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Circulatory microRNAs in acute coronary syndrome: An update

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ABSTRACT

Micro-ribonucleic acids (miRs) are small, non-coding RNAs, which play an important role in atherosclerotic plaque formation, development and stability. Plaque destabilization and rupture lead to acute coronary syndromes (ACS). Previous studies have implicated several different miRs in the pathogenesis of atherosclerosis. A number of circulating miRs emerged as promising diagnostic and prognostic biomarkers in ACS. Particularly cardiac- and muscle-enriched miRs including miR-1, miR-133a, miR-133b, miR-208a, and miR-499 were associated with myocardial damage and thus proposed as potential biomarkers of ACS. In this review we summarize the role of circulating miRs as biomarkers for diagnosis and prognosis in patients with ACS, as well as recent advances and remaining challenges of miRs assessment.

Key words: acute coronary syndrome, microRNA

INTRODUCTION

Micro RNAs (miRs) are small, non-coding RNAs that regulate posttranscriptional gene expression by inhibiting translation or causing degradation of their target messenger RNA (mRNA) [1]. miRs bind to the 3'-untranslated region of their target mRNA through the so called "seed region" on nucleotides 2-8, and a single miR is able to target and regulate hundreds of miRs, thus possibly influencing various cellular pathways simultaneously [2].

Previous studies have implicated several different miRs in pathogenesis of atherosclerosis. miRs are involved in regulation of crucial processes of atherogenesis such as endothelial cell activation, inflammation, angiogenesis, smooth muscle cell proliferation, migration and neointima formation, respectively [3, 4].

Circulating miRs are stable in the circulation and resistant to endogenous ribonuclease activity due to transportation within extracellular vesicles or in protein/lipoprotein complexes with high-density lipoprotein, argonaute2, and nucleophosmin [5–8], and can be quantified using polymerase chain reaction. Circulating miRs are not only passively released into the circulation during cellular death, but also actively secreted and may contribute to intercellular signaling. All major cell-types that play a role in formation and progression of atherosclerotic plaques, such as endothelial cells, monocytes, macrophages, smooth muscle cells and platelets, may secrete miRs into the circulation or take up miRs from the circulation as well. We could show previously, that platelet-related miR-21 and miR-126 are associated with monocyte/platelet aggregate formation in ACS patients on dual antiplatelet therapy [9]. Thus, both increase and decrease or loss of certain miRs could serve as a potential marker for atherosclerotic plaque progression, instability, myocardial damage or platelet activation [9, 10].

Several studies have proposed various miRs as biomarkers for early detection of acute myocardial infarction, stable coronary artery disease [CAD], in-stent restenosis, outcome in acute and chronic heart failure, and for cardiovascular risk factors such as type II diabetes and obesity [11–19]. In this review we summarize the clinical utility of circulating miRs as diagnostic and prognostic biomarkers in ACS.

MICRORNAS AS DIAGNOSTIC BIOMARKERS IN ACS

A number of circulating miRs emerged as promising candidates for diagnosis of ACS (Table 1). Particularly cardiac- and muscle-enriched miRs including miR-1, miR-133a, miR-133b, miR-208a, and miR-499 were associated with myocardial damage and thus

proposed as potential diagnostic biomarkers of ACS [11, 12, 20, 21]. Since miRs can be actively secreted into the circulation by living cells, it was hypothesized that cardiac-specific miRs might be detected in the circulation prior to cardiac troponins (cTn) and therefore represent early biomarkers for the detection of acute myocardial infarction (AMI) [11, 20, 22]. Liebetrau et al. [22] demonstrated that miR-1 and miR-133a are increased only 15 min after transcoronary septal ablation in patients with hypertrophic obstructive cardiomyopathy. Widera et al. [23] could show that miR-1, miR-133a and miR-208b were increased in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) as compared to patients with unstable angina and were independently associated with high-sensitivity cardiac troponin (hs-cTn) levels. The expression of miR-1 was not only elevated in plasma, but also in urine of AMI patients, and showed strong correlation with cTn [24]. Circulating miR-499 was elevated in STEMI patients as compared to controls and stable CAD, and could discriminate cases from controls independently of clinical risk factors [25]. Serum miR-499 could also discriminate unstable angina and NSTEMI from non-cardiac chest pain in patients presenting within 3 h of symptom onset [26]. Furthermore, miR-499 was proposed as an early marker of perioperative AMI in patients undergoing coronary artery bypass surgery [27].

