis	HF	39	(89)
miR-30c	↑	Diagnosis	HF	90	(90)
miR-26b	↑	Diagnosis	HF	81	(91)
miR-18a	↑	Diagnosis/Mortality	AHF	137	(92)
miR-21	↑	Diagnosis	HF	61	(93)
miR-499	↑	Diagnosis/Mortality/HF	MI	319	(94)
miR-423	↓	Diagnosis/Mortality	AHF	137	(92)
		Diagnosis	HF	30	(95)
miR-126	↓	Diagnosis	AHF	236	(96)
miR-1254	↑	Diagnosis/Mortality/HF	CHF	2203	(97)
miR-652	↓	Diagnosis/Mortality	AHF	137	(92)
miR-223	↓	Diagnosis/Mortality	AHF	137	(92)
miR-182	↑	Diagnosis/Mortality	CHF	42	(98)
miR-1306	↓	Diagnosis/Mortality	CHF	30	(99)

HF: heart failure; CHF: chronic heart failure; AHF: acute heart failure; MI: myocardial infarction; CRT: cardiac resynchronization therapy.

Table 3. Therapeutic applications of miRNAs in cardiovascular diseases

Disease Ref.	miRNA	Modulation	Effect
MI (107)	miR-15b	Antagomir	Infarct size↓
(108)	miR-24	Lentiviral overexpression	Infarct size↓, fibrosis↓
(109)	miR-145	Antagomir	Infarct size↓, FS↑
(110)	miR-92a	Antagomir	Infarct size↓
(111)	miR-210	Minicircle vector	FS↑, neovascularization
(112)	miR-17	Antagomir	Infarct size↓, FS↑
(113)	miR-99a	Lentiviral overexpression	FS↑, apoptosis↓
(114)	miR-320	Antagomir	Infarct size↓

(115)	miR-29a/29c	Antagomir	Infarct size↓, apoptosis↓
Atherosclerosis (116)	miR-122	Antagomir	Cholesterol↓
(117)	miR-145	Lentiviral overexpression	plaque size↓, fibrosis↓
(118)	miR-21	Antagomir	Neointimal proliferation↓
(119)	miR-126	Apoptotic bodies	Lesion size↓, vascular repair↑
Arrhythmia (120)	miR-26	Mimic, AAV overexpression	AF vulnerability↓
(121)	miR-328	Antagomir	AF permanence↓
(122)	miR-1	Antagomir	AF↓, VT↑
Hypertrophy and fibrosis (123)	miR-1	AAV9 vector	Hypertrophy↓, fibrosis↓
(124)	miR-34	Antagomir	Fibrosis↓
(125)	miR-132	Antagomir	Hypertrophy↓, fibrosis↓
(126)	miR-208	Antagomir	Cardiac remodeling↓
(127)	miR-378	AAV9 vector	Heart Function and EF↑
(128)	miR-199b	Antagomir	Hypertrophy↓, fibrosis↓
(129)	miR-25	Antagomir	Hypertrophy↓, fibrosis↓
(124)	miR-34	Antagomir	Fibrosis↓
(130)	miR-101	AAV overexpression	Fibrosis↓

AF:atrial fibrillation; MI:myocardial infarction; FS:fractional shortening; HDL-C: high density lipoprotein cholesterol; AAV:adeno associated virus; VT: ventricular tachycardia.