



Transthyretin Silencing Therapies and the Cardiology Clinic: Selection, Cost and the Diagnostic Bottleneck Upstream

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Abstract

HELIOS-B, a 654-patient randomised trial of the RNA-silencing agent vutrisiran in transthyretin amyloid cardiomyopathy, found a 28% reduction in the composite risk of death and recurrent cardiovascular events (hazard ratio 0.72) and a 36% reduction in all-cause mortality (hazard ratio 0.64), with a low and similar rate of treatment discontinuation for adverse events in both arms. This is a genuinely strong trial result for a disease that previously had little to offer beyond symptomatic management. Two practical problems sit upstream and downstream of that result, however. Upstream, a real-world analysis found a median delay of 494 days between a heart failure diagnosis and the correct diagnosis of transthyretin amyloid cardiomyopathy -- longer still, 840 days, when measured from a patient's first loop-diuretic prescription -- with 64% of patients waiting at least six months, a pattern attributed to diagnostic anchoring on more common heart failure causes; annual diagnoses have quadrupled since 2016 without that delay shortening. Downstream, the treatment itself carries a list price of approximately \$450,000 per year, against an independent cost-effectiveness assessment that would place a fair price for this drug class between \$13,600 and \$39,000 per year. This review sets out the trial evidence for gene-silencing therapy, the diagnostic bottleneck that determines how many patients ever reach that therapy in time to benefit, and the pricing gap that determines how many health systems can afford to give it to them.

Keywords: Transthyretin amyloid cardiomyopathy; Vutrisiran; RNA interference; Diagnostic delay; Drug pricing

Introduction

Transthyretin amyloid cardiomyopathy, once a disease with little to offer beyond diuretics and symptomatic heart failure management, now has a genuinely effective, mechanistically targeted treatment option: RNA-interference therapy that silences hepatic production of the transthyretin protein at its source, rather than merely stabilising the misfolded protein once it is already circulating [1]. HELIOS-B, a large randomised trial of the gene-silencing agent vutrisiran, reported results substantial enough to change how this disease

is discussed in the cardiology clinic [1].

This review sets out that trial result, and two practical problems that determine how much difference it actually makes: a diagnostic bottleneck upstream of treatment that keeps many patients undiagnosed for years, and a price attached to the treatment itself that sits far above what independent cost-effectiveness analysis considers fair value.

Material and Methods

This is a narrative review of the HELIOS-B primary trial publication, a real-world data analysis of diagnostic delay in transthyretin amyloid cardiomyopathy, and an independent cost-effectiveness evidence report, identified through the sources cited above and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, hazard ratios, time intervals, and price figures reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Results

HELIOS-B demonstrated a substantial mortality and morbidity benefit

HELIOS-B randomised 654 patients with transthyretin amyloid cardiomyopathy -- 326 to vutrisiran, 328 to placebo -- to subcutaneous dosing every three months for up to 36 months [1]. The primary composite endpoint, all-cause mortality plus recurrent cardiovascular events assessed at month 33, favoured vutrisiran in the overall population (hazard ratio 0.72, 95% CI 0.56-0.93, $p=0.01$) and, separately, in the subgroup of patients not also receiving background tafamidis (hazard ratio 0.67, 95% CI 0.49-0.93, $p=0.016$) [1]. All-cause mortality alone, assessed at 42 months, showed an even larger relative reduction: hazard ratio 0.64 (95% CI 0.46-0.90, $p=0.01$) overall and 0.65 (95% CI 0.44-0.97, $p=0.045$) in the monotherapy subgroup [1]. Figure 1 sets all four of these hazard ratios out together. Discontinuation for adverse events was low in both arms -- 3.1% with vutrisiran versus 4.0% with placebo -- and the trial also reported significant improvement on functional and quality-of-life measures, including six-minute walk distance, the Kansas City Cardiomyopathy Questionnaire, and NYHA functional class, all favouring vutrisiran [1].

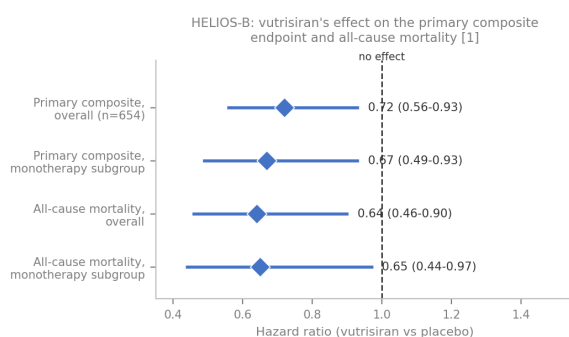


Figure 1: HELIOS-B hazard ratios for the primary composite endpoint and all-cause mortality, overall population and monotherapy subgroup [1].

