Editorial

Circulating microRNAs as predictors of cardiovascular disease—more than a miRage?

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Comment on: Jakob P, Kacprowski T, Briand-Schumacher S, *et al.* Profiling and validation of circulating microRNAs for cardiovascular events in patients presenting with ST-segment elevation myocardial infarction. Eur Heart J 2017;38:511-5.

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Coronary artery disease (CAD) is a leading cause of morbidity and mortality globally, and reliable prognostic tools for identifying subjects at risk of developing a cardiovascular event is currently a great unmet clinical need (1). Despite the considerable effort that has been put into developing risk prediction model, the accuracy of traditional risk factors is insufficient for predicting cardiovascular events in a substantial proportion of patients. The use of coronary imaging holds promise in improving cardiovascular risk prediction, but the technique is costly and unsuitable for population-wide screening. Thus, there is great interest in identifying circulating biomarkers that could complement the assessment of traditional risk factors. In a recent paper, Jakob *et al.* make a powerful claim for miRNAs as prognostic biomarkers in patients with CAD (2).

MicroRNA (miRNA) is a class of short, non-coding RNAs with a seemingly pervasive role in mammalian biology and disease (3). Through binding to complimentary sequence motifs, mainly in the 3'-untranslated region of target messenger RNAs, miRNAs repress gene expression and play pivotal roles in many essential cellular processes. With the realization that miRNAs are also released from cells upon activation or stress and that circulating miRNAs are protected from RNase-degradation (4), there has been a surging interest in using these molecules as biomarkers in a wide array of human disease states.

In 2010, the first studies showing increased levels of miRNAs of cardiac origin in the circulation of patients with myocardial infarction were published (5-7), providing the first proof-of-principle that miRNAs could have potential clinical use as biomarkers in CAD. Since then, a plethora of papers have been published showing that the miRNA profile in plasma is rapidly and robustly altered as a result of ACS (8-10). However, most studies have been limited in size and have lacked validation in larger cohorts.

Zampetaki *et al.* published the first large, prospective study investigating the association of circulating miRNAs with incidence of myocardial infarction (11). In this cohort of 820 participants, 47 of which experienced an MI, 3 miRNAs (miR-126, miR-223 and miR-197) were consistently and significantly associated with incident myocardial infarction, with hazard ratios of 2.69, 0.47 and 0.56, respectively. Although the addition of the three miRNAs to the Framingham Risk Score with CAD as an endpoint resulted in an improved C-index, the gain was not statistically significant.

Widera *et al.* assessed the diagnostic and prognostic value of a select set of cardiac-enriched miRNAs in a large ACS cohort (n=444) and patients were followed for 6 months with regards to all-cause mortality (12). miR-133a and miR-208b levels were significantly and independently associated with risk of death, but association was lost upon adjustment with the established myocardial necrosis marker Troponin T, dampening the expectation on miRNAs as clinically useful biomarkers in CAD.

However, in the first multicenter, prospective study including both a derivation and a validation cohort, Jakob *et al.* shows that circulating miRNA might still have a clinical value; as independent predictors of adverse cardiovascular outcomes in patients with ST-elevation myocardial infarction (STEMI) (2). Sixty-three patients in a cohort of 1002 STEMI patients experienced a major cardiovascular event (MACE, defined as cardiovascular

mortality or recurrent MI) within 1 year of follow-up. A comprehensive profiling of circulating miRNAs in the derivation cohort resulted in 14 dysregulated miRNAs which were carried over to the validation phase. In the subsequent validation cohort of 63 cases and 126 matched controls, miR-26b-5p, miR-660-5p and miR-320a were confirmed to be dysregulated in patients with a MACE within the follow-up period. The area under the receiver operator characteristic curves of Cox regression models could significantly discriminate patients with MACE from controls in the case of all three miRNAs, and a combination of the three yielded an incremental increased in the AUC-ROC. Furthermore, addition of miR-26b-5p, but not miR-660-5p or miR-320a, to the Global Registry of Acute Coronary Events (GRACE)-score increased AUC, and a combination of the three miRNAs increased net reclassification improvement (NRI). Interestingly, these three miRNAs have previously been shown to play roles in cardiomyocyte apoptosis (13), platelet activation (14), and cardiac hypertrophy (15), indicating that the presence of these miRNAs in the circulation is a reflection of underlying disease mechanisms. The study is the first to assess miRNAs related to adverse prognosis in a secondary prevention cohort of STEMI patients, but confirmation of these potential biomarkers in larger cohorts is required if clinical utility is to be established.

The notion of circulating miRNAs as diagnostic and prognostic tools for patients with cardiovascular disease has gained ever-increasing traction in recent years, but clinical implementation still seems distant. Sources of technical and biological variation still need elucidation (16) and the analytical workflow for plasma miRNA samples must be streamlined and standardized. Still, the results of Jakob *et al.* shows that clinical utility for miRNAs in cardiovascular risk prediction is perhaps not simply a fading "miRage".

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Footnote

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