**Name of Journal: *World Journal of Cardiology***

**ESPS manuscript NO: 21861**

**Manuscript Type: MINIREVIEWS**

**Novel epigenetic-based therapies useful in cardiovascular medicine**

Napoli C *et al*. Epidrugs in Cardiovascular Medicine

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**Conflict-of-interest statement:** No potential conflicts of interest. No financial support.

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**Received:** July 30, 2015

**Peer-review started:** July 31, 2015

**First decision:** September 16, 2015

**Revised:** December 11, 2015

**Accepted:** December 16, 2015

**Article in press:**

**Published online:**

**Abstract**

Epigenetic modifications include DNA methylation, histone modifications, and microRNA. Gene alterations have been found to be associated to cardiovascular diseases and epigenetic mechanisms are continuously being studied to find new useful strategies for clinical management of such patients. Numerous cardiovascular disorders are characterized by abnormal methylation of CpG islands and specific drugs that could inhibit DNA methyltransferase directly or by reducing its gene expression (*e.g.*, hydralazine and pocainamide) are currently under investigation. The anti-proliferative and anti-inflammatory properties of histone deacetylase inhibitors and their cardio-protective effects have been confirmed in preclinical studies. Furthermore, the regulation of the expression of microRNA targets through pharmacological tools is still under development. Indeed, large controlled trials are required to establish whether current possible candidate antisense microRNAs could offer better therapeutic benefits in clinical practice. Here, we updated therapeutic properties, side effects and feasibility of emerging epigenetic-based strategies in cardiovascular diseases by highlighting specific problematic issues that still affect the development on large scale of these novel therapeutic protocols.

**Key words**: Epigenetics; Cardiovascular diseases; Heart failure; Inhibitors of histone deacetylases; Antisense microRNAs

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**Core tip:** Recent evidence suggests that specific epigenetic regulatory mechanisms play key roles in cardiac differentiation, homeostasis, response to injury and development of disease. Drug therapies that work through epigenetic mechanisms are currently limited to antineoplastic agents; large controlled trials are required to establish whether current possible candidate antisense microRNAs or histone deacetylase inhibitors could offer better therapeutic benefits in cardiovascular disease. We review recent findings on the epigenetic control of several cardiovascular diseases and new challenges for therapeutic strategies in cardiovascular diseases.

Napoli C, Grimaldi V, De Pascale MR, Infante T, Soricelli A, Sommese L. Novel epigenetic-based therapies useful in cardiovascular medicine. *World J Cardiol* 2015; In press

**INTRODUCTION**

Cardiovascular diseases (CVDs) are the primary cause of death worldwide and 17.5 million people died for CVDs in 2012 representing 31% of all global deaths. CVDs include a number of alterations affecting heart and vascular structures such as heart valves, heart muscle (*e.g.*, cardiomyopathy), pericardial, and coronary arteries diseases. All these conditions may result in cardiomyocyte loss and in a cardiac~~-~~remodeling with a consequent heart failure (HF) and increased risk of arrhythmias and death. Also cardiac fibroblasts have a pivotal role in HF[1]. Indeed, endothelial cell activation and inflammation promote the transdifferentiation of fibroblasts to myofibroblasts that after the extensive collagen production, the release of chemokines and the activation of inflammatory cells, causes in turn cardiomyocyte stiffness by contributing to pathogenesis of HF[1]. Increasing evidence have shown that epigenetic mechanisms control and influence the expression of cell cycle central genes involved in human disease progression[2]. Toward this context, significant epigenetic and epigenomic findings have open a new scenario by exploring the role of genetic heritability and environmental interaction in CVDs[3]. Some deregulated epigenetic steps are involved in the pathophysiology of CVDs[4]. Specific epigenetic regulatory mechanisms could impact on endothelium, cardiac muscle, smooth muscle, and fibroblasts[5]. Thus, the pharmacological setting of these pathways might represent a specific target for CVDs. Since the reversible nature of these modifications, researchers continuously are engaged on the development of novel epigenetic-based drugs (epidrugs) for CVD treatment[6,7]. The primary goal of the future studies will be to allow the identification of selective therapeutic molecules conceived to act on specific epigenetic-related pathogenic events.

Here, we summarize the current knowledge on epigenetic-based strategies in CVDs by outlining novel therapeutic steps in the clinical practice.

