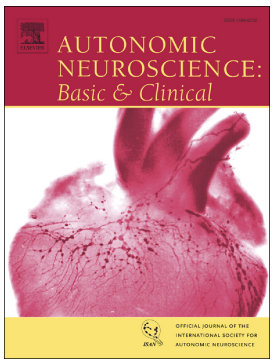

Blood pressure and orthostatic hypotension as measures of autonomic dysfunction in patients from the transthyretin amyloidosis outcomes survey (THAOS)

Alejandra González-Duarte, Fabio Barroso, Rajiv Mundayat, Bryan Shapiro

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BLOOD PRESSURE AND ORTHOSTATIC HYPOTENSION AS MEASURES OF AUTONOMIC DYSFUNCTION IN PATIENTS FROM THE TRANSTHYRETIN AMYLOIDOSIS OUTCOMES SURVEY (THAOS)

Alejandra González-Duarte, MD,[1] Fabio Barroso, MD,[2] Rajiv Mundayat, MS,[3] and Bryan Shapiro, MB ChB, BSc[3]

[1] Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[2] Institute for Neurological Research Raúl Carrea, FLENI, Buenos Aires, Argentina
[3] Pfizer Inc, New York, New York, USA

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Correspondence to: Alejandra González-Duarte, MD; Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Av. Vasco de Quiroga #15, Belisario Domínguez Sección XVI, Tlalpan, Mexico City, DIF, CP14080, Mexico; e-mail: gonzalezduarte@aol.com

Running title: Orthostatic Hypotension in THAOS

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BLOOD PRESSURE AND ORTHOSTATIC HYPOTENSION AS MEASURES OF AUTONOMIC DYSFUNCTION IN PATIENTS FROM THE TRANSTHYRETIN AMYLOIDOSIS OUTCOMES SURVEY (THAOS)

ABSTRACT

Introduction: Autonomic dysfunction, an early symptom of transthyretin amyloidosis (ATTR amyloidosis), requires investigations not readily available in many clinics. Although monitoring of orthostatic hypotension (OH) will not be a substitute for more specialized tests, it can add important information about initiation of dysautonomia. The aim of this study was to investigate whether simple blood pressure (BP) monitoring may be a useful tool for evaluation of disease progression and an early sign of autonomic dysfunction.

Methods: BP and OH data were from subjects enrolled in the Transthyretin Amyloidosis Outcomes Survey (THAOS). Characteristics associated with changes in BP and orthostatic difference were identified by regression analyses.

Results: OH tended to be present relatively early in the course of disease and was more common at enrollment (11.7%) than either diarrhea (2.4%) or unintentional weight loss (3.1%). In subjects with OH at enrollment, progressive increase in systolic and diastolic orthostatic difference was observed. OH was also associated with significantly worse quality of life.

Discussion: BP variability is a useful tool for assessing disease onset and severity in ATTR amyloidosis, particularly in patients with OH.

Trial Registration: ClinicalTrials.gov: NCT00628745.

Key words: amyloidosis; autonomic neuropathy; blood pressure; orthostatic hypotension; registry; transthyretin amyloidosis

Highlights (maximum 85 characters including spaces)

- Orthostatic hypotension (OH) is an early symptom in ATTR amyloidosis
- Significantly worse quality of life was observed in patients with OH at enrollment
- Progressive increase in orthostatic differences was observed in patients with OH
- Changes in blood pressure can be a useful measure in ATTR amyloidosis

INTRODUCTION

Transthyretin amyloidosis (ATTR amyloidosis) is a life-threatening disorder caused by the deposition of amyloid fibrils composed of misfolded monomers of the transport protein transthyretin (TTR).[1,2] Extracellular deposits of amyloid transthyretin fibrils give rise to hereditary ATTR (ATTRm) amyloidosis when resulting from mutations in the *TTR* gene, and wild-type ATTR (ATTRwt) amyloidosis when non-mutated protein is deposited.[3] These amyloid deposits progressively interfere with normal cell and organ functions and give rise to the variety of symptoms associated with ATTR amyloidosis.[1,2]

ATTR amyloidosis is often underdiagnosed, or in many cases the diagnosis is delayed for years relative to the symptom onset.[4,5] The clinical presentation of the disease is heterogeneous with multi-organ involvement, and individual patients tend to exhibit symptoms of progressive neuropathy or restrictive cardiomyopathy. [5] The major causes of morbidity and mortality in patients with ATTR amyloidosis are cardiomyopathy and autonomic neuropathy, which can lead to death within approximately 3–5 or 10 years of disease onset, respectively.[3].[4,6] [7] Symptoms of autonomic neuropathy, such as gastrointestinal problems, loss of bladder control, or sexual impotence in men, often occur in the early stages of ATTR amyloidosis and tend to precede motor impairment.[8] [9] Autonomic dysfunction requires investigations that may not be readily available in many clinical centers, but blood pressure (BP) monitoring is available in most settings, and observable changes in BP could be predictive of the need for more complex autonomic dysfunction testing.

