Post Hoc Analysis of Diastolic Dysfunction in the HELIOS-B Study of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

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HELIOS-B

Scan to View

Conclusions

- Patients with a worse diastolic dysfunction grade (DDG) at baseline showed worse outcomes across multiple endpoints during the DB period; the worsening trend was statistically significant in patients receiving placebo
- Vutrisiran reduced the risk of the primary endpoint of ACM and CV events and improved secondary and exploratory endpoints in the overall and monotherapy populations irrespective of baseline DDG; substantial improvements vs placebo were seen in patients with baseline DDG III
- The findings further support the benefits of vutrisiran for patients irrespective of diastolic dysfunction and for vutrisiran as a first-line therapy in ATTR-CM

Key takeaway

Vutrisiran reduced the risk of ACM and recurrent CV events and improved HELIOS-B endpoints irrespective of patients' baseline diastolic dysfunction grade

Introduction

ATTR with Cardiomyopathy

- ATTR-CM is a progressive disease caused by accumulation of misfolded wild-type or variant TTR protein as amyloid fibrils in the heart[1,2]
- ATTR-CM manifests as progressive heart failure, arrhythmias, declines in functional status/QOL, hospitalizations, and reduced survival[1,3]
  - Diastolic dysfunction is a prominent feature of worsening heart failure in ATTR-CM[1]
  - Echocardiographic measures of LV systolic and diastolic function are prognostic of mortality[4]

HELIOS-B Study

- In HELIOS-B, the RNAi therapeutic vutrisiran significantly reduced risk of ACM and recurrent CV events in patients with ATTR-CM compared with placebo, and met all secondary endpoints in the overall population and vutrisiran monotherapy (not receiving tafamidis at baseline) population[5]

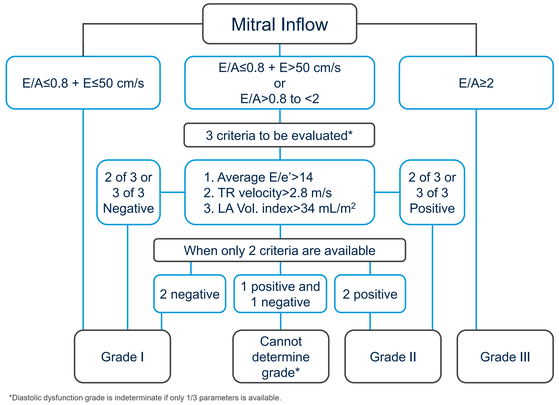
Objective

- This post hoc analysis of the HELIOS-B population aimed to explore the association between diastolic dysfunction at baseline with outcomes, and the effect of vutrisiran in patients with different diastolic dysfunction severities

Methods

- Certified sonographers at each study site performed serial echocardiograms at baseline and months 12, 18, 24, and 30[5]
- DDG at baseline was evaluated using the American Society of Echocardiography and European Association of Cardiovascular Imaging 2016 recommendations[6]
  - DDG I: Mild diastolic dysfunction, impaired relaxation with preserved filling pressures
  - DDG II: Moderate diastolic dysfunction, abnormal filling pattern with elevated filling pressures
  - DDG III: Severe diastolic dysfunction, restrictive filling pattern with significantly elevated filling pressures

Figure 1. Diastolic Dysfunction Grade Recommendations: American Society of Echocardiography and European Association of Cardiovascular Imaging 2016[6]



*Diastolic dysfunction grade is indeterminate if only 1/3 parameters is available.

Results

Table 1. Baseline Demographics and Disease Characteristics Were Generally Worse in Patients with DDG Grade III

- A larger proportion of vutrisiran patients had DDG III at baseline compared to placebo
- Baseline characteristics were generally balanced between the vutrisiran and placebo groups at baseline. Of note, patients in the vutrisiran DDG III group had higher baseline NT-proBNP
- There were a substantial number of patients with missing (placebo n=157; vutrisiran n=144) or indeterminate (placebo n=13; vutrisiran n=11) DDG

