The role of circulating microRNAs in acute coronary syndromes: ready for prime time?

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Recently Navickas *et al*. published a review on the role of microRNAs (miRs) as biomarkers of cardiovascular disease in *Cardiovascular Research* (1). Based on a systematic literature research their aim was to determine the diagnostic and prognostic value of miRs in healthy subjects, subjects with stable coronary artery disease and patients with different forms of unstable coronary artery disease (unstable angina, non-STEMI and STEMI). They identified n=487 papers and extracted n=19 studies, reporting on 52 different miRs, after a rigorous quality check. The largest amount of evidence, through all stages of cardiovascular disease, was found for miR-133a/b (5 studies), miR-208a/b (6 studies) and miR-499 (7 studies). Furthermore the promising role of miR-1 (3 studies) in the diagnosis of acute coronary syndromes and the regulation of miR-145 in STEMI patients is highlighted. A meta-analysis, however, is not presented because of heterogeneous study designs and analytical reasons (1).

Especially in patients with acute coronary syndromes the role of novel biomarkers is rapidly evolving (2). Cardiac troponin measured with standard (3) and high-sensitive (4) assays has improved our abilities to define patients with acute coronary syndromes (5), estimate the amount of myocardial necrosis (3), predict functional impairment (6,7) and prognosis (8). Another well-established biomarker in acute coronary syndromes is NT-pro-BNP (9). Today these two biomarkers impact clinical decisions of cardiologist every day. However their diagnostic performance is hampered by diagnostic windows, their relatively low specificity (10) and their correlation with renal function (11). Therefor there is indeed a need to identify novel biomarkers in acute coronary syndromes.

miR-1 is very specific for cardiac skeletal muscle and plays an important role during cardiogenesis and proliferation of cardiomyocytes (12). Three different studies, with a total of n=583 patients with acute coronary syndromes and n=259 controls (13-15), investigated the role of miR-1 in the initial diagnosis of patients with chest pain and suspected acute coronary syndrome. Wang *et al*. observed that miR-1 levels in patients with acute myocardial infarction are elevated compared to controls, but the diagnostic performance of miR-1 was inferior to cardiac troponin I (AUC: 0.85 *vs*. 0.99) (13). Oerlemans *et al*. described an increase in miR-1 even in patients with initially negative troponin levels or in patients presenting within 3 hours after symptom onset (14). Furthermore, Widera *et al*. showed that miR-1 levels are significantly higher in patients with NSTEMI or STEMI than in patients with unstable angina, although they did not predict mortality at 6 months (15). Anyhow, these results identify miR-1 as one of the most promising miRs for the early diagnosis of acute coronary syndromes, especially in the combination with other biomarkers.

The largest study included in this review was performed by Devaux *et al*. (16). It prospectively investigated the use of six different miRs in n=1,155 patients with acute chest pain and suspected acute myocardial infarction. Finally,

n=179 patients were diagnosed as NSTEMI and n=45 patients as suffering from a STEMI. miR-133a, miR-208b and miR-499 were identified as univariate predictors of myocardial infarction. As noted by Navickas *et al*. all these three miRs control cardiomyocyte identity (17). However, their predictive value did not remain significant after correction for troponin levels. Furthermore, the area under the receiver operating curves were low (AUC: 0.53–0.76) compared to high sensitive troponin (AUC: 0.94). The miR-133a, miR-208b and miR-499 levels were significantly higher in STEMI patients than in NSTEMI patients (16). These findings are in line with the findings of Widera *et al*. on miR-133a and miR-208a (15), although both studies failed to demonstrate an independent prognostic value of all miRs studied.

The potential unique role of miR-133a in STEMI patients is further highlighted by a study by Eitel *et al*. (18). In this study miR-133a levels were associated with decreased myocardial salvage, larger infarct size and microvascular obstruction (19) as determined by cardiac magnetic resonance in a clearly defined study population of n=216 consecutive STEMI patients. Although miR-133a was a univariate predictor of mortality and MACE (HR: 1.28) the use of cardiac magnetic resonance for infarct characterisation (20) allowed the authors to demonstrate, that this association is not independent of infarct characteristics (18).

Another study focusing exclusively on patients with STEMI was performed by Dong *et al*. (21) who investigated the prognostic value of miR-145, which regulates vascular smooth muscle cell and cardiomyocyte differentiation and has been shown to correlate with infarct size (22). In n=245 with STEMI they demonstrated that miR-145 levels above the median predicted 12-months MACE independent of NT-pro-BNP, creatine kinase or troponin levels (HR: 5.6) (21). Interestingly miR-145 levels have been observed to be generally lower in patients with severe coronary artery disease or acute coronary syndromes which might indicate altered expression of miR-145 in these patients (23). As these findings seem controversial further research should clarify the role of miR-145 in cardiovascular disease.

Navickas *et al*. have done a valuable work in identifying five, out of more than 2,000 described in humans, miRs which have great potential to improve our daily clinical work in the future. Their review is based on the data of 19 studies with more than 6,000 participants (1). These miRs are ready for prime time in cardiovascular research but further studies are warranted to provide reliable and standardised quantification with faster PCR and microarray technologies. Then it should be possible to include these promising biomarkers in controlled, large-scale, well-powered trials and, perhaps someday, into clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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