

# Is there a role for microRNAs as novel predictors of prognosis in myocardial infarction?

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*Comment on:* Coskunpinar E, Cakmak HA, Kalkan AK, *et al.* Circulating miR-221-3p as a novel marker for early prediction of acute myocardial infarction. *Gene* 2016;591:90-6.

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MicroRNAs (miRNAs) are endogenous, non-coding, single stranded RNAs of 19–25 nucleotides in length that regulate gene expression at the post-transcription processing steps (1). Although the exact biological functions of miRNAs are still not fully understood they have been implicated in cellular development, differentiation, metabolism and death (2,3).

The discovery that stable miRNAs could be identified in human plasma/serum (4) enabled researchers to investigate their expression levels in various cardiovascular conditions (5). Circulating levels of specific miRNAs have been found to be significantly increased in AMI patients compared to controls, leading to speculation that they may have a role to play as novel diagnostic biomarkers (6).

In this edition of *Gene*, Coskunpinar *et al.* present data from a small (27 patients), single centre study, demonstrating the use of circulating miRNAs as novel markers for early prediction of acute myocardial infarction and LV dysfunction post AMI (7). Real time PCR was used to determine the expression levels of 1,116 miRNAs in 27 patients post AMI and 16 control subjects. Six miRNAs were identified as being significantly upregulated in the AMI group compared with the control group.

The most promising miRNA, miR-221-3p was shown to correlate modestly with GRACE and SYNTAX scores as well as serum troponin. In practical terms, the paper suggests that this may represent a novel marker for the early prediction of AMI. However, when miR-221-3p was assessed via receiver operator curves for the prediction of

AMI, the AUC was calculated at 0.881, which was inferior to that of the current standard clinical test of troponin (AUC 0.954). Moreover, the addition of miR-221-3p to troponin did not appear to add additional diagnostic capacity.

Ongen *et al.* also observed an inverse relationship with LV ejection fraction. Such relationships would be expected of any biomarker which is collinear with troponin and is therefore not unusual. Moreover, the relationship was demonstrated in uni-variable analysis only and has not been tested in more robust multi-variable analysis.

The observation of relationship between miR-221-3p and LV function is interesting but certainly not a unique finding for miRNAs. Devaux *et al.* (8,9) have previously demonstrated miRNAs to be associated with LV function, remodelling and cardiac contractility post MI in a larger cohort of patients and other studies have shown similar (10).

The utility of miR-221-3p as a prognostic marker has not been tested in this study as no clinical endpoint data were presented. However, one may expect that a biomarker which is associated with Troponin, GRACE and LV function would also be associated with adverse outcomes. Indeed, long term follow up data from the AtheroGene Study identified three miRNAs which precisely predict cardiovascular mortality following AMI establishing their potential as predictors of prognosis (11).

As acknowledged by the authors, the small sample size is the major limitation of this study. Further studies are required both to validate the findings of this small single

centre investigation and also to expand to allow use as a marker of prognosis and adverse LV remodelling. In addition, the authors link the increased expression of miRNAs identified in the study, with the down regulation of four target genes that have previously been found to regulate various cardioprotective molecular pathways. The authors infer that this relationship may hence increase susceptibility to AMI. Further research is required in order to establish any potential causative mechanisms.

In conclusion, this study adds to the expanding list of biomarkers in the prediction of AMI. With over 2,000 miRNAs already catalogued (12) this remains a vast topic with many exciting research avenues to pursue in the future. The ability to identify the genetic functions of specific miRNAs and their influence on particular cellular processes significantly increases our understanding of complex pathophysiological mechanisms involved in the development of conditions such as AMI.

Combining this knowledge with the rapidly evolving science of genetic engineering is already allowing infections such as Hepatitis C to be tackled in revolutionary ways (13) and may radically change the way we manage numerous cardiovascular diseases in the future.

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## Footnote

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

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