One measure associated with autonomic dysfunction that can easily be detected from BP measurements is orthostatic hypotension (OH).[10] The clinical signs and symptoms of OH can include light-headedness, dizziness, blurred vision,

confusion, or fainting after standing up.[2,10] OH has been commonly reported as a symptom of ATTR amyloidosis.[11-13] Monitoring of OH may be a useful measure to detect early disease or to monitor disease progression.

The Transthyretin Amyloidosis Outcomes Survey (THAOS), established in 2007, is the largest ongoing observational and noninterventional registry of patients with ATTR amyloidosis.[5,14] THAOS collects multinational longitudinal data on the natural history of the disease from a large and diverse patient population, and helps to inform the characterization of ATTR amyloidosis and improve diagnosis and patient management.[5,14]

The aim of this study was to identify clinically meaningful variations in subsequent BP measurements that may be indicative of the symptoms of disease onset or progression. Using data from THAOS, we assessed the associations between the presence or absence of OH at enrollment, together with changes in BP and orthostatic difference over time, and clinical characteristics and disease progression.

METHODS

Data Collection. THAOS is a multinational longitudinal observational registry (ClinicalTrials.gov: NCT00628745), in which symptomatic subjects with ATTR amyloidosis, together with asymptomatic subjects with a confirmed *TTR* mutation, are eligible to be enrolled.[14] All participating study sites were approved by their local ethical or institutional review board prior to subject enrollment. Written informed consent was signed by all eligible subjects. Subjects' data were submitted electronically and remained confidential according to the country-specific regulations and guidelines. The study was carried out in accordance with the Declaration of Helsinki.

Demographic and clinical characteristics, *TTR* genotype, family history, and medical history were recorded at enrollment. Thereafter, subjects' neurological, cardiac, gastrointestinal, ophthalmic, and renal functions were regularly assessed. The design and methodology of THAOS have previously been described in detail.[14]

Study Population. All subjects in THAOS, including all subjects with ATTRwt and all symptomatic and asymptomatic subjects with ATTRm, were included in the analysis (analysis cut-off date: January 30, 2017). In addition, those subjects with OH recorded at enrollment were assessed separately and were divided into those with OH present and those with OH absent at enrollment.

End Points and Measures. OH is commonly defined as a drop of 20 mm Hg or more in systolic BP (SBP) or 10 mm Hg or more in diastolic BP (DBP) when standing up after sitting or lying down (supine).[13,15,16] In this analysis, SBP and DBP, both sitting/supine and after 3 minutes of standing, and orthostatic difference were

assessed at enrollment, with results each year up to 3 years after enrollment included in the analysis.

Systolic and diastolic orthostatic differences were analyzed in all subjects with recorded BP measurements. Systolic orthostatic difference was calculated as the mean of the differences between standing and sitting SBP (SBP after 3 minutes of standing minus sitting SBP) for each subject. Diastolic orthostatic difference was calculated as the mean of the differences between standing and sitting DBP (DBP after 3 minutes of standing minus sitting DBP) for each subject.

Quality of life (QoL) was quantified using Norfolk Quality of Life Questionnaire-Diabetic Neuropathy Total Quality of Life (TQoL) score (range –4 to 136, with higher scores indicating poorer QoL).[17] In addition to the total score, the items of this self-administered questionnaire were grouped into 5 categories: physical functioning (large fiber score), small fiber, activities of daily living, symptoms, and autonomic scores, with higher scores indicating worse QoL. EuroQoL Five Dimensions (EQ-5D) is a standardized measure of health and was also used to assess QoL. EQ-5D includes a descriptive EQ-5D Index (range 0–1, with 1 indicating full health) and a visual analog scale (EQ-5D Health State; VAS; full health equals 100), with higher scores indicating better health status. Data on diarrhea, unintentional weight loss, and modified Polyneuropathy Disability (mPND) score were also included in the analysis. The mPND score evaluates walking capacity according to the following criteria: 0 – symptomatic, but no lower limb sensory/motor deficit; I – sensory disturbances in feet, but able to walk without difficulty; II – some difficulties walking, but can walk without aid; IIIa – able to walk with 1 cane or crutch; IIIb – able to walk with 2 canes or crutches; IV – confined to wheelchair or bedridden.