**EPIGENETICS INVOLVEMENT IN CVDs**

***DNA methylation as therapeutic target***

DNA methylation is the most studied epigenetic modification and mainly involve methylation of CpG islands in the promoter genes. It is a long-term stable and the most common modification involved into regulation of gene expression in the mammalian genome. All changes in methylation are modulated by specific catalytically active enzymes including “maintenance” methyltransferase (DNMT1) and “*de novo*” methyltransferase (DNMT3a and DNMT3b). DNMTs act adding methyl groups on CpG residues modifying the accessibility of DNA to the transcriptional machinery. Altered regulation of cytosine methylation has been linked to CVD development and progression[8] as well as to cancer cell development[9]. In addition, DNA methylation has been shown to regulate biological processes underlying CVDs such as atherosclerosis, inflammation, hypertension, and diabetes[10,11]. DNA methylation is also involved in essential arterial hypertension[12,13]. To date, DNA methylation, for its reversible nature, remains an attractive target for interventions in CVDs. Dietary compounds including polyphenols and catechins acting on DNA methylation processes[14,15]. In particular, some interesting clinical studies showed that the elevate consumption of polyphenols decreases the global DNA methylation of peripheral leukocytes in humans with cardiovascular risk factors ([NCT00511420](http://clinicaltrials.gov/ct2/results?term=NCT00511420) and NCT00502047)[16]. However, the role of nutrients in the evolvement of CVDs through epigenetic link remains yet to be studied. Conversely, the cardiovascular implication of pharmacological epigenetic compounds appear to be more direct and far-reaching. Indeed, some drugs are known to affect DNA methylation. Hydralazine, a vasodilator used to treat hypertension[17], is an example of compound that has been shown to inhibit DNA methyltransferase directly or by reducing its gene expression[18]. There are several clinical trials focusing on the use of Hydralazine to threat hypertensive conditions (Table 1). Many of these completed trials have highlighted the beneficial effect of hydralazine assumption compared to other compounds on both hypertension or other cardiovascular conditions. Several evidence supported that Hydralazine might function both by modulating the effect of purine-like compounds released from sympathetic nerve endings and/or by inducing an altered Ca2+ balance in vascular smooth muscle cells[19,20]; unfortunately, to date, fundamental unresolved issues remain to be clarified.

Procainamide is another drug that inhibits DNA methyltransferase I. It is a sodium channel blocker that belongs to the class of benzamides used against arrhythmias[21]. Clinical trials have evaluated this anti-arrhythmic drug in the acute treatment of monomorphous ventricular tachycardia with positive effects (Table 1). Nevertheless, recent evidence have shown a toxic effects of procainamide on the lung after orthotopic cardiac transplantation[22].

Despite the use of these drugs in cancer treatment would seem to be a promising road[23], the implication of their epigenetic effects in CVDs remains to be studied.

***Histone modifications as therapeutic target***

Epigenetic alterations occur in the histone code that can modulate histone–DNA interactions and significantly influence chromatin structure by modifying the accessibility of transcriptional regulators to DNA-binding elements[24]. The most common modifications are lysine acetylation and methylation, arginine methylation, and serine phosphorylation. Histone acetylation is catalyzed by histone acetyltransferases (HATs) while histone deacetylation is carried out by histone deacetylases (HDACs)[25].

Inhibitors of histone deacetylases (HDACi) represent a significant group of epidrugs that could be highly relevant to the treatment of CVDs. Indeed, HDACi exert anti-proliferative and anti-inflammatory effects and their cardio-protective therapeutic use recently has been confirmed in preclinical studies[26,27].

According to their chemistry, HDACi can be divided into four main groups: hydroxamates, aliphatic acids, benzamides and cyclic peptides. Hydroxamates like Trichostatin A (TSA), and Vorinostat (suberoylanilide hydroxamic acid, SAHA) serve as pan-HDACi and are most generally used for preclinical studies[28-30].

Principal histone modifications and therapeutic targets involved in CVDs are reported in Table 2. Animal studies *in vivo* showed that TSA treatment improved functional myocardial recovery after myocardial infarction  (MI) through a reduction in myocardial and serum TNF-α. Neo-angiogenesis was demonstrated in MI animals after receiving TSA treatment[31]. Taken together, these results indicate that this HDACi could preserve cardiac performance and mitigate myocardial remodeling through stimulating endogenous cardiac regeneration[31]. HDAC inhibition was also shown to attenuate ischemic injury in the heart as well as in other tissues. Pre-treatment with TSA resulted in improvements in post-ischemic ventricular function with a reduction in infarct size in both early and delayed preconditioning models[32]. Despite the high activity of TSA, it was disqualified as a clinical drug due to its many side effects such as non-transformed cell apoptosis and increased DNA damage[33].