In a meta-analysis including 2136 participants from 15 studies, sensitivity and specificity of cardiac- and muscle-enriched miRs in ACS were evaluated (miR-1, miR-133a, miR-208a, and miR-499). miR-133a and miR-499 were identified as promising diagnostic biomarkers for both STEMI and NSTEMI with an excellent discriminative power (miR-133a: sensitivity: 0.89 [95% CI, 0.83–0.94]; specificity: 0.87 [95% CI, 0.79–0.92]; miR-499: sensitivity: 0.88 [95% CI, 0.86–0.90]; specificity: 0.87 [95% CI, 0.84–0.90]) [28]. Other meta-analyses came to similar promising results [29–31]. However, the results obtained from those meta-analyses have to be interpreted with caution, since the included studies exhibited substantial methodological discrepancies regarding sample preparation, normalization method and miRs quantification.

Beside cardiac- and muscle enriched miRs, several other miRs were proposed as diagnostic biomarkers for ACS as well. The expression of miR-22 was higher in ACS as compared to stable coronary artery disease [32]. Circulating levels of miR-122, miR-2861 and miR-3149 could discriminate ACS from non-ACS patients with an area under the curve (AUC) of 0.925 [33]. The same group also demonstrated that these miRs are released by peripheral blood mononuclear cell during the early stage of ACS

[34]. Moreover, it was shown that patients with ACS have lower expression of miR-145 when compared to stable CAD [35]. The pro-atherogenic miR-19a was upregulated in ACS patients as compared to controls, and could discriminate cases from controls with high sensitivity and specificity [36]. Other high-density lipoprotein-associated members of the miR-17/92 cluster showed an inverse trans-coronary gradient in ACS as compared to stable CAD and healthy controls [37]. Higher level of plasma miR-4286 was associated with an increased risk of ACS and with higher triglyceride levels, which may mediate the effect of triglyceride on incident ACS [38]. Plasma levels of miR-125b and miR-30d were higher in patients with ACS compared to healthy controls and had similar sensitivity and specificity as hs-cTn [39]. The combination of circulating miR-150 and miR-486 could discriminate NSTEMI patients from controls, but not between STEMI and NSTEMI patients [40]. Using a novel self-learning pattern recognition algorithm, Meder et al. identified a signature of 20 dysregulated miRs in total peripheral blood of AMI patients, which were able to discriminate cases from controls with 90% sensitivity and 96% specificity [41].

Despite initial promising results from the studies using conventional troponin assays, none of the studies could demonstrate the benefit of assessing circulating miRs in addition to hs-cTn for diagnosis of ACS [33, 42–44]. miR-208b and miR-499 were elevated in STEMI and NSTEMI patients as compared to controls, and both miRs could discriminate cases from controls with an AUC comparable or lower to hs-cTn [43, 45, 46]. Assessment of miR-208b or miR-499 could not improve the diagnostic accuracy of hs-cTn [43, 45, 46]. Similarly, the expression of miR-1, miR-133a, miR-208b, miR-499 was increased in STEMI and NSTEMI patients as compared to controls, but the sensitivity and specificity to detect ACS was lower as compared to hs-cTn [47]. Moreover, although in one study the miRs-signature consisting of miR-1, miR-134, miR-186, miR-208, miR-223 and miR-499 had a slightly higher AUC for discriminating ACS from angina and controls than hs-cTn, the investigators did not test for statistical significance between the ROC curves and did not assess whether these miRs provide added diagnostic values on top of hs-cTn [48]. In a large prospective, multi-center study Devaux et al. [42] measured levels of 6 miRs in 1155 unselected patients with acute chest pain: miR-133a, miR-208b, miR-223, miR-320a, miR-451 and miR-499. Although miR-208b, miR-499 and miR-320 could discriminate patients with ACS from other diagnosis, none of these miRs was superior to hs-cTn [42].

Increased sensitivity of new hs-cTn comes at the price of reduced specificity, and accurate discrimination of patients with NSTEMI and unstable angina from other causes of chest pain with rapid “rule-in” and “rule-out” remaining an unmet clinical need [49–51]. miR-499 was superior to hs-cTn in discriminating NSTEMI and acute heart failure in elderly patients with modest hs-cTn increase at presentation [52]. Oerlemans and co-workers showed in a prospective study that miR-1, miR-21, miR-146a, miR-208a and miR-499 were increased in ACS patients [53]. More importantly, combination of miR-1, miR-21 and miR-499 showed better diagnostic performance than hs-cTn alone, and increased diagnostic accuracy of hs-cTn and clinical risk factors [53]. This effect was especially pronounced in early presenters and in patients with initially negative troponin. Zeller et al. proposed a panel of 3 miRs consisting of miR-132, miR-150 and miR-186 for discrimination of patients with unstable angina from other causes of chest pain with high discriminatory power (AUC 0.91; 95% CI, 0.84–0.98). The diagnostic accuracy of the 3-miRs signature was superior to the combination of hs-cTn, B-type natriuretic peptide (BNP), C-reactive protein and cystatin C, respectively [54]. All of the patients had negative hs-cTn at baseline and STEMI patients were excluded [54]. Jaguszewski et al. [55] identified miRs-signature consisting of differentially expressed stress- and ischemia-related miRs (miR-1, miR-16, miR-26a and miR-133a) that could distinguish takotsubo cardiomyopathy and STEMI patients with 96.77% sensitivity and 70.37% specificity (AUC 0.88; 95% CI, 0.79–0.97).