Statistical Analyses. Multiple regression analyses were carried out to identify potential predictors of sitting and standing SBP and DBP at enrollment. Age at enrollment, gender, genotype, symptomatic or asymptomatic, mPND score, presence or absence of diarrhea, and presence or absence of unintentional weight loss at enrollment were included in the regression model as independent variables. Multiple regression analyses were also carried out to identify potential predictors of change in sitting and standing BP and orthostatic difference from enrollment to Year 3. BP at enrollment, age at enrollment, gender, genotype, symptomatic or asymptomatic, mPND score at Year 3, presence or absence of diarrhea at Year 3, presence or absence of unintentional weight loss at Year 3, TQoL at Year 3, and EQ-5D Index score at Year 3 were included in the regression model as independent variables. In addition, BP at enrollment and orthostatic difference at enrollment were included in the analysis of change in sitting and standing BP and orthostatic difference at Year 3, respectively. Age, BP, orthostatic difference, TQoL, and EQ-5D Index score were treated as continuous variables, whereas gender (male or female), *TTR* genotype (mutated or wild-type TTR), symptomatic or asymptomatic, mPND score, diarrhea (presence or absence), and unintentional weight loss (presence or absence) were categorical variables.

RESULTS

Demographic and Clinical Characteristics. A total of 3,231 subjects (1,834 men [56.8%] and 1,397 women [43.2%]) were included in the analysis, 1,896 (58.7%) of whom were symptomatic (subjects with definite symptoms linked to ATTR amyloidosis). The majority of subjects had ATTRm (2,850 [88.2%]), and the rest had ATTRwt (381 [11.8%]). Mean (SD) age at enrollment was 50.2 (18.1) years, with the mean age of men being 8.7 years older than that of women. Mean (SD) age at symptom onset was 49.9 (17.6) years, and subjects had a mean duration of symptoms of 5.4 (5.5) years at enrollment.

Comparison of Subjects With or Without OH at Enrollment. Of those subjects with the presence or absence of OH recorded at baseline (*n* = 2,083), 243 (11.7%) presented with OH and 1,840 (88.3%) without OH. Subjects with OH at enrollment were older, more likely to be male, and symptomatic compared with those without OH (Table 1).

Table 1. Demographic and baseline characteristics, by OH status at enrollment.*

Demographic and baseline characteristics	OH at enrollment	
	Present	Absent
	N = 243	*N* = 1,840
Age at enrollment		
Mean (SD), years	49.9 (16.4)	44.1 (16.0)
Median (10th–90th percentile), years	49.5 (29.2–71.7)	40.7 (25.1–68.7)
Gender		
Male, n (%)	141 (58.0)	893 (48.5)
Female, n (%)	102 (42.0)	947 (51.5)
ATTR amyloidosis		
ATTRm, n (%)	240 (98.8)	1,792 (97.4)
ATTRwt, n (%)	3 (1.2)	48 (2.6)
Symptomatic at enrollment, n (%)	219 (90.1)	1,268 (68.9)
Diarrhea at enrollment, n (%)	14 (5.8)	36 (2.0)
Unintentional weight loss at enrollment, n (%)	14 (5.8)	50 (2.7)

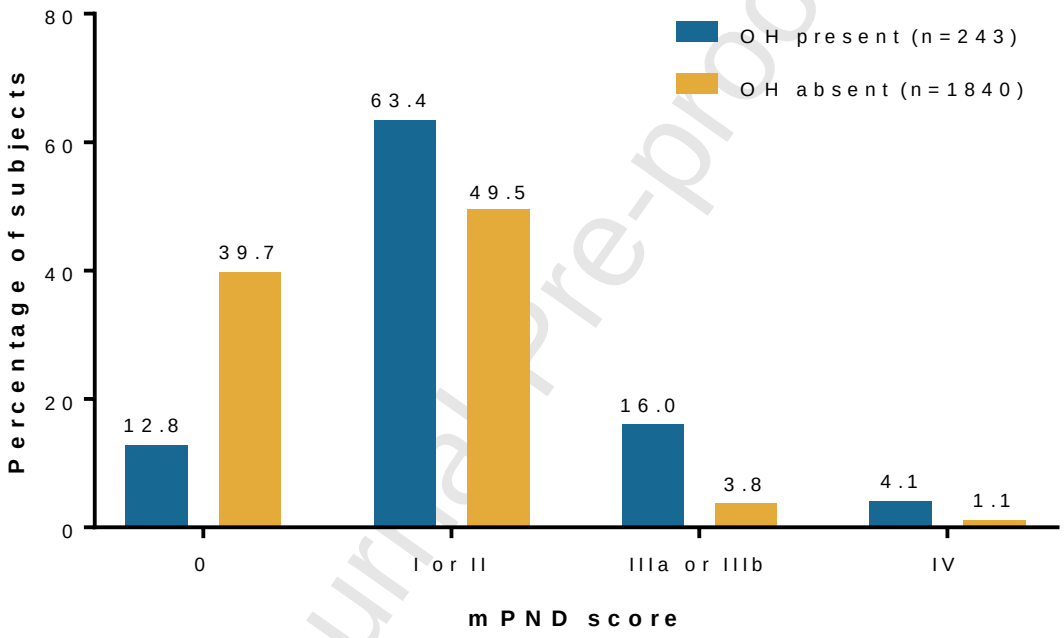
ATTRm, hereditary ATTR; ATTRwt, wild-type ATTR; OH, orthostatic hypotension.