Vorinostat was approved by the Unites States Food and Drug Administration for the treatment of advanced cutaneous T cell lymphoma[34]. Suberoylanilide hydroxamic acid (SAHA/vorinostat) reduced myocardial infarct size in a large animal model, even when delivered in the clinically relevant context of reperfusion[35,36].

Aliphatic acids like valporoic acid(VPA, 2-propylpentanoic acid) inhibits class I HDACs causing accumulation of hyperacetylated histone tails (H3 and H4 histones) and other protein targets such as p53. VPA has anti-proliferative and pro-apoptotic activities. Lee *et al*[37] demonstrated attenuation of ventricular remodeling following MI *in vivo* when VPA or tributyrinwas administered to rats 24h after ligation of the left anterior descending artery. However, these short chain fatty acids are known to weakly inhibit HDAC activity with a number of off target effects[38].

Benzamides are small molecules active mostly against class I HDACs. Importantly, class I HDACi is entinostat (MS-275A) that prompted protective effects against ischemia reperfusion injury in the isolated rat heart. MS-275A is not effective against class IIb HDAC6[39]. Entinostat might be more advantageous than the first-generation such as TSA, vorinostat, romidepsin, VPA because less profound side effects are observed[40]. Some studies have suggested that tranilast also has cardiovascular-protective effects[41]. Cyclic peptideslikedepsipeptideis a natural cyclic peptide that inhibits HDAC 1 and 2, selectively modulating the expression levels of different genes, such as c-myc, Hsp90, and p53. The cyclic peptide family includes more HDACi like apicidin. The apicidin derivative, API-D, is capable of reducing hypertrophy and, consequently, the transition to HF in mice subjected to thoracic aortic constriction. Therefore, the treatment with this substance establishes a relevant therapeutic approach for HF[42].

Cardiovascular protective effects of p300 HAT inhibitor curcumin have been demonstrated[43,44]. In rat model of HF and primary cultured rat cardiac myocytes and fibroblasts, curcumin prevented ventricular hypertrophy and preserved systolic function[45].

