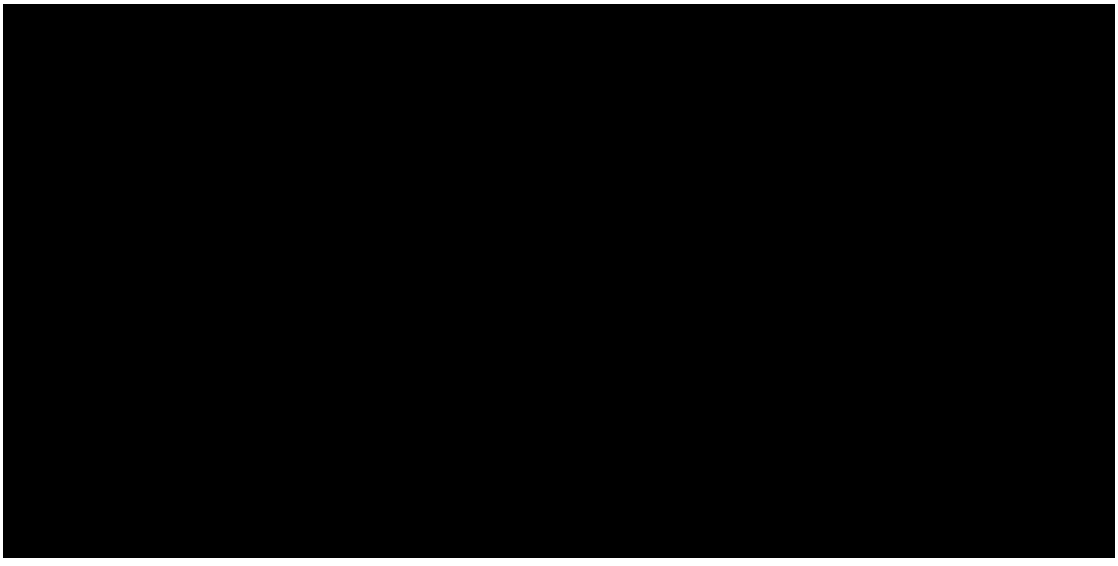

Patisiran in Patients with Transthyretin Cardiac Amyloidosis

TO THE EDITOR: The primary end point in the APOLLO-B trial conducted by Maurer et al. (Oct. 26 issue)[1] was the change from baseline in the distance covered on the 6-minute walk test at 12 months. The decline in the distance was lower in the patisiran group than in the placebo group (median difference, 14.69 m; 95% confidence interval [CI], 0.69 to 28.69; P=0.02). However, the minimal clinically important difference in the distance on 6-minute walk test for adults with pulmonary arterial hypertension is approximately 33 m.[2] The first secondary end point was the change in score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), on which scores range from 0 to 100, with higher scores indicating better health status. The KCCQ-OS score increased in the patisiran group and decreased in the placebo group (mean between-group difference in the change in score, 3.7 points; 95% CI, 0.2 to 7.2; P=0.04). This difference is again below the minimal clinically important difference, which is approximately a 5-point change in the KCCQ-OS score.[3] Significant benefits were not observed for the second and third secondary end points. Arthralgia and muscle spasms occurred more often among the patients in the patisiran group than among those in the placebo group (arthralgia in 8% vs. 4% and muscle spasms in 7% vs. 2%). The authors conclude that patisiran therapy resulted in preserved functional capacity, health status, and quality of life. In my opinion, the conclusions should be different.

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No potential conflict of interest relevant to this letter was reported.

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2. Moutchia J, McClelland RL, Al-Naamani N, et al. Minimal clinically important difference in the 6-minute-walk distance for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2023;207:1070-9.
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THE AUTHORS REPLY: What constitutes a meaningful change is determined by many factors, including the condition being studied and the study duration. Transthyretin cardiac amyloidosis is a progressive condition in which declines in functional capacity, quality of life, and cardiac function are not reversible with currently available therapy. Thus, patients do not regain their losses. The APOLLO-B trial was only 12 months in duration and showed clinical benefit with respect to functional capacity, health status, cardiac biomarkers,

and echocardiographic measures in participants assigned to receive patisiran as compared with those assigned to receive placebo. The relentless clinical decline associated with disease progression, coupled with the sustained clinical benefits of patisiran therapy that were shown in the open-label extension of the APOLLO-B trial, would be expected to yield progressively larger differences over time in clinical outcome measures between patients receiving patisiran and those receiving placebo.

Patisiran has been available since 2018 and has an acceptable safety profile. However, regulatory approval for patisiran has been granted only for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, which prevents its use in patients with transthyretin cardiac amyloidosis, unless they are enrolled in studies. However, the data from our trial give cause for hope that ongoing trials of RNA interference therapeutic agents, such as the HELIOS-B trial (ClinicalTrials.gov number, NCT04153149) will show benefits with respect to cardiovascular outcomes.

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