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BRIEF REPORT

Comorbidity Burden in Transthyretin Amyloidosis With Cardiomyopathy

Insights From the HELIOS-B Trial

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Patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM) present with multiple comorbidities. As previously reported in the HELIOS-B trial,[1] vutrisiran, a subcutaneously administered RNA interference therapeutic agent (25 mg), showed a significant reduction in morbidity and mortality in patients with ATTR-CM treated with vutrisiran compared with placebo. Using HELIOS-B data, we assessed how comorbidity burden, as assessed by the CCI (Charlson Comorbidity Index), influences morbidity and mortality in ATTR-CM and whether it modifies the treatment effect of vutrisiran.

What is the clinical question being addressed?
Vutrisiran reduced morbidity and mortality in patients with ATTR-CM compared with placebo. Do comorbidities affect the outcome of patients with ATTR-CM and impact the treatment effect of vutrisiran?

What is the main finding?
The clinical benefits and safety profile of vutrisiran were consistent regardless of the burden of coexisting conditions.

METHODS

All participants provided informed consent, and the study protocol was approved by the Institutional Review Boards or Ethics Committees at each center. The CCI incorporates 17 weighted medical conditions plus age, with higher scores indicating more severe comorbidity and higher mortality risk. Patients' demographics, outcomes (death from any cause and recurrent cardiovascular [CV] events), treatment effect, and adverse events were assessed in participants with low (CCI: 0-5) and high (CCI >5) comorbidity burden at enrolment, and we assessed whether comorbidity burden modified the treatment effect of vutrisiran. A dichotomized threshold of CCI >5 was used to identify patients with higher multimorbidity, beyond the baseline point attributed to heart failure.

Clinical outcomes according to the CCI categories were reported as the number of events and incidence rates per 100 person-years. Event rates across the CCI, as a continuous variable, were examined using Poisson regression with restricted cubic splines with 3 knots placed at the 10th, 50th, and 90th percentiles. The outcome analysis was stratified by tafamidis use. The models for treatment effect and adverse effects were adjusted for treatment assignment, ATTR

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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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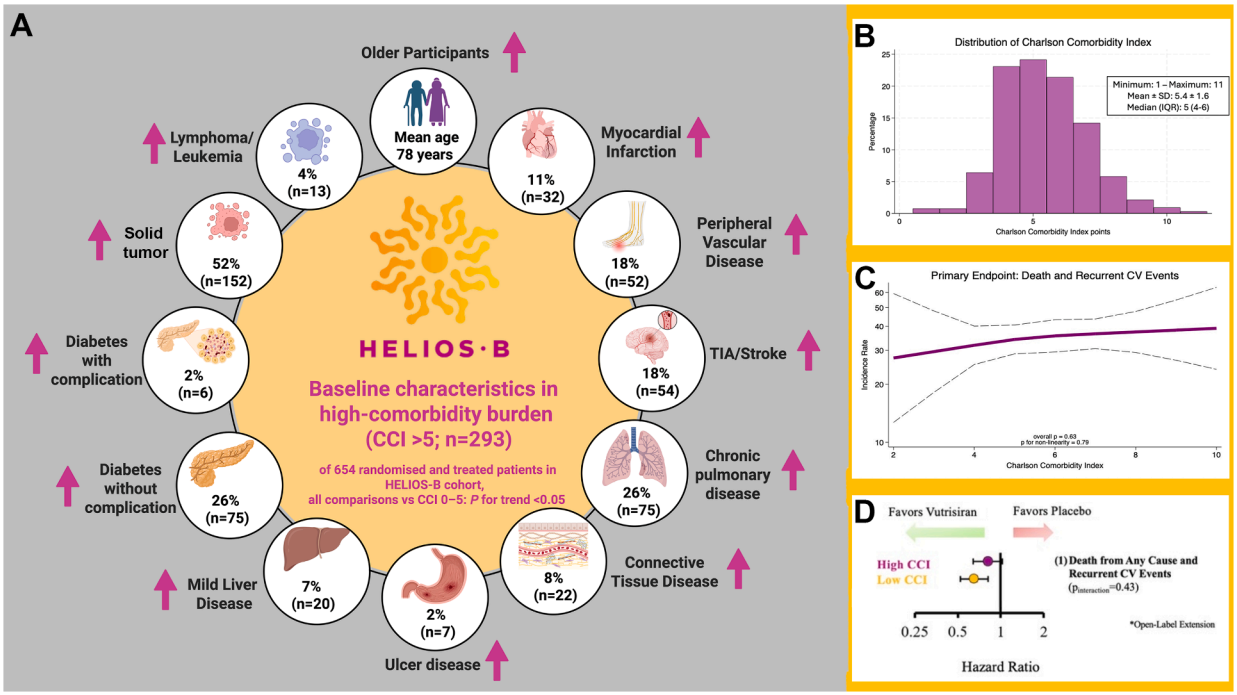
FIGURE 1 Comorbidity Burden, Outcomes, and Treatment Effect in HELIOS-B



(A) Baseline characteristics in high-comorbidity burden in the HELIOS-B cohort. (B) Histogram of distribution of CCI in HELIOS-B. (C) Primary endpoint of death and recurrent CV events across the continuous CCI. (D) Forest plot of treatment effect of vutrisiran vs placebo between low (CCI: 0-5) and high (CCI >5) comorbidity burden (CCI) for primary endpoint of death from any cause and recurrent CV events. CCI = Charlson Comorbidity Index; CV = cardiovascular; TIA = transient ischemic attack.

amyloidosis disease type (variant vs wild type), NYHA functional class (I or II vs III), and log-transformed baseline N-terminal pro-B-type natriuretic peptide level and were stratified by tafamidis use at baseline (yes vs no). For each CCI category, treatment effects of vutrisiran compared with placebo for the composite of death + total CV events were analyzed by a semi-parametric proportional rate model, with mortality serving as both a clinical outcome event as well as a censoring event. Subgroup-specific effect estimates were obtained using separate models for each CCI category. All efficacy analyses were assessed using an intention-to-treat approach; all safety analyses were assessed in participants who received at least 1 dose of study drug. All P values were 2-sided; a value of $P < 0.05$ was used to denote statistical significance. All statistical analyses were performed using STATA version 18.

