However, current recommendations do not take LV dimensions as a continuous variable into consideration. As previously described by Gaasch et al. (2), RV is influenced by LVEDV, and therefore, the use of an absolute value of RV is limited in defining severe MR. A new concept of indexing RV for LVEDV was proposed that in essence takes into account the interplay between RV and LV remodeling (LVEDV) and reflects the impact of the RV on the LV. In our study, patients with a RV/EDV ratio ≥20% more frequently underwent mitral valve (MV) inter-vention and when the MR was resolved, these patients had a better outcome compared with their counterparts (RV/EDV ratio <20%). This might suggest, in these patients, that the degree of MR contributed more to their underlying disease than the LVEDV. The concept that aortic stiffness may affect forward stroke volume and RV in patients with heart failure and significant secondary MR is of interest (3), and as previously shown, it may affect clinical outcomes (4). A previous study showed that in patients with heart failure, increased aortic stiffness was independently associated with the composite endpoint of all-cause death and heart failure hospitalization after correcting for LV ejection fraction, transmitral early wave peak velocity, LV stroke volume, systolic blood pressure, and heart rate (4). An increased aortic stiffness may affect the forward stroke volume; however, the calculation of the forward stroke volume, based on 2-dimensional measurement of the LVEDV and RV calculation, which is based on proximal isovelocity surface area (PISA) needs to be considered with caution because the method has important limitations (5). In secondary MR, the regurgitant orifice is usually elliptical or crescent shaped, and therefore, the quantification of the effective regurgitant orifice area based on the PISA method may lead to significant underestimation. In addition, patients with heart failure present with low-flow status, which may lead to reduced RV. Other methods to quantify RV have been proposed, but they also have limitations (5). Selection of patients with heart failure and severe secondary MR who may benefit from intervention remains challenging, and assessment of the severity of MR is only one part of the evaluation. The clinical condition of the patients, associated comorbidities, and optimization of heart failure therapy (including cardiac resynchronization therapy and coronary revascularization) need to be considered. Aortic stiffness is not assessed routinely, but as previously shown (4), it is an important factor to be addressed in the treatment of patients with heart failure.

Farnaz Namazi, MD
Victoria Delgado, MD, PhD
Jeroen J. Bax, MD, PhD*
*Department of Cardiology
Heart Lung Center
Leiden University Medical Center
Albinusdreef 2
2300 RC Leiden
the Netherlands
E-mail: j.j.bax@lumc.nl

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Assessing Cardiac Response to Patisiran by Changes in Extracellular Volume

Potential Issues

We have read with interest the paper by Fontana et al. (1) that reports a 6.2% decrease in extracellular volume (ECV) in 16 patients with variant amyloid transthyretin cardiomyopathy (vATTR-CM) after a 12-month treatment with patisiran administered with diflunisal in 12 patients. As pointed out by the investigators, changes in ECV were highly heterogeneous, with only 6 patients (38%) experiencing an absolute ECV reduction greater than the 0.03% arbitrary threshold and 3 (19%) showing an increase (1). This may explain why median ECV values at 12 months were 2% higher among treated patients (46% vs. 48%), whereas the reported 6.2% ECV reduction refers to the adjusted

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difference with the 16 patients with untreated ATTR, retrospectively matched, who experienced a 4% increase in median ECV (49% vs. 53%) (1). Control subjects were older (69 years of age vs. 62 years of age; p = 0.023), and 9 of them had wild-type ATTR (1). Moreover, no change in left ventricular wall thickness, mass, and systolic and diastolic function was observed in the treated cohort, neither in absolute values, nor in comparison with matched untreated patients (1). As acknowledged by the investigators, even the outstanding results of diphosphonate scintigraphy that suggested amyloid regression in as many as 15 of 16 treated patients might be confounded by the complex kinetics of bone tracers (1). Together with the small sample size, the preceding considerations advise for some caution before concluding that there was a "reduction in CMR derived extracellular volume with patisiran" as stated (1).

The title includes another point that is open to criticism, namely, that an ECV reduction "indicates cardiac amyloid regression" (1). ECV changes do not necessarily mirror amyloid burden changes, because ECV might be influenced by several other extracellular components (fibrosis, edema, microcirculation) and also by the relative amount of cellular volume (2), which, in this study, was assumed to be unchanged over 12 months. Furthermore, although there is some evidence that ECV expansion in ATTR-CM is driven only by amyloid deposition, as recapitulated by the investigators (1), there is also a histological study demonstrating that patients with cardiac amyloidosis have extensive myocardial fibrosis (3). Clarifying the relative burden of amyloid and fibrosis in the heart of patients with ATTR-CM would be important to understand the potential for recovery of cardiac structure and function in response to treatment. Histological studies, possibly also in transplanted hearts or autoptic specimens, are warranted to elucidate this point.

As another perspective for future research, we suggest that high-sensitivity troponin T or I (hs-TnT/I) be considered in addition to ECV and other variables reflecting the severity of cardiac involvement (from B-type natriuretic peptides and diphosphonate uptake) (1). hs-TnT and -I are cardiac-specific biomarkers with a low intraindividual variability (4), which is lower than ECV (11.5% at 3.0-T) (5). This means that smaller changes in hs-Tn values (down to a few nanograms per liter) are significant and may be sensitive marker of reduced cardiac damage in response to treatment (4).

Finally, 12 of the 16 treated patients also received diflunisal, so that it is impossible to ascertain the relative benefit of TTR stabilization versus TTR knockdown. We agree with the investigators that further larger studies are needed to study the relative effect of the 2 diverse TTR therapies, preferably with a randomized, placebo-controlled design.

Andrea Barison, MD, PhD
Alberto Aimo, MD*
Michele Emdin, MD, PhD
*Institute of Life Sciences
Scuola Superiore Sant'Anna
and Cardiology Division
Fondazione Toscana Gabriele Monasterio
Piazza Martiri della Libertà 33
56124 Pisa
Italy
E-mail: a.aimo@santannapisa.it or aimoalb@ftgm.it

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THE AUTHORS REPLY:

We thank Dr. Barison and colleagues for their interest in our study (1). The principle that amyloid deposits are in a dynamic equilibrium and that precursor protein reduction can result in amyloid regression is firmly established in amyloidosis (2). However, transthyretin (ATTR) amyloid regression is novel for 2 reasons: 1) tracking cardiac amyloid burden has only recently been possible (3); and 2) disease-modifying therapies that significantly reduce plasma TTR concentration have only recently become available. Our findings are important because, for the first time, therapy can be used to probe the biology of human myocardial amyloid regression. We agree