MICRORNAS AS PROGNOSTIC BIOMARKERS IN ACS

Several studies proposed the role of cardiac-enriched miRs as prognostic biomarkers after ACS (Table 2) [23, 46, 56–58]. Widera et al. [23] could show that miR-133a and miR-208b were independent predictors of all-cause mortality after adjusting for age and sex. However, when adjusted for hs-cTn levels, both miRNAs lost their predictive value for death. Similar results were obtained by Gidlöf et al [46]: miR-208b and miR-499 were strongly correlated with hs-cTn and predicted 30-days mortality after ACS, but in an adjusted analysis for hs-cTn their independent association with outcome was lost. In elderly patients, miR-499 independently predicted cardiovascular mortality 1 year after NSTEMI (59). In contrast, Goretti et al. showed that miR-208b and miR-499 were not associated with 6-year mortality after ACS [60]. In a recent study by De Rosa et al. [56], a lower transcoronary concentration gradient of miR-133a was associated with

increased mortality and major adverse cardiovascular events in patients with ACS and stable CAD, demonstrating not only that miR-133a is a potential prognostic marker in ACS, but also identifying myocardial tissue as the source of miR-133a. However, again, after adjustment for hs-cTn, this significant association was lost [56]. In a cohort of unselected acute chest pain patients none of the analyzed cardiac- and platelet- enriched miRs (miR-133a, miR-208b, miR-223, miR-320a, miR-451 and miR-499) predicted long-term outcome [42].

Not only cardiac- and muscle-enriched miRs have the potential as prognostic biomarkers in ACS: A relative increase of circulating liver-specific miR-122 predicted adverse outcome almost 2 years after STEMI independently of left ventricular function [61]. However, the authors did not compare miR-122 to established risk markers such as hs-cTn, BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP). Thus, although miR-122 might be an interesting biomarker in ACS, further studies are needed [34, 61]. Increased miR-145 on day 5 after STEMI and primary PCI predicted adverse outcome after 1 year follow-up independently of cTn and BNP [62]. Several miRs involved in the regulation of the innate immune response are associated with left ventricular remodeling and ventricular rupture following ACS [63, 64]. Downregulation of miR-150 in the failing human heart is detectable in the circulation [64, 65]. Decreased levels of circulating miR-150 predicted adverse ventricular remodeling after STEMI and were superior to clinical and laboratory risk factors including BNP [65]. Whole blood sequencing in patients with NSTEMI identified five circulating miRs, namely miR-28, miR-126, miR-142, miR-144 and miR-3135 that were associated with chronic heart failure and GRACE-Score [66]. miR-150 together with miR-16, miR-27a and miR-101 predicted left ventricular dysfunction 6 months after ACS independently of BNP and clinical risk factors, thus improving identification of patients at risk of adverse left ventricular remodeling [67]. Furthermore, p53-responsive miR-34a, miR-192 and miR-194 were increased in patients who developed ischemic heart failure within one year after AMI, and were associated with adverse ventricular remodeling [68]. In contrast, miR-133a and miR-423 were not associated with left ventricular remodeling after ACS [69]. Although miR-1 and miR-29b correlated with infarct size and change in left ventricular end diastolic volume, they did not predict adverse clinical outcome [70]. Low circulating miR-652 was independently associated with readmission for heart failure after 5 years follow-up, but not with cardiovascular mortality [71].

Karakas et al. [72] identified circulating miR-132, miR-140 and miR-210 as independent predictors of cardiovascular death after 4 years follow-up in a large cohort of over 1000 patients with documented CAD including both ACS as well as patients with stable angina. The predictive power was more pronounced in the subgroup of patients with ACS. A combination of several circulating miRs did not provide additional prognostic information when compared to single miRs [72]. In another prospective, case-control study, miR-26b, miR-320a and miR-660 were identified as prognostic biomarkers for major adverse cardiovascular events after STEMI. All 3 miRs were superior to hs-cTn in risk stratification of STEMI patients and added prognostic information on top of GRACE-Score and hs-cTn [73]. miR-26b and miR320a were previously shown to play a role in ventricular remodeling in heart failure, whereas miR-660 may have a prothrombotic effect by increasing platelet activation [74–76].