Overall Population	DDG I/II[a]		DDG III	
	Placebo (n=95)	Vutrisiran (n=90)	Placebo (n=76)	Vutrisiran (n=92)
Age, years, mean (SD)	76.0 (6.7)	75.3 (8.5)	74.3 (7.1)	74.6 (7.2)
Male sex, n (%)	86 (90.5)	80 (88.9)	71 (93.4)	84 (91.3)
wtATTR, n (%)	82 (86.3)	77 (85.6)	64 (84.2)	77 (83.7)
Baseline tafamidis use, n (%)	40 (42.1)	38 (42.2)	32 (42.1)	41 (44.6)
Time since diagnosis, years, median (range)	1.0 (0.0, 9.1)	0.8 (0.0, 5.7)	0.6 (0.0, 6.0)	0.7 (0.0, 11.1)
NYHA class, n (%) I II III	15 (15.8) 74 (77.9) 6 (6.3)	16 (17.8) 67 (74.4) 7 (7.8)	11 (14.5) 59 (77.6) 6 (7.9)	15 (16.3) 71 (77.2) 6 (6.5)
6-MWT, m, mean (SD)	391.2 (94.3)	388.6 (102.4)	392.6 (99.4)	386.1 (99.4)
KCCQ-OS, pts, mean (SD)	75.4 (19.8)	75.0 (17.7)	75.0 (18.6)	72.7 (22.1)
Troponin I, ng/L, median (IQR)	57.3 (36.6, 78.5)	58.2 (33.6, 86.5)	71.4 (41.7, 123.8)	70.9 (42.7, 102.6)
NT-proBNP, ng/L, median (IQR)	1124.0 (695.0, 1865.0)	1221.0 (661.0, 2127.0)	1568.0 (1257.0, 3084.5)	1813.0 (1161.5, 2915.0)

[a]Subgroup includes patients with indeterminate grades.

Table 2. Strong Treatment Effects at Month 30 in Patients across Baseline DDG Subgroups in the Overall Population Support Vutrisiran as an Effective Treatment Irrespective of Diastolic Dysfunction

Overall Population Month 30	DDG I/II[a]		DDG III	
	Placebo (n=95)	Vutrisiran (n=90)	Placebo (n=76)	Vutrisiran (n=92)
ACM HR (95% CI) Vutrisiran/Placebo[b]	0.67 (0.28, 1.57)		0.39 (0.20, 0.75)	
6-MWT, LS mean difference (95% CI)	11.5 (–11.0, 34.0)		31.8 (3.9, 59.7)	
KCCQ-OS, LS mean difference (95% CI)	6.0 (0.0, 11.9)		7.5 (0.4, 14.6)	
NT-proBNP, ng/L, adjusted geometric mean fold-change ratio (95% CI)	0.68 (0.55, 0.82)		0.70 (0.56, 0.88)	
Troponin I, ng/L, adjusted geometric mean fold-change ratio (95% CI)	0.81 (0.69, 0.96)		0.64 (0.53, 0.77)	
NYHA class, % stable or improved	72.8	73.1	55.6	70.8

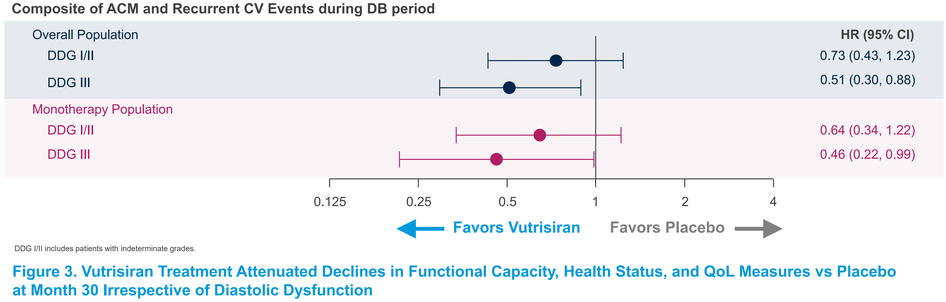
[a]Subgroup includes patients with indeterminate grades. [b]During the DB and 6 months of OLE, through 42 months

Table 3. Strong Treatment Effects at Month 30 across Baseline DDG Subgroups in the Monotherapy Population Support Vutrisiran as an Effective Treatment Irrespective of Diastolic Dysfunction