**Including 2,083 subjects with OH recorded at enrollment.*

Notably, OH was more common (11.7%) than either diarrhea (2.4%) or unintentional weight loss (3.1%) in subjects who had OH status recorded at enrollment. The majority of subjects with OH at enrollment presented with more advanced functional deterioration in the lower limbs as measured by mPND score (Fig. 1). Nevertheless,

OH as a symptom tended to be present relatively early in the course of disease progression (mPND stages 0, I, and II), before patients' ability to walk deteriorated further (Fig. 1). Diarrhea and unintentional weight loss were reported marginally more frequently by subjects with OH at enrollment (Table 1).

FIGURE 1. mPND score of subjects with and without OH at enrollment.*



mPND score: 0 – symptomatic, but no lower limb sensory/motor deficit; I – sensory disturbances in feet, but able to walk without difficulty; II – some difficulties walking, but can walk without aid; IIIa – able to walk with 1 cane or crutch; IIIb – able to walk with 2 canes or crutches; IV – confined to wheelchair or bedridden.

**Including 2,083 subjects with OH recorded at enrollment.*

Subjects with OH at enrollment tended to have significantly higher TQoL scores (indicating worse QoL) than those without OH at enrollment (Table 2).

Similarly, subjects with OH at enrollment had significantly higher scores in all TQoL item categories (Table 2). The EQ-5D Index and EQ-5D Health State scores were significantly lower (indicating worse health status) in subjects with OH present at enrollment (Table 2).

Table 2. QoL in subjects with OH present and absent at enrollment.*

QoL measures, mean (SD), [*n*]	OH at enrollment		
	OH present *N* = 243	OH absent *N* = 1,840	*p* value
TQoL score	42.2 (34.9), [197]	18.9 (25.7), [1,543]	< 0.0001
Physical functioning/ large fiber	20.9 (17.6), [197]	9.4 (14.0), [1,541]	< 0.0001
ADLs	5.1 (6.4), [197]	1.7 (4.0), [1,541]	< 0.0001
Symptoms	7.8 (6.7), [198]	4.4 (5.3), [1,542]	< 0.0001
Small fiber	5.2 (5.3), [197]	2.0 (3.6), [1,543]	< 0.0001
Autonomic	3.1 (3.2), [197]	1.4 (2.3), [1,540]	< 0.0001
EQ-5D Index	0.7 (0.2), [189]	0.8 (0.2), [1,544]	< 0.0001
EQ-5D Health State	64.8 (21.8), [184]	75.5 (19.3), [1,517]	< 0.0001

TQoL score – higher scores indicate worse QoL; EQ-5D – higher scores indicate better health status. EQ-5D Index, range 0–1; EQ-5D Health State, range 0–100. ADLs, Activities of Daily Living; EQ-5D, EuroQoL Five Dimensions; OH, orthostatic hypotension; QoL, quality of life; TQoL, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy Total Quality of Life.

**Including 2,083 subjects with OH recorded at enrollment.*

At enrollment and at Years 1, 2, and 3 after enrollment, both systolic and diastolic orthostatic differences were greater in subjects with OH than in those without OH at enrollment (Table 3).