In a population-based study, Zampetaki et al. [77] proposed a signature of 3 circulating miRs, namely miR-126, miR-197 and miR-223 as prognostic marker for occurrence of ACS within 10 years of follow-up. Assessment of these 3 platelet-related miRs improved risk stratification when added to the Framingham risk score [77]. Moreover, miR-197 and miR-223 predicted cardiovascular death in patients with documented coronary artery disease [78]. In another smaller population study in apparently healthy subjects, a combination of let-7g, miR-106a, miR-424, miR-144 and miR-660 was associated with increased risk of AMI after 10 years follow up, and improved the AUC when added to the Framingham risk score [79]. Thus, circulating miRs as stand-alone markers or as part of miRs-signatures might be used for risk stratification in both primary and secondary prevention.

CURRENT CHALLENGES

Assessment of circulating miRs as diagnostic and prognostic biomarkers is after almost two decades of intensive research still in its infancy. Due to discrepancies in sample handling, preparation and quantification, the results of the different studies are not comparable. Furthermore, routine use in clinical practice is limited by time consuming and expensive analysis, requiring specific laboratory resources and highly trained personal. The development of fast and reproducible RNA assays for fast and reliable quantification of miRs is of paramount importance. Finally, a consensus on minimal standards regarding sample collection, RNA preparation, quantification, data

normalization and analysis is necessary. Once these requirements are met, larger, well-powered multi-center trials can be performed, which could deliver valuable data and possibly lead to translation of miRs assessment into clinical practice.

CONCLUSION

Circulating miRs hold potential as promising diagnostic and prognostic biomarkers in ACS. Specific miRs-signatures might improve diagnostic accuracy in patients with suspected ACS, as well as risk stratification following ACS by providing valuable prognostic information on top of clinical judgement and cardiovascular risk factors. As of yet, some circulating miRs such as the cardiac- and muscle-enriched miRs miR-1, miR-133a, miR-133b, miR-208a, and miR-499 offer promise as potential diagnostic and prognostic biomarkers in ACS as they associated with myocardial damage. However, before the implementation of miRs in daily clinical routine, a better understanding of miRs regulation/dysregulation in different pathophysiological settings as well as the development of faster, reproducible and standardized analytical procedures are warranted.

Article information

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Table 1. MicroRNAs as diagnostic biomarkers in acute coronary syndrome (ACS)

Study	**Dysregulated miRs**	**Study population**	**Normalization**	**Sample**
Wang et al. [11]	**miR-1**↑ **miR-133a** ↑ miR-208a ↑ **miR-499** ↑	33 AMI vs. 33 non-cardiac chest pain vs. 30 controls	cel-miR-39	Plasma
D'Allesandra et al. [12]	**miR-1** ↑ miR-122 ↓ **miR-133a** ↑ miR-133b ↑ miR-375 ↓ **miR-499** ↑	33 STEMI vs. 17 controls	miR-17	Plasma
Kuwabara et al. [20]	**miR-1** ↑ **miR-133a** ↑	29 ACS vs. 42 non-ACS	Not specified	Serum

Corsten et al. (21)	**miR-133a ↑** **miR-208b ↑** **miR-499 ↑** miR-223 ↓	32 AMI vs. 36 non-cardiac chest pain	3 C. elegans spike-ins	Plasma citrate
Widera et al. [23]	**miR-1 ↑** **miR-133a ↑** **miR-208b ↑**	444 ACS patients (196 STEMI and 131 NSTEMI vs. 117 unstable angina	cel-miR-54	Plasma
Cheng et al. [24]	**miR-1 ↑**	20 AMI vs. 20 controls	Not specified	Urine
O'Sullivan et al. [25]	**miR-499 ↑**	50 STEMI vs. 50 stable CAD vs. 50 controls	Average Ct of the normalizer assays detected in all samples	Plasma
Shalaby et al. [26]	miR-210 ↑ **miR-499 ↑**	37 unstable angina and 48 NSTEMI vs. 25 non-cardiac chest pain	U6	Serum
Yao et al. [27]	**miR-499 ↑**	117 CABG patients (28 perioperative AMI vs. 89 without perioperative AMI)	Median Ct of all samples	Plasma
Darabi et al. [32]	**miR-21 ↑**	50 ACS vs. 50 stable CAD	U6	Serum
Li et al. [33]	miR-122 ↑ miR-140 ↑ miR-720 ↑ miR-3149 ↑	402 ACS vs. 169 non-ACS	miR-1228	Plasma