Monotherapy Population Month 30	DDG I/II[a]		DDG III	
	Placebo (n=55)	Vutrisiran (n=52)	Placebo (n=44)	Vutrisiran (n=51)
ACM HR (95% CI) Vutrisiran/Placebo[b]	0.68 (0.24, 1.92)		0.39 (0.17, 0.92)	
6-MWT, LS mean difference (95% CI)	20.3 (–11.9, 52.5)		50.4 (10.1, 90.7)	
KCCQ-OS, LS mean difference (95% CI)	10.6 (1.9, 19.3)		9.2 (–1.5, 19.9)	
NT-proBNP, ng/L, adjusted geometric mean fold-change ratio (95% CI)	0.48 (0.35, 0.65)		0.56 (0.37, 0.83)	
Troponin I, ng/L, adjusted geometric mean fold-change ratio (95% CI)	0.58 (0.45, 0.74)		0.51 (0.38, 0.69)	
NYHA class, % stable or improved	71.1	75.8	53.2	70.8

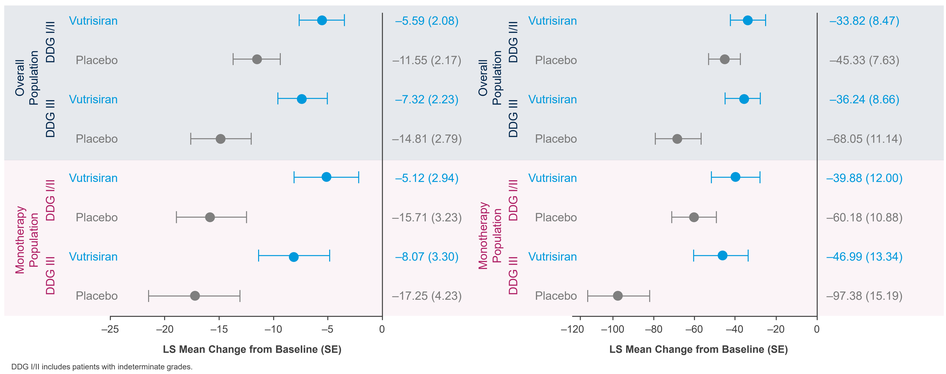
[a]Subgroup includes patients with indeterminate grades. [b]During the DB and 6 months of OLE, through 42 months

Figure 2. Vutrisiran Reduced the Risk of the Primary Composite Endpoint of ACM and Recurrent CV Events in Both Baseline DDG Subgroups in the Overall and Monotherapy Populations



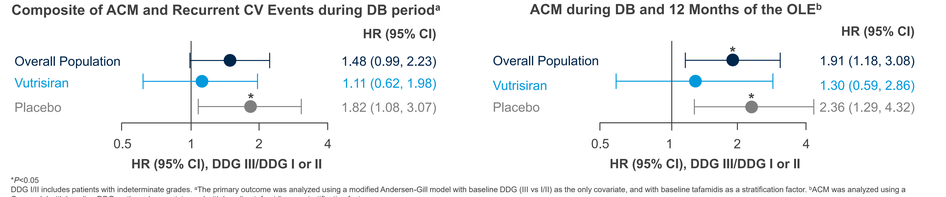
DDG I/II includes patients with indeterminate grades.

Figure 3. Vutrisiran Treatment Attenuated Declines in Functional Capacity, Health Status, and QoL Measures vs Placebo at Month 30 Irrespective of Diastolic Dysfunction



DDG I/II includes patients with indeterminate grades.

Figure 4. Vutrisiran Treatment Mitigated the Risk Associated with Having Baseline DDG III in the Composite Endpoint of ACM and CV Events and the Risk of ACM through the DB Period and Month 12 of the OLE



*$P<0.05$
DDG I/II includes patients with indeterminate grades. [a]The primary outcome was analyzed using a modified Andersen-Gill model with baseline DDG (III vs I/II) as the only covariate, and with baseline tafamidis as a stratification factor. [b]ACM was analyzed using a Cox model with baseline DDG as the only covariate, and with baseline tafamidis as a stratification factor.

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Abbreviations: 6-MWT, 6-minute walk test; ACM, all-cause mortality; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DB, double-blind; DDG, diastolic dysfunction grade; E, diastolic transmitral flow velocity; E/A, early to late diastolic transmitral flow; E/e', early diastolic mitral annular tissue velocity; HCP, healthcare professional; HR, hazard ratio; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LA, left atrial; LS, least squares; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; ODI, oral diuretic intensification; OLE, open-label extension; QOL, quality of life; RNAi, RNA interference; SD, standard deviation; SE, standard error; TR, tricuspid regurgitation.

If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.