Table 3. Orthostatic difference by year in subjects with OH present and absent at enrollment.*

Year	Systolic orthostatic difference		Diastolic orthostatic difference	
	OH present	OH absent	OH present	OH absent
Enrollment				
n	149	1,169	144	1,163
Mean (SD), mm Hg	–6.2 (14.2)	–4.4 (13.0)	–6.2 (14.2)	–4.4 (13.0)
Year 1				
n	96	746	93	741
Mean (SD), mm Hg	–5.9 (13.7)	–4.0 (13.8)	–5.9 (13.7)	–4.0 (13.8)
Year 2				
n	77	522	75	547
Mean (SD), mm Hg	–5.6 (14.0)	–4.4 (12.1)	–5.6 (14.0)	–4.4 (12.1)
Year 3				
n	60	466	55	456
Mean (SD), mm Hg	–5.2 (14.2)	–4.2 (13.9)	–5.2 (14.2)	–4.2 (13.9)

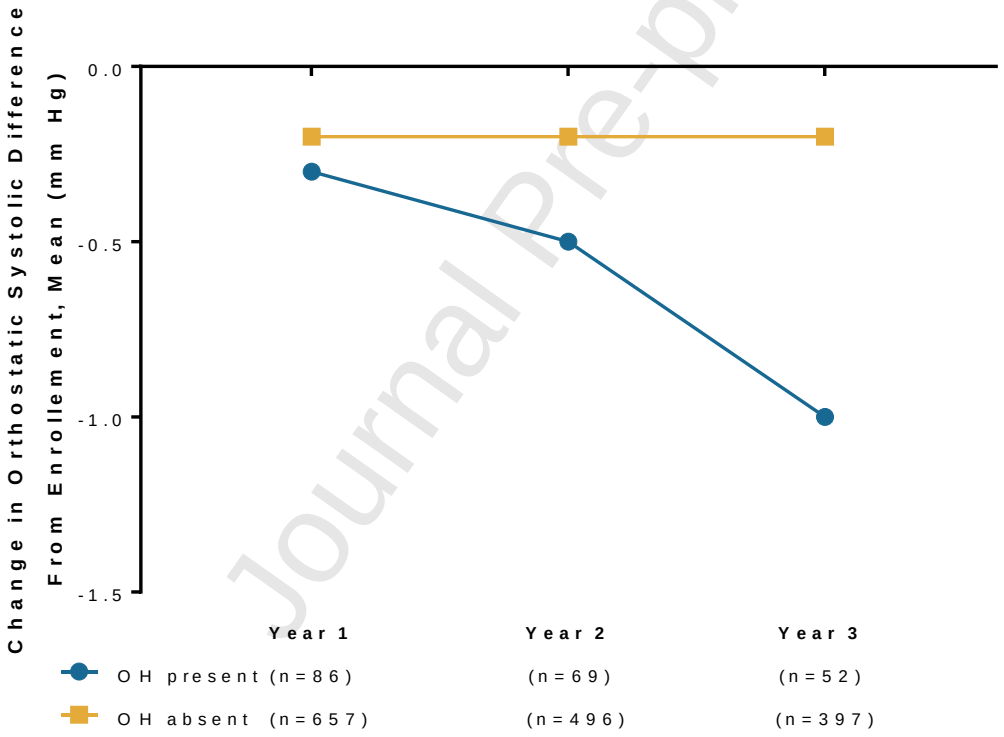
OH, orthostatic hypotension.

**Including 2,083 subjects with OH recorded at enrollment.*

The change from enrollment in systolic orthostatic difference increased progressively over time in subjects with OH at enrollment, whereas there was no change in systolic orthostatic difference in subjects without OH at enrollment (Fig. 2a). Similarly, diastolic orthostatic difference increased over time in subjects with OH, but not in those without OH, at enrollment (Fig. 2b).

FIGURE 2. Change in orthostatic difference from enrollment.* **(a)** Systolic orthostatic difference. **(b)** Diastolic orthostatic difference.