Gao et al. [35]	miR-145 ↓	141 ACS vs. 54 non-ACS	cel-miR-39	Plasma
Zhong et al. [36]	**miR-1 ↑** miR-19a ↑	156 AMI vs. 145 controls	5S	Plasma citrate
Choteau et al. [37]	Inverse transcoronary gradient for miR-16 miR-92a miR-223	17 ACS vs. 19 stable CAD vs. 6 controls	cel-miR-39	HDL from plasma
Jia et al. [39]	miR-30d ↑ miR-125b ↑	230 ACS vs. 79 controls	cel-miR-39	Plasma
Zhang et al. [40]	miR-150 ↑ miR-486 ↑	110 AMI vs. 110 controls	U6	Plasma
Devaux et al. [42]	**miR-208b ↑** miR-320 ↑ **miR-499 ↑**	224 AMI vs. 931 non-AMI	3 C. elegans spike-ins	Plasma
Devaux et al. [43]	**miR-208b ↑** **miR-499 ↑**	510 AMI vs. 87 controls; 397 STEMI vs. 113 NSTEMI	3 C. elegans spike-ins	Plasma
Zhang et al. [45]	**miR-499 ↑**	142 AMI vs. 85 non-AMI vs. 100 controls	U6	Plasma citrate
Gidlöf et al. [46]	**miR-1 ↑** **miR-208b ↑** **miR-499 ↑**	319 AMI vs. 88 non-AMI	miR-17	Plasma
Li et al. [47]	**miR-1 ↑** **miR-133a ↑** **miR-208b ↑**	67 AMI vs. 39 controls	cel-miR-39	Plasma
Olivieri et al. [52]	**miR-21 ↑** **miR-499 ↑** miR-423 ↓	92 NSTEMI vs. 81 acute CHF	miR-17 cel-miR-39	Plasma

Oerlemans et al. [53]	**miR-1** ↑ **miR-21** ↑ miR-146a ↑ **miR-208b** ↑ **miR-499** ↑	106 ACS vs. 226 non-ACS	U6	Serum
Zeller et al. [54]	miR-19a miR-19b miR-132 miR-140 miR-142 miR-150 miR-186 miR-210	48 unstable angina vs. 47 non-cardiac chest pain	cel-miR-39	Plasma
Jaguszewski et al. [55]	miR-16 ↑ miR-26a ↑ let-7f ↑ miR-133a ↓	36 Takotsubo vs. 27 STEMI	cel-miR-39	Plasma
***MiRs with reproducible changes in 3 or more independent studies are highlighted in bold**				

Table 2. MicroRNAs as prognostic biomarkers in acute coronary syndrome (ACS)

Study	**Major findings**	**Study population**	**Follow-up**	**Normalization**	**Sample**
Widera et al. [23]	miR-133a and miR-208b predict all-cause mortality, significance lost after adjustment for hs-cTn	444 ACS patients	6 months	cel-miR-54	Plasma

Devaux et al. [42]	miR-133a, miR-208b, miR-223, miR-320a, miR-451 and miR-499 were not associated with patients' outcome	1155 acute chest pain	2 years	3 C. elegans spike-ins	Plasma
Gidlöf et al. [46]	miR-208b and miR-499 predict 30-days mortality; association lost after adjustment for hs-cTn	319 AMI	1 month	miR-17	Plasma
De Rossa et al. [56]	Transcoronary gradient of miR-133a predicts mortality and MACE in ACS and stable CAD; association lost after adjustment for hs-cTn	82 stable CAD and 29 ACS	32 months	cel-miR-39	Not specified
Olivieri et al. [59]	miR-499 predicts cardiovascular mortality in elderly NSTEMI patients	155 NSTEMI	1 year	miR-17 cel-miR-39	Plasma
Goretti et al. [60]	miR-208b and miR-499 did not predict long-term mortality after AMI	510 AMI	6 years	Not specified	Not specified

Cortez-Dias et al. [61]	higher miR-122-5p/133b ratio predicts MACE after STEMI independently of LVEF	142 STEMI	20 months	UniSp6	Serum
Dong et al. [62]	miR-145 predicts MACE after STEMI	246 STEMI	1 year	Not specified	Serum
Karakas et al. [72]	miR-132, miR-140 and miR-210 independent predictors of cardiovascular death	1112 CAD	4 years	cel-miR-39	Serum
Jakob et al. [73]	miR-26b, miR-320a and miR-660 predict MACE after STEMI	1002 STEMI	1 year	UniSp6	Plasma