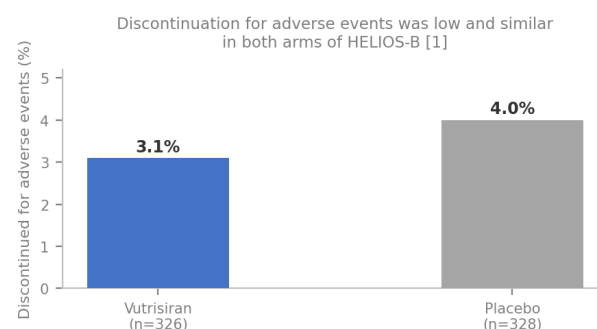


Figure 2: Rate of treatment discontinuation for adverse events, vutrisiran versus placebo, HELIOS-B [1].

A diagnostic bottleneck keeps many patients from ever reaching treatment promptly

A strong trial result changes little for a patient who is never correctly diagnosed, or who is diagnosed only after years of misattributed symptoms. A real-world data analysis of ATTR-CM diagnostic pathways found a median delay of 494 days (interquartile range 63-1340 days) between a heart failure diagnosis and the correct diagnosis of transthyretin amyloid cardiomyopathy, with 64% of patients waiting at least six months [2]. The delay looked different depending on which clinical milestone it was measured from: 276 days from first heart-failure hospitalisation, but 840 days from a patient's first loop-diuretic prescription, the earliest and least specific signal of the three [2]. Figure 2 traces annual diagnosis counts in parallel with this delay: diagnoses rose from 415 in 2016 to 1,930 in 2021, a near-fivefold increase, but the diagnostic interval itself did not shorten over the same period, suggesting that expanded awareness increased detection without accelerating recognition in any individual patient's diagnostic pathway [2]. Figure 3 sets the three delay measurements out side by side. The authors attributed the bottleneck to diagnostic anchoring: clinicians attributing heart failure symptoms to more common causes rather than pursuing amyloid-specific testing such as bone scintigraphy, and women experienced longer delays than men after adjustment for other factors (adjusted odds ratio 1.28) [2]. Figure 4 illustrates the scale of that disparity.

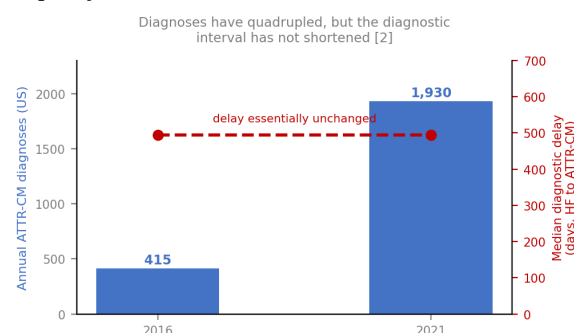


Figure 3: Annual ATTR-CM diagnoses in the United States, 2016 versus 2021, against a diagnostic delay that did not shorten over the same period [2].

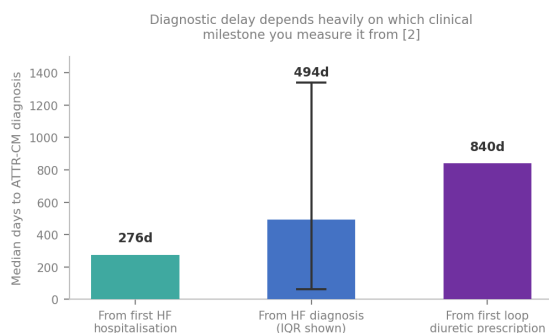


Figure 4: Median diagnostic delay to ATTR-CM diagnosis, measured from three different clinical starting points [2].

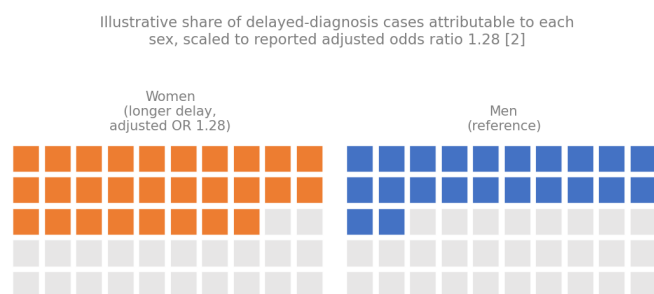


Figure 5: Illustrative share of delayed-diagnosis cases attributable to each sex, scaled to the reported adjusted odds ratio of 1.28 [2].