A



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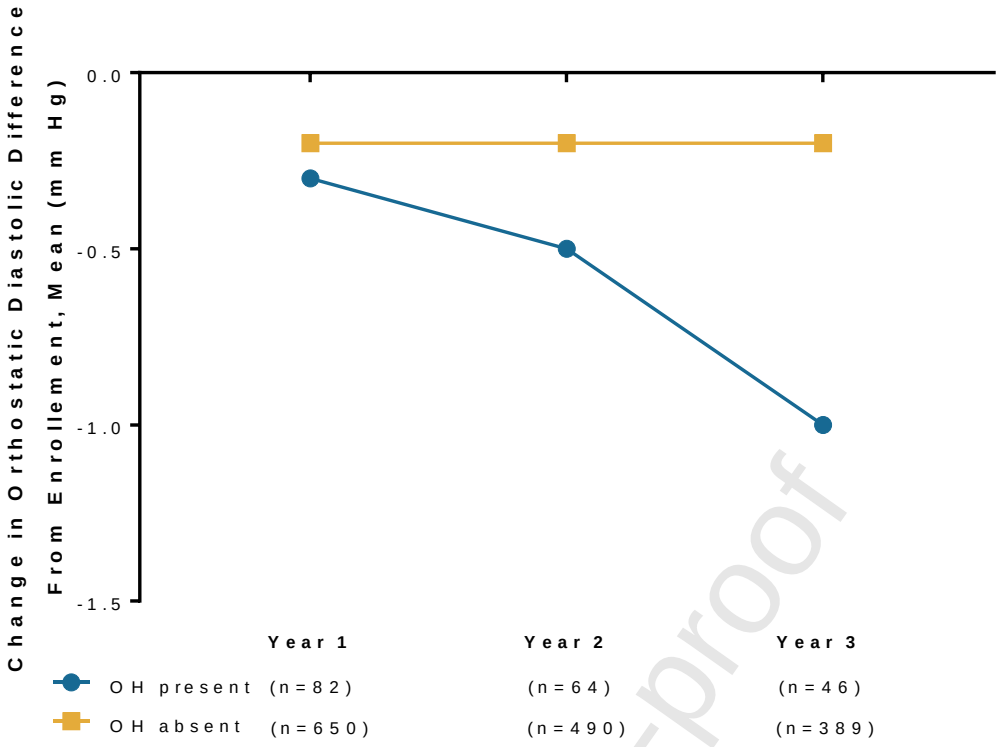

**Including 2,083 subjects with OH recorded at enrollment.*

BP and Orthostatic Difference at Enrollment and up to 3 Years From Enrollment. In all subjects, sitting and standing SBP and DBP were recorded at enrollment (mean mm Hg: sitting SBP 122.8; standing SBP 120.4; sitting DBP 75.5; standing DBP 78.8) and each year for up to 3 years.

Variables Associated With BP and Orthostatic Difference at Enrollment. Greater diastolic orthostatic difference at enrollment was significantly associated with older age (parameter estimate [SE], *p* value: 0.05 [0.022], 0.0308), higher mPND stage (1.10 [0.371], 0.0030), presence of diarrhea (3.56 [0.944), 0.0002), and unintentional weight loss (2.30 [0.861], 0.0077) (all at enrollment), whereas systolic orthostatic difference was not significantly associated with any of the assessed variables.

Variables Associated With Change in BP and Orthostatic Difference From Enrollment to Year 3. Reduction in sitting SBP was significantly associated with lower sitting SBP and older age, both at enrollment (Table 4). Reduction in standing SBP was significantly associated with lower standing SBP and older age, both at enrollment, and increase in mPND stage at Year 3 (Table 4). Reduction in sitting DBP was significantly associated with lower sitting DBP at enrollment, presence of diarrhea, and higher EQ-5D Index score, both at Year 3 (Table 4). Reduction in standing DBP was significantly associated with lower standing DBP at enrollment (Table 4).

Table 4. The relationship between independent variables and change in BP from enrollment to Year 3.*

Independent variables	Change in sitting BP				Change in standing BP			
	Systolic		Diastolic		Systolic		Diastolic	
	Parameter estimate (SE)	*p* value	Parameter estimate (SE)	*p* value	Parameter estimate (SE)	*p* value	Parameter estimate (SE)	*p* value
BP at enrollment	–0.63 (0.05)‡	< 0.0001	–0.61 (0.06)§	< 0.0001	–0.55 (0.03)‖	< 0.0001	–0.59 (0.05)¶	< 0.0001
Age at enrollment	0.19 (0.05)	0.0011	0.11 (0.07)	0.4209	0.20 (0.07)	< 0.0001	0.04 (0.03)	0.5284
Female	–0.95 (1.41)	0.4519	–0.81 (1.01)	0.6163	0.45 (1.75)	0.7129	–0.93 (1.02)	0.6317
TTR mutation	9.27 (6.81)	0.2107	6.57 (5.07)	0.3765	–†	–†	–†	–†
Symptomatic at enrollment	0.67 (1.90)	0.5411	1.13 (1.79)	0.6390	0.08 (1.91)	0.8910	0.91 (1.83)	0.4749
mPND stage at Year 3	1.77 (0.72)	0.0591	0.07 (0.53)	0.8881	1.91 (0.68)	0.0394	–0.25 (0.87)	0.9102
Diarrhea at Year 3	3.47 (1.92)	0.0619	2.89 (1.04)	0.0396	0.09 (2.11)	0.7159	–0.86 (1.81)	0.6513
Unintentional weight loss at Year 3	–3.02 (1.98)	0.1012	–1.91 (1.65)	0.2458	–3.06 (1.89)	0.2018	–1.62 (1.91)	0.3827
TQoL at Year 3	–0.02 (0.03)	0.6257	0.04 (0.02)	0.1071	–0.06 (0.03)	0.0983	–0.02 (0.02)	0.4489
EQ-5D Index score at Year 3	5.09 (4.44)	0.2521	6.93 (3.06)	0.0236	5.94 (4.66)	0.2028	3.60 (3.26)	0.2680