RESULTS

Among 654 randomized and treated participants (75 ± 7 years of age; 8% women), the CCI at baseline ranged from 1 to 11 (see Figure 1B), with a mean CCI of 5.4 ± 1.6; 361 (55%) participants had a low (CCI: 0-5) and 293 (45%) a high comorbidity burden (CCI >5). Participants with high CCI were older (78 ± 5 vs 73 ± 7 years), more commonly had wild-type ATTR (93 vs 85%; $P < 0.001$), and had higher N-terminal pro-B-type natriuretic peptide (2,095 vs 1,844 ng/L; $P = 0.003$) than those with a low CCI (see Figure 1A). We observed a weak relationship between increasing CCI and the primary endpoint (high CCI vs low CCI; HR: 1.21 [95% CI: 0.92-1.59]; HR per unit CCI: 1.05 [95% CI: 0.96-1.16]). Vutrisiran improved the primary endpoint of all-cause death and recurrent CV events, irrespective of CCI category (see Figure 1C); the rate ratio for the comparison of vutrisiran and placebo for the primary outcome was 0.65 (Q1-Q3: 0.45-0.93) in low CCI (0-5), as compared with 0.80 (Q1-Q3: 0.56-1.18) in high CCI (>5) (see Figure 1D). The treatment effect of vutrisiran was consistent across the continuous spectrum of CCI for the primary endpoint ($P_{\text{interaction}} = 0.14$). There was no difference in adverse events between high and low comorbidity burden; however, adverse events occurred less

frequently with vutrisiran than with placebo regardless of comorbidity burden.

In this post hoc analysis of the HELIOS-B trial, we demonstrated that general non-ATTR-related comorbidities, as captured with the CCI, are highly prevalent in ATTR-CM. Patients with a higher comorbidity burden had a higher risk of death and CV events than those with a lower comorbidity burden. Importantly, however, there was no evidence of attenuation of the treatment effect of vutrisiran vs placebo across the range of comorbidity burden and between low and high comorbidity burden. Regardless of comorbidity burden, adverse events were less common with vutrisiran than with placebo.

DISCUSSION

Current published reports in ATTR-CM has largely focused on disease severity rather than overall patient complexity and multimorbidity. Comorbidity burden, measured by the CCI, showed only a weak association with adverse outcomes, suggesting that, unlike in other heart failure populations, where noncardiac comorbidities affect prognosis,[2] in ATTR-CM, comorbidity burden may not meaningfully stratify risk in this population. Although conventional comorbidities contribute to prognosis in ATTR-CM, their impact may be attenuated by the dominant pathophysiological burden of multiorgan amyloid deposition. The consistent treatment effect of vutrisiran across the full spectrum of comorbidity burden reinforces that amyloid remains the key driver of disease progression, irrespective of multimorbidity. Therefore, therapy should not be withheld based on multimorbidity alone, which is prevalent in the real-world ATTR-CM caseload,[3] reinforcing the distinct clinical profile of ATTR-CM compared with other heart failure phenotypes. Serious and cardiac-specific adverse events were common across comorbidity burden but lower with vutrisiran thanwith placebo, suggesting good tolerability and supporting the fact that neither age nor multimorbidity should preclude access to disease-modifying therapy.[4]

STUDY LIMITATIONS. These results should be interpreted in the context of multiple limitations. First, the CCI was designed for general medical populations and does not account for several clinically relevant comorbidities specific to ATTR-CM. Furthermore, the exclusion criteria of the HELIOS-B trial[1] favored a patient group with a lower baseline risk profile by excluding patients with symptomatic coronary artery disease, active malignancy, estimated glomerular filtration rate <30 mL/min/1.73 m^2, and NYHA functional class IV. In addition, because age is incorporated within the CCI, the independent effect of age and multimorbidity cannot be fully separated. Caution is therefore required when extrapolating these findings to more complex, higher-risk patients of advanced age, where treatment decisions are often most challenging. Second, the CCI was designed to predict 1-year mortality alone, not CV events or treatment response, and may lack sensitivity for amyloid-specific outcomes. Third, this is a post hoc analysis of the HELIOS-B trial, which was not powered to detect treatment-effect heterogeneity by comorbidity and age. Therefore, the findings require confirmation in a pooled analysis across multiple ATTR-CM trials.

CONCLUSIONS

In this analysis, a higher CCI was associated with a trend toward worse clinical outcomes; the treatment effect of vutrisiran appeared consistent across comorbidity burden. These data suggest that comorbidity burden and age alone may not preclude benefit from novel ATTR-targeted therapies, but confirmation in further studies is warranted.

DATA AVAILABILITY The data that support the findings of this study are available from the study sponsor upon reasonable request.

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