The treatment's price sits far above its own independent cost-effectiveness range

Even a correctly and promptly diagnosed patient faces a second practical barrier: cost. An independent evidence report from the Institute for Clinical and Economic Review found that transthyretin-stabilising and gene-silencing therapies for this disease would meet common cost-effectiveness thresholds if priced between \$13,600 and \$39,000 per year [3]. Vutrisiran's actual list price is approximately \$450,000 per year -- roughly 11 to 33 times above that range -- and the reviewing body's own chief medical officer stated publicly that current pricing in this drug class is much too high relative to the benefit it delivers [3,4]. Figure 6 plots the list price directly against the cost-effective range as a shaded reference band.

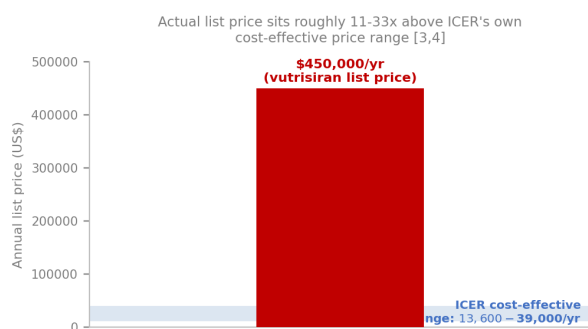


Figure 6: Vutrisiran's annual list price plotted against the ICER cost-effective price range for this drug class [3,4].

Discussion

Three separate findings need to be held together rather than read in isolation. The trial evidence for gene-silencing therapy in transthyretin amyloid cardiomyopathy is genuinely strong: a 28% reduction in a clinically meaningful composite endpoint and a 36% reduction in all-cause mortality, with low and balanced discontinuation for adverse events, is not a marginal result [1]. But a median 494-day delay between heart failure diagnosis and correct ATTR-CM diagnosis means a meaningful share of the population who could benefit from this therapy will not be identified as candidates for it within a clinically useful window, and the fact that rising diagnosis counts have not been accompanied by a shortening diagnostic interval suggests this is a systematic pattern-recognition problem, not simply a volume problem that more testing capacity alone will resolve [2]. And even a patient who is identified promptly faces a price that independent cost-effectiveness analysis places an order of magnitude above fair value, which will constrain which health systems and which patients within those systems can actually access the drug regardless of how quickly they are diagnosed [3,4].

None of these three problems cancels the others out, and none is really a counterargument to the others: strong trial efficacy does not shorten the diagnostic pathway, a shortened diagnostic pathway would not by itself make the drug affordable, and a lower price would not help patients who are never correctly diagnosed in time to be offered it. The most defensible reading is that gene-silencing therapy has solved the scientific half of this problem -- efficacy in patients who reach it -- while the diagnostic and pricing halves remain open, parallel problems that the specialty and the health systems it operates within will need to address separately from the drug development itself [1-4].

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws on sources with different designs: one randomised trial, one real-world observational analysis of diagnostic pathways, and one independent health-economic evidence report [1-3]. The HELIOS-B trial's functional and quality-of-life secondary endpoints were reported qualitatively as significant improvements without specific numeric deltas being extracted for this review, and are described but not charted here for that reason [1]. The ICER cost-effective price range applies to a class of ATTR-CM therapies rather than to vutrisiran specifically in every source consulted, and list price is not the same as the net price any individual payer or health system actually negotiates, which this review does not have visibility into [3,4]. Finally, this review does not address the separate and clinically important question of how a clinician should choose between gene-silencing therapy and transthyretin-stabilising agents such as tafamidis for an individual patient, including combination use, which was outside its scope.

Conclusion

Gene-silencing therapy for transthyretin amyloid cardiomyopathy has produced a substantial, well-powered trial benefit on both mortality and a broader composite outcome. That benefit's real-world reach, however, is bounded on one side by a diagnostic delay measured in years rather than months, and on the other by a list price that independent analysis places far above fair value. Reconciling the promise of this drug class with its actual impact on patients will depend as much on shortening the diagnostic pathway and closing the pricing gap as on any further refinement of the therapy itself.

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