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Reply: Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis

Marianna Fontana, MD[*,†,‡], **Silvia Pica, MD**[*], **Patricia Reant, MD, PhD**[*], **Amna Abdel-Gadir, MBBS**[*,†], **Thomas A Treibel, MBBS**[*,†], **Sanjay M Banypersad, MBChB**[*,†,‡], **Viviana Maestrini, MD**, **William Barcella, BFIN, MSc**[*], **Stefania Rosmini, MD**[*,‡], **Heerajnarain Bulluck, MBBS**[*,‡], **Rabya H Sayed, MBBS**[‡], **Ketna Patel, MBBS**[‡], **Shameem Mamhood, MBBCh.BAO**[‡], **Chiara Bucciarelli-Ducci, PhD**[#], **Carol J Whelan, MD**[‡], **Anna S Herrey, MD**[*], **Helen J Lachmann, MD**[‡], **Ashutosh D Wechalekar, MD**[‡], **Charlotte H Manisty, PhD**[*], **Eric B Schelbert, MD**[∞], **Peter Kellman, PhD**[§], **Julian D Gillmore, MD, PhD**[‡], **Philip N Hawkins, FMedSci**[‡], and **James C Moon, MD**[*,†]

[*]The Heart Hospital, 16-18 Westmoreland Street, London, UK

[†]Institute of Cardiovascular Science, University College London, London, UK

[‡]National Amyloidosis Centre, University College London, Royal Free Hospital, London, UK

[#]Bristol Heart Institute, University of Bristol, Bristol, UK

[∞]University of Pittsburgh School of Medicine, 200 Lothrop Street, Pittsburgh, PA, USA

[§]National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

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We thank Dr Aquaro, Dr Cohen and colleagues for their interest in our paper.[1] Cardiac involvement is a chief driver of prognosis in systemic amyloidosis and stratification of patients is essential for prognosis and choosing management strategies. Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) has good diagnostic accuracy for cardiac amyloidosis, but its prognostic impact was uncertain.[2–6] This study confirms incremental prognostic information after adjusting for known prognosis factors.

We note the comments of Dr Aquaro and colleagues regarding cardiac biopsy, but point out that microscopic histologic analyses of these tiny samples is not only open to sampling error but, crucially, the presence of amyloid in heart muscle is not actually proof of cardiac amyloidosis. It is essential to make the distinction between the presence of amyloid deposits and the clinical syndromes of amyloidosis. Amyloid deposits occur widely throughout the tissues in patients with systemic amyloidosis, often without any clinical consequences,

Address for Correspondence. Prof. James Moon, Barts Heart Centre, London, UK. j.moon@ucl.ac.uk, Phone No: +44 2034563081, Fax No: +44 2034563086.

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providing the basis for rectal, salivary gland, skin and fat biopsies to support diagnosis. It is likely that some cardiac amyloid deposits could be identified histologically in most patients with systemic amyloidosis. There is plainly a wide spectrum of cardiac involvement in systemic amyloidosis, ranging from small incidental deposits that have no clinical consequences, to very extensive deposits that cause restrictive cardiomyopathy and death within weeks. Cardiac biopsy merely gives a dichotomous result on presence or absence of amyloid in a tiny sample, and there are barriers to its broader use that are unlikely to be overcome, whereas we have demonstrated that CMR and LGE studies have the potential to be used widely and more routinely and can evaluate the evident continuum of interstitial amyloid load and its effect on cardiac muscle throughout the whole heart.

Regarding the generalizability of the results, this was a single centre, single scanner manufacturer study. The PSIR technique (invented by author PK) solves a major problem with the LGE technique in amyloid. Whilst the principles suggest it should be the same for other scanner manufacturers, we agree that implementations may differ and further work is indeed appropriate.

The issue was raised about other markers of prognosis. Progressive cardiac amyloid infiltration is associated with thickening of the myocardium, concentric remodeling and myocardial dysfunction. The longitudinal contraction is usually the component that is more affected leading to poor systolic performance with low stroke volume in spite of a relatively preserved ejection fraction. Cohen and colleagues therefore hypothesized that a novel measure of myocardial shortening, the myocardial contraction fraction (MCF – an indexless ratio like the ejection fraction), the ratio of the LV stroke volume to myocardial volume, could predict survival in our study population.[7] We performed the analyses. MCF was indeed a good predictor of mortality in univariate analysis in the overall population ($p<0.0001$, hazard ration, HR, 0.26, 95% confidence interval, 95%CI, 0.006-0.116) and both AL ($p<0.0001$, HR 0.009, 95%CI 0.001-0.063) and ATTR patients ($p<0.05$, HR 0.031, 95%CI 0.002-0.476). MCF was unequivocally superior to the ejection fraction, but further studies are needed to assess the possible incremental prognostic power over other functional markers. Nevertheless, we thank the authors for championing this index - we are impressed by its potential given how easy it is to measure, and recommend further study. We will incorporate it into our future research.

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