***RNA-based mechanisms as novel biomarkers***

MicroRNAs are key regulators of gene expression acting at the post-transcriptional level. MiRNAs are implicated in the pathogenesis of several CVDs[46]. The modulation of miRNA expression could represent innovative therapeutic approach to treat cardiovascular conditions by targeting a single cell type or specific pathways as demonstrated in animal model[47,48]. Recently, several study population have investigated the involvement of transcriptionally regulated miRNAs as an attractive targets for the trearment of several cardiovascular conditions (Table 3**)**. Preclinical studies by using antisense oligonucleotide (antagomiR) -mediated knockdown have demonstrated the role of specific miRNAs in HF[47,49,50]. Indeed it was shown that a single treatment with the infusion of a miR133 antagomiR induced cardiac hypertrophy in mice[49]. Recently, Wahlquist *et al*[47] demonstrated that high levels of miR25 can depress cardiac function but the inhibition of this miRNA by anti-miR25 effectively restore cardiac function in an HF mouse model. Interestingly, it was demonstrated that miRNAs secreted by cardiac fibroblasts may also act as mediators of cardiomyocyte hypertrophy trough a paracrine mechanism[50]. During hypertension or pathological cardiac hypertrophy, a reactivation of fetal cardiac genes such as atrial natriuretic peptide (ANP)/B-type natriuretic peptide (BNP) and beta-myosin heavy chain (β-MHC) can occur. In hypertensive mouse model, aldosterone-dependent inhibition of miR-208a can occur by resulting in β-MHC inhibition and increase of cardiac hypertrophy[51]. To this regard, it was shown that therapeutic inhibition of miR-208a led to a reduction in cardiac remodeling, which coincided with a significant improvement in survival and cardiac function during heart disease[48]. In addition, in hypertensive rat models changes in β-MHC expression were observed after treatment with anti-miR-208a that acted by reverting the levels of several miRNAs including miR-16, -19b, -20b[52]. Recently the regulation of miR-208a and endoglin in AMI were investigated[53]. The authors have demonstrated that the overexpression of antagomiR-208a significantly inhibited the increase of myocardial endoglin and β-MHC protein expression induced by infarction. In addition, pretreatment with atorvastatin and valsartan, members of drug class known as [statins](https://en.wikipedia.org/wiki/Statin) primarily used for prevention of events associated with cardiovascular disease, can decrease myocardial fibrosis induced by AMI through attenuating miR-208a and endoglin expression[53]. Clinical evidence have supported the different levels of miR-143, miR-145, miR-21, miR-133 and miR-1 expression in patients with essential hypertension suggesting that these miRNAs can act in the vascular smooth muscle cell phenotypic modulation and could represent potential therapeutic targets in essential hypertension[54]. It was found that the chronic restoration of miR-1 gene expression in animal model, reverted the pressure-induced cardiac hypertrophy and prevented the adverse cardiac remodeling induced by pressure overload[55]. Recently, Han *et al*[56] have found higher levels of miR-29a in patients with hypertension and left ventricular (LV) hypertrophy compared to patients with hypertension alone. MiR-29a levels were significantly associated with collagen type I and III and MMP-9 expression. The same authors, employing a mouse model of pressure overload, have shown that the antagomiR-29a significantly suppressed the hypertrophy of cardiomyocytes and reduced the expression of ANP and β-MHC suggesting the possible role of miR-29a as therapeutic target[56]. Several preclinical studies showed beneficial effects of antagomiR-92a administration on small and large animal models before MI[57-59]. Inhibition of miR-92a by repeated intravenous injections of antagomiR-92a induced angiogenesis and improved recovery of ventricular function in MI mouse model[57]. In MI large animal model, antagomiR-92a treatment revealed cardio-protection against ischemia/reperfusion[58]. Recent evidence have demonstrated favorable post-ischemic myocardial repair after intravenous administration of antagomiR-92a in adult large animal model[59]. Indeed, neovasculogenesis and prevention of adverse ventricular remodeling, the major cause of contractile dysfunction and HF after a MI, were observed after intravenous administration of antagomiR-92a[59]. These results emerge as a promising therapeutic approach to translate to patients affected by MI. Progression of post-infarction LV remodeling in mice was studied by Tolonen *et al*[60]. These authors have observed that the inhibition of Let-7c was associated with decreased apoptosis, reduced fibrosis, and reduction in the number of discoidin domain receptor 2–positive fibroblasts while the number of c-kit+ cardiac stem cells and Ki-67+ proliferating cells remained unaltered[60]. Although Let-7c inhibitor injection improved cardiac function after MI, the safety of the Let-7c inhibition has yet to be clarified since of its dualistic function that in various cancer diseases appear to have a causative role.

On the other hand, circulating miRNA patterns are analyzed as potential disease specific biomarkers in CVDs in 2 observational prospective studies on aortic aneurism in hereditary aortopathy syndromes (NCT02213484), coronary artery diseases and myocardial infarction (NCT02076153). Three interventional randomized studies are focusing on the association between miRNA profile modifications and the administration of specific molecules like anti-platelet agents (NCT02071966) (NCT02447809) in coronary syndromes and anti-diabetics drugs in diabetic stable and unstable angina (NCT01331967).

**CONCLUSIONS**

To date, several epidrugs (such as Verinostat and Panobinostat) are approved for the treatment of cancer and myeloplastic syndromes, and are, therefore, commercially available. No epigenetic drugs for CVDs are actually approved by FDA. Nevertheless, the opportunity to control genetic and epigenetic processes could be considered a promising and attractive tool also in cardiovascular medicine. For this reason, the continuous investigation of epigenetic-related mechanisms might help to explain how environmental and lifestyle factors can influence aberrant gene expression patterns lifetime that can resulting in an increased cardiovascular risk. Preclinical experiments have identified some HDACi that could have future implications to treat several cardiovascular conditions including atrial fibrillation, cardiac hypertrophy and HF. Ongoing human clinical controlled studies are emphasizing the ability of some drugs such as hydralazine and procainamide to act on DNA methylation in CVDs. However, in CVDs, the clinical experience with HDACi is limited due to the observed toxic cardiac side effects in oncologic patients.

The study of human genome will find biomarkers that might affect CVDs. Probably, only epigenetic profiles obtained from large cohorts of patients with the same genetic mutations will be able to promote the development of surveillance programs and novel effective drugs for the transition of *in vitro* to *in vivo* treatments for the early stage of CVDs[61-63].

