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**Letter by Pinet et al Regarding Article,**

**“Comparative Analysis of Circulating Non-Coding RNAs Versus Protein Biomarkers in the Detection of Myocardial Injury”**

*To the Editor:*

We read the article written by Schulte *et al*<sup>1</sup> with great interest and appreciation. In this study, the authors performed a comparative analysis of circulating non-coding RNAs versus protein biomarkers to detect myocardial injury. Two cohorts of patients have been selected: patients undergoing transcatheter ablation of septal hypertrophy (TASH) with serial blood sampling (0-1-8-24h) and patients hospitalized for acute myocardial infarction (MI) with blood sampling (on admission, 1h and 3h). The non-coding RNAs were selected from literature or array screening for circulating RNAs. The authors treated all samples with heparinase to overcome the problem of heparin which interferes with quantification of RNAs by RT-qPCR<sup>2</sup>. Their conclusion was that cardiac myosin-binding protein C was the most sensitive cardiac biomarker with miR-1 and miR-133a as promising candidates in patients with acute myocardial injury.

However, results from the study should be interpreted with the following considerations for data on the lncRNA LIPCAR presented in this article. The authors refute a predominant cardiac origin of LIPCAR, because they did not detect modulation of LIPCAR during the short-time course of blood sampling (0-1-8-24h) of TASH patients. They hypothesize that its rise in plasma may be explained by a release of mitochondria from blood cells rather than cardiac injury<sup>1</sup>. We disagree with the authors for a number of points:

First, our discovery of the potential of LIPCAR was performed in patients hospitalized for an inaugural anterior MI with serial echocardiography (admission, 3 months and 1 year post-MI) and blood sampling (5 day, 1 month, 3 months and 1 year post-MI)<sup>3</sup>. We observed a down-regulation at early stage (5 days) but an upregulation during later stages (1, 3 months and 1

year post-MI) in patients with cardiac remodeling<sup>4</sup>. The time-course of measurements after MI is completely different to the study by Schulte *et al.*<sup>1</sup> as LIPCAR seems to be regulated only at later stages.

Second, the cohorts of the investigated patients are different. In the present paper, the authors observed a modulation of miR-133a in TASH patients<sup>1</sup>. We previously showed in patients enrolled in the REVE-2 study that circulating levels of miR-133a fail as a biomarker for left ventricular remodeling after myocardial infarction<sup>5</sup>.

Third, in the myocardial tissue spike-in experiment, in which the authors spiked different amounts of human heart tissue (0 to 25 ug/100 uL plasma) into human plasma, LIPCAR was consistently detected and was among the 11 lncRNA quantified with the lowest raw Cq values (between 25 and 30) compared to the other non-coding RNAs (lncRNA, miRNAs, and circRNAs).

Fourth, LIPCAR was detectable at all-time points in samples from TASH patients, conversely to other non-coding RNAs, but not dysregulated after onset of MI.

Based on these data the authors cannot conclude about the usefulness of LIPCAR as a good or bad marker in comparison to proteins or other miRNAs in general as surprisingly broadly stated in this article. The authors cannot conclude that LIPCAR is not of predominant cardiac origin as mentioned in the abstract, only because it was not modulated in plasma taken very early after the TASH procedure.

From the data shown by the authors, LIPCAR is not a marker for detecting acute MI. Indeed, we previously have shown prognostic rather than diagnostic evidence for LIPCAR levels to identify patients developing cardiac remodeling. LIPCAR levels were independently to other risk markers associated with future cardiovascular deaths.

We think that the evidence of cardiac-tissue specific origin of LIPCAR remains to be evaluated by using cardiac and non-cardiac human cells as well as cell-type specific genetic deletion studies.

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F. Pinet and T Thum conceived the study design and drafted the article. C Bär and C Bauters participated in the study design and helped to revise the article. All authors read and approved the final article.

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### **Disclosures**

F. Pinet, C. Bauters and T Thum filed and licensed a patent about LIPCAR. T. Thum is founder and shareholder of Cardior Pharmaceuticals.

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