Peer Review File

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Reviewer A

Comment 1. References previous to 2010 should be updated.

Response. We thank the Reviewer for this comment and understand the importance of publishing reviews that contain cutting edge and up-to-date information. When examining our references, we observed 19 articles published prior to 2010. Of these, five were review articles and 14 were original research articles. Taking this comment into account, we have replaced all five review articles with updated versions. However, we have chosen to keep the remaining 14 research articles as they contain important information to this review. Some of these articles represent seminal research in the field (e.g. early natriuretic peptide studies or collagen kinetics for infarct healing). Alternatively, some of these studies contribute to the miRNA research that is discussed in this review, and that was selected using our search strategy that did not include a time-specific cut off.

Comment 2. A description of the miRNA biogenesis, as well as a brief description of their extracellular circulation needs to be added.

Response. We have added further information on miRNA biogenesis and extracellular circulation to the paragraph describing miRNAs in the introduction (Page 7, Lines 110-113; Page 8, Lines 121-122)

Comment 3. Although the review is well written and has a clear message, two reviews of the same topic were recently published (2019 and 2020):

1- doi:10.1615/CritRevEukaryotGeneExpr.2019028211

2- doi:10.3389/fphys.2020.01088

I strongly recommend the authors to study them extensively and to cite them.

Response. Thank you for your suggestion to include these articles. While we agree that they are on a similar topic to our narrative review, we believe that our article contains additional information that is useful to the field. In this review, we have extensively discussed the usefulness of combined miRNA panels, and in addition, we include recommendations for future work based on the limitations in this field. This is also a rapidly developing area of research, and our review includes additional primary articles that have been published

subsequent to the abovementioned reviews. However, we agree that these articles should be included in our narrative review and have cited them in the introduction section (Page 7, Line 110) and have specifically indicated for readers to further explore the Zhang et al. 2020 review for more information on miRNA biogenesis (Page 7, Lines 112-113).

Reviewer B

Comment 1. NT-proBNP does have good prognostic value: this should be mentioned on page 5 (line 82): eg see work by Thomas Wang for example.

Response. We thank the Reviewer for this comment, and agree that NT-proBNP does have prognostic value in this context. As such, we have updated the introduction section to include this information (Page 7, Lines 101-102). Alongside this, we have also outlined some of the limitations of natriuretic peptides that make miRNA a desirable alternative prognostic tool (Page 7, Lines 102-107)

Comment 2. On page 89: I would not say 'more effective' for miRNAs: there are few validated comparative studies that suggest that. Could work it as 'potential'.

Response. We thank the Reviewer for this recommendation. We have replaced the term ‘more effective’ with ‘have some potential’ to more accurately reflect the current position of research on this topic (Page 7, Line 109)

Comment 3. For the acute diagnosis, would discuss if miRNA diagnostics are superior to hsTnT (they are not in most studies) and can discuss the study by Yan Devaux.

Response. We agree that much of the current literature has focused on investigating the diagnostic utility of miRNA in AMI, and agree that we should include an acknowledgement of this in our narrative review. Therefore, we have included a sentence in the introduction, and have also included a recent systematic review and meta-analysis for further reading on this topic (Page8, Lines 125-131). However, we have chosen not to discuss any further details regarding the diagnostic utility of miRNAs in this review, as the purpose was to investigate miRNAs as a prognostic tool following AMI. We believe that this is a strength of our review, as many other articles in this space combine both diagnosis and prognosis together, which prevents a strong discussion surrounding the limitations that specifically hinder the progression of circulating miRNA biomarkers as prognostic tools. As such, we have been able to provide

a broad discussion surrounding studies that have solely investigated prognostication of miRNAs and we have also outlined key limitations within this field.

Comment 4. One point of discussion to bring up is that effect sizes of miRNA are generally small and CVs are high which makes replication in small cohorts difficult.
Response. We agree with the Reviewer and have included this information in our discussion section (Page 23, Lines 461-463)

Comment 5. On aspect which should be discussed is sudden death in the post-MI patients (an outcome of electrical remodeling); two studies (31971908) and the Atherogene study (https://doi.org/10.1093/eurheartj/ehw250) identify circulating mIRNAs associated with risk of sudden death. Notably, unlike the myomiRs, these studies suggest miRNAs arising from other cell types (eg immune cells) as possibly contributing to this.
Response. We thank the Reviewer for this comment and agree that sudden cardiac death is an interesting area of discussion. Indeed, this nicely demonstrates a key point in our limitation section that discusses how the heterogeneity in MACE endpoints can obscure miRNA of interest. As such, we have included a paragraph that discusses the Silverman et al. 2020 findings and how the miRNAs associated with SCD in this study differ from other studies that have more broadly investigated mortality and MACE in this review (Pages 22/23, Lines 437-450). We have also included the findings from the AtheroGene Study in Table 3.