To date, few clinical trials are investigating the link between drugs and specific miRNA profiles, which might be considered as biomarkers for the classification of CVDs with scarce compliance to the standard therapy and affected by the incidence of more aggressive clinical phenotypes. Unfortunately, until now antagomiR in the cardiovascular field are not yet tested in clinical trials. However, these promising studies reflect the open debated for possible future applications of miRNA therapeutics in CVDs.

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**P-Reviewer:** O-Uchi J, Gong KZ **S-Editor:** Kong JX **L-Editor: E-Editor:**

**Table 1 Interventional and randomized ongoing clinical trials on the use of Hydralazine and Procainamide in cardiovascular diseases**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Number** | **Status** | **Condition** | **Number of enrolled patients** | **Intervention** |
| NCT00684489 | Completed | Hypertension | 52 | Hydralazine and other drugs |
| NCT02305095 | Not open for participant recruitment | Heart Failure | 500(Estimated enrollment) | Hydralazine in combination with isosorbide dinitrate |
| NCT00661895 | Completed | Hypertension | 99 | Hydralazine and other drugs |
| NCT00599235 | Completed | Hypertension | 30 | Hydralazine, sildenafil and placebo |
| NCT00223717 | Recruiting participants | Hypertension | 160(Estimated enrollment) | Hydralazine and other drugs |
| NCT01255475 | Completed | Heart failure, Cardiac failure, Congestive heart failure | 21 | Hydralazine/amlodipine and placebo |
| NCT01516346 | Recruiting participants | Heart failure, Congestive heart failure | 54(Estimated enrollment) | Hydralazine, isosorbide dinitrate and placebo |
| NCT01822808 | Recruiting participants | Acute heart failure,Left ventricular dysfunction | 500(Estimated enrollment) | Hydralazine, isosorbide dinitrate and placebo |
| NCT00000499 | Completed | Cardiovascular diseases,Heart diseases,Hypertension,Vascular diseases | Not provided | Hydralazine, reserpine, chlorthalidone and metoprolol |
| NCT02050529 | Recruiting participants | Hypertension, Pregnancy induced | 180(Estimated enrollment) | Hydralazine, labetalol |
| NCT01538875 | Completed | Hypertension, Pregnancy induced | 261 | Hydralazine, labetalol |
| NCT00383799 | Unknown | Ventricular tachycardia | 302(Estimated enrollment) | Procainamide, amiodarone |
| NCT00000464 | Completed | Arrhythmia, Cardiovascular diseases | 115 | Procainamide, quinidine, disopyramide, and other drugs |
| NCT00702117 | Completed | Atrial fibrillation,Tachycardia | 123 | Procainamide, ajmaline, flecainide |
| NCT00589303 | Terminated | Atrial fibrillation,Heart failure | 27 | Rhythm control drugs: Procainamide and other drugs |
| NCT00000556 | Completed | Arrhythmia,Atrial fibrillation,Cardiovascular diseases | 4060 | Procainamide and other drugs |
| NCT01205529 | Recruiting | Atrial fibrillation | 750(Estimated enrollment) | Procainamide |

**Table 2 Histone modifications and therapeutic targets involved in cardiovascular diseases**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Target** | **Epigenetic mechanisms** | **Condition** | **Organism/*****in vitro*, *in vivo*** | **Effects** | **Ref.** |
| TSA | Inhibition of HDAC4 | Ischemic injury | mouse, *in vitro* and *in vivo* | HDACi would be predicted to have a beneficial effect in the context of active ischemia | Granger *et al*[28] (2008) |
| TSA/VAL | Class I HDACs | Cardiac hypertrophy | mouse, *in vitro* and *in vivo* | Therapeutic target for preventing or reversing cardiac hypertrophy and subsequent heart failure | Kee *et al*[29] (2006) |
| TSA | Inhibition of HDACs | Atrial fibrosis and arrhythmias | mouse, *in vitro* and *in vivo* | It reversed myocardial fibrosis | Liu *et al*[30] (2008) |
| TSA | Inhibition of HDACs | Acute myocardial ischemia and reperfusion injury | mouse, *in vitro* and *in vivo* | It improved cardiac functional recovery and antagonized myocardial remodeling in chronic myocardial infarction | Zhang *et al*[31] (2012) |
| TSA/SAHA | HDAC inhibitor | Myocardial Infarct | mouse, rabbit, *in vivo* | It reduced infarct size in a large animal model | Xie *et al*[35] (2014) |
| SAHA/sodium valproate | Inhibition of HDACs | Ischemic Injury | mouse, *in vitro* and *in vivo* | Potential therapeutic strategy for restoring compromised cardiac proteostasis | Wang *et al*[36] (2011) |
| VPA or tributyrin | Inhibition of HDACs | Infarct | rat, *in vitro* | They attenuateventricular remodeling after infarction | Lee *et al*[37] (2007) |
| MS-275A | Inhibition of class I/II HDACs | Infarct | rat, *in vivo* | It observed a significant reduction of infarct area | Aune *et al*[39] (2014) |
| Apicidin | Inhibition of class I HDACs | Cardiac hypertrophy and Heart failure | rat pups, *in vitro* mouse, *in vivo* | It preserved cardiac function in the long-term | Gallo *et al*[42] (2008) |
| Curcumin | p300 HAT inhibitor | Heart failure | rat, *in vitro* | It prevented deterioration of systolic function and heart failure | Morimoto *et al*[45] (2008) |