Reduction in sitting SBP at Year 3 was significantly associated with lower sitting SBP and older age at enrollment. Reduction in sitting DBP was significantly associated with lower sitting DPB at enrollment, presence of diarrhea at Year 3, and higher EQ-5D Index score at Year 3. Reduction in standing SBP was significantly associated with lower standing SBP and older age at enrollment, and higher mPND stage at Year 3. Reduction in standing DBP was significantly associated with lower standing DBP at enrollment.

ATTRwt, wild-type ATTR; BP, blood pressure; DBP, diastolic blood pressure; EQ-5D, EuroQoL Five Dimensions; mPND, modified Polyneuropathy Disability; SBP, systolic blood pressure; TTR, transthyretin; TQoL, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy Total Quality of Life.

**Including all subjects out of 3,231 subjects with recorded BP measurements and orthostatic difference at enrollment and Year 3. †There were no ATTRwt subjects with standing BP data at Year 3. BP at enrollment: ‡sitting systolic; §sitting diastolic; ‖standing systolic; ¶standing diastolic.*

Greater increase in systolic or diastolic orthostatic difference was significantly associated with smaller systolic or diastolic orthostatic difference at enrollment, the presence of diarrhea at Year 3, lower TQoL, and higher EQ-5D, both at Year 3 (Table 5). Greater increase in diastolic orthostatic difference was also significantly associated with higher mPND stage at Year 3 (Table 5).

Table 5. The relationship between independent variables and change in orthostatic difference from enrollment to Year 3.*

Independent variables	Change in orthostatic difference			
	Systolic		Diastolic	
	Parameter estimate (SE)	*p* value	Parameter estimate (SE)	*p* value
Orthostatic difference at enrollment	0.79 (0.04)†	< 0.0001	0.69 (0.04)‡	< 0.0001
Age at enrollment	–0.10 (0.16)	0.5900	0.02 (0.06)	0.5189
Female	–0.92 (1.75)	0.3451	–0.59 (0.93)	0.2574
Symptomatic at enrollment	0.83 (1.61)	0.5268	0.83 (1.41)	0.6941
mPND stage at Year 3	0.66 (0.94)	0.4701	1.09 (0.52)	0.0391
Diarrhea at Year 3	4.46 (1.42)	0.0201	3.19 (1.05)	0.0016
Unintentional weight loss at Year 3	0.62 (1.92)	0.8769	–0.65 (1.79)	0.8635
TQoL at Year 3	–0.09 (0.01)	0.0438	–0.14 (0.02)	0.0316
EQ-5D Index score at Year 3	7.03 (2.96)	0.0324	6.99 (3.19)	0.0212

Greater increase in systolic orthostatic difference was significantly associated with lower systolic orthostatic difference at enrollment, diarrhea, lower TQoL, and higher EQ-5D at Year 3. Greater increase in diastolic orthostatic difference was significantly associated with lower diastolic orthostatic difference at enrollment, diarrhea, lower TQoL, and higher EQ-5D at Year 3.

BP, blood pressure; EQ-5D, EuroQoL Five Dimensions; TTR, transthyretin; mPND, modified Polyneuropathy Disability; TQoL, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy Total Quality of Life.

**Including all subjects out of 3,231 subjects with recorded BP measurements and orthostatic difference at enrollment and Year 3. Orthostatic difference at enrollment: †systolic; ‡diastolic.*

DISCUSSION

Orthostatic hypotension is a sign of autonomic dysfunction in patients with ATTR amyloidosis[1] that can easily be diagnosed using sitting and standing BP measurements. In patients with polyneuropathy, symptoms of autonomic dysfunction occur frequently with early-onset disease (symptom onset at < 50 years of age) but are less common in those with late-onset disease (symptom onset at ≥ 50 years of age),[4] occurring at least not until the later stages of the disease.[18] In this analysis, subjects with OH at enrollment were older, more likely to be symptomatic, and had higher mPND score and worse QoL than those without OH at enrollment. This, combined with the fact that systolic and diastolic orthostatic differences increased over time in subjects with OH at enrollment but not in subjects without OH at enrollment, is indicative of a faster progression of autonomic dysfunction in subjects with OH. As such, OH may be a useful parameter to monitor disease progression.