TSA: Trichostatin A; HDAC: Histone deacetylases; HDACi: Inhibitors of histone deacetylases; VAL: Valproic acid; SAHA: Suberoylanilide hydroxamic acid; VPA: Valporoic acid.

**Table 3 Recent evidence investigating the role of circulating miRNAs as biomarkers in several cardiovascular diseases**

|  |  |  |  |
| --- | --- | --- | --- |
| **miRNAs** | **Sources** | **Conditions** | **Ref.** |
| ↑miR-339-5p, miR-483-3p↓miR-139-5b | Plasma | LVI | Saddic *et al*[64] (2015) |
| ↓miR-145 | Plasma | AMI | Gao *et al*[65] (2015) |
| ↑miR-122, miR-140-3p, miR-720, miR-2861, miR-3149 | Plasma | ACS, AMI | Li *et al*[66] (2015) |
| ↑Let-7e, miR-15a, miR-196b↓miR-411 | Plasma | AAA, Aterosclerosis | Stather *et al*[67] (2015) |
| ↓ miR-125b, miR-320b | Plasma | AMI, CAD | Huang *et al*[68] (2014) |
| ↓miR-21 | Serum | CAD | Fan *et al*[69] (2014) |
| ↓miR-31 | Plasma | CAD | Wang *et al*[70] (2014) |
| ↑miR-146a, miR-186, miR-208b, miR-499 | Serum | ACS, Stable CAD, CV risk | Wu *et al*[71] (2014) |
| ↑miR-210 | PBMC | HF | Endo *et al*[72] (2013) |
| ↑miR-21, miR-25, miR-92a, miR-106b, miR-126, miR-451, miR-590-5p | Plasma | AP, UA | Ren *et al*[73] (2013) |
| ↔ miR-1, miR-208a, miR-423-5p | Plasma | AMI, CAD | Nabialek *et al*[74] (2013) |
| ↑miR-30a, miR-210 | Serum | HF | Zhao *et al*[75] (2013) |
| ↑miR-337-5p, miR-433, miR-485-3p, miR-1, miR-122, miR-126, miR-133a/b, miR-199a↔miR-17-5p, miR-92a, miR-145, miR-155, miR-208a, miR-375, miR-799-5p | Plasma | AP, UA | D’Alessandra *et al*[76] (2013) |
| ↓miR-103, miR-142-3p, miR-30b, miR-342-3p | Plasma | HF | Ellis *et al*[77] (2013) |
| ↑miR-122, miR-200b, miR-520d-5p, miR-622↓miR-558 | WB and serum | HF | Vogel *et al*[78] (2013) |
| ↑miR-21, miR-133a, miR-423-5p, miR-499-5p↔miR-1, miR-208a | Plasma | HF, NSTEMI | Olivieri *et al*[79] (2013) |
| ↑miR-133a | Plasma | AMI, AP | Wang *et al*[80] (2013) |
| ↓miR-214 | Plasma | AMI, AP, UA | Lu *et al*[81] (2013) |

AAA: Abdominal aortic aneurysm; ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; AP: Angina pectoris; CAD: Coronary artery disease; CV: Cardiovascular; HF: Heart failure; LVI: Left ventricular ischemia; NSTEMI: Non-ST-elevation myocardial infarction; PBMC: Peripheral blood mononuclear cells; UA: Unstable angina; WB: Whole blood.