These results are in accordance with earlier studies in which OH was reported as a common symptom in subjects with more severe ATTR amyloidosis.[11,12,18] However, in this analysis, it is worth noting that OH was more common at enrollment than either diarrhea or unintentional weight loss, which are considered common early symptoms of autonomic dysfunction in ATTR amyloidosis.[1,4] Analyzed subjects with OH tended to be at a more advanced disease stage than subjects without OH and it is possible that, for some patients, the presence of OH was the symptom which lead to diagnosis and enrollment in THAOS. Nevertheless, OH was present relatively early in the course of the disease (predominantly mPND stages 0, I, and II). In addition, nearly a third of subjects without OH were asymptomatic, while over 90% of those with OH were symptomatic. This suggests that OH could be utilized in conjunction with other signs and symptoms as an early diagnostic tool in a wide

group of patients, as it may occur before other symptoms, such as diarrhea, are present.

Recent studies have focused on “inter visit” variations in BP, however, it is not clear to what extent these variations are clinically significant. When treating hypertension, BP variations, defined as the difference between BP measured at various visits, have been identified as predictors of stroke, coronary events and heart failure.[19] In this analysis we observed a trend towards lower SBP and DBP from enrollment to Year 3, in addition to an increase in the orthostatic differences. Larger reductions in BP and increased orthostatic differences were associated with a higher degree of neuropathy, reflected by a higher mPND score. This suggests that inter visit BP variability may reflect changes in disease progression in ATTR amyloidosis.

Data collection from observational surveys has several limitations. Consequences of gathering data from multiple centers and countries include the possibility of variations in the assessments, reduced completeness of data over time, and variations in the rigor with which the data are acquired. An important weakness of this study lies in the fact that the methods used to assess orthostatic differences varied between the examiners. Although some guidelines have suggested that sitting and supine BP readings can be considered equivalent,[20] clinical observations have provided evidence that SBP and DBP are higher in the supine than in the sitting position;[21-23] thus, there is a possibility that more patients met the criteria for OH than were identified in this analysis in which sitting BP was measured. At the same time, it was not clear whether heart rate was measured simultaneously or after the BP measurement and was thus excluded from the analysis. Without heart rate measures to confirm otherwise, it may have been that some instances of OH could have been related to decreased blood volume as a consequence of dehydration, although

diarrhea (and unintentional weight loss) were present in only ~6% of patients with OH. There are a number of other confounding variables that can influence orthostatic changes, including diurnal variability, age, medications, hydration, and food intake, and care should be taken to ensure consistent measurement of OH.[16] Nevertheless, BP measurement and assessment of OH are largely objective measures that are less likely to vary to a meaningful degree between different centres than more complex or subjective assessments.

One should also be careful in the interpretation of the cause-to-effect correlation; for example, the amplitude of variation could be largely due to increased episodes of diarrhea rather than solely due to increased neurogenic failure. While variation in BP might arise from the hydration status of an individual—which might be difficult to control in patients with ATTR amyloidosis, especially those in the later stages of the disease—the impact of this potential variability is likely limited by the large number of subjects in this analysis. Additionally, correlation to increased mPND score suggests that visit-to-visit blood BP variability may be a surrogate for homeostasis disruption and not solely caused by volume changes.

What is the clinical significance of these findings? We suggest that the clinician treating patients with ATTR amyloidosis integrates a standardized method for recording BP repeatedly in the same fashion at every visit, and that as many BP values as possible are recorded to allow for the determination of the variations over time. With data collected in this manner, the trend towards lower BP measurement can be analyzed as a possible marker of the disease progression over time when compared to earlier visits.

Of paramount importance, this study showed that OH was present more frequently than other common early symptoms associated with autonomic

dysfunction in ATTR amyloidosis, and hence it could be a useful sign in early diagnosis. Visit-to-visit BP measurements when carefully assessed and analyzed can be used in real-world medical practice and evaluating changes in BP-related parameters over time might help to improve knowledge of the clinical course of ATTR amyloidosis and may translate to new therapeutic targets.

Abbreviations: ADLs, Activities of Daily Living; ATTRm, hereditary ATTR; ATTRwt, wild-type ATTR; BP, blood pressure; DBP, diastolic blood pressure; EQ-5D, EuroQoL Five Dimensions; mPND, modified Polyneuropathy Disability; OH, orthostatic hypotension; QoL, quality of life; SBP, systolic blood pressure; THAOS, Transthyretin Amyloidosis Outcomes Survey; TQoL, Norfolk Quality of Life Questionnaire-Diabetic Neuropathy Total Quality of Life; TTR